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Quality of life as a prognostic factor of overall survival in patients with advanced hepatocellular carcinoma: results from two French clinical trials

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Abstract
Aim The aims of our study were to assess quality of life (QoL) as a prognostic factor of overall survival (OS) and to determine whether QoL data improved three prognostic classifications among French patients with advanced hepatocellular carcinoma (HCC).
Methods We pooled two randomized clinical trials conducted by the Fédération Francophone de Cancérologie Digestive in a palliative setting. In each trial QoL was assessed at baseline using the Spitzer QoL Index (0–10). Three prognostic classifications were calculated: Okuda, Cancer of the Liver Italian Program (CLIP), and Barcelona Clinic Liver Cancer group (BCLC) scores. To explore whether the scores could be improved by including QoL, univariate Cox analyses of all potential baseline predictors were performed. A final multivariate Cox model was constructed including only significant multivariate baseline variables likely to result in improvement of each scoring system. In order to retain the best prognostic variable to add for each score, we compared Akaike information criterion, likelihood ratio, and Harrell's C-index. Cox analyses were stratified for each trial.
Results Among 538 included patients, QoL at baseline was available for 489 patients (90%). Longer median OS was significantly associated with higher Spitzer scores at baseline, ranging from 2.17 months (Spitzer = 3) to 8.93 months (Spitzer = 10). Variables retained in the multivariate Cox model were: jaundice, hepatomegaly, hepatalgia, portal thrombosis, alphafetoprotein, bilirubin, albumin, small HCC, and Spitzer QoL Index (hazard ratio = 0.84 95% CI [0.79–0.90]). According to Harrell's C-index, QoL was the best prognostic variable to add. CLIP plus the Spitzer QoL Index had the most discriminating value ($C = 0.71$).
Conclusions Our results suggest that QoL is an independent prognostic factor for survival in HCC patients with mainly alcoholic cirrhosis. The prognostic value of CLIP score could be improved by adding Spitzer QOL Index scores.

Keywords Quality of life · Hepatocellular carcinoma · Prognostic factor · Overall survival · Validation

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Introduction

Primary liver cancer is the fifth most frequent cancer and the third most common cause of cancer-related death in the

world [1]. Hepatocellular carcinoma (HCC) is the main form of liver cancer; this cancer generally develops following cirrhosis or hepatitis B (HBV) or C (HCV) infections. The incidence of HCC has substantially increased in developed countries during the last three decades [2, 3]. In France, 6,000 deaths per year are due to this cancer, whose main aetiology is related to alcohol abuse.

Quality of life (QoL) is a major aspect in the care of cancer patients, and has been recognized as an important end point in cancer clinical trials and clinical practice, along with the traditional end points including tumor response rate, disease-free survival, and overall survival [4–8]. More recently, pretreatment QoL has been recognized as a potential prognostic factor of survival in cancer patients [8–9]. Classification of patients according to their prognosis is a central issue since inclusion criteria in clinical trials supposes that homogenous groups of patients can be identified. Various prognostic factors of overall survival have thus been explored and several classifications have been proposed for patients with HCC [10–13]. The most commonly used scores are Okuda Stage, Cancer of the Liver Italian Program (CLIP), Barcelona Clinic Liver Cancer group (BCLC), and Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire (GRETCH). Different studies have compared and ranked these classifications [14–22] according to their prognostic value. The results of the different studies have been discordant and remain controversial. Furthermore, most of the studies focused on HBV/HCV-infected patients, even though it is very likely that overall survival depends on the aetiology of the cirrhosis. Therefore, the conclusions of these studies may not be consistent with those based on alcohol-related HCC.

This study focuses on patients with advanced-stage HCC mainly associated with alcoholic cirrhosis. Based on a pooled analysis of two randomized clinical trials (RCT) carried out by the Fédération Francophone de Cancérologie Digestive (FFCD), we have assessed the value of quality-of-life scores for predicting overall survival. We have also explored whether staging systems for HCC could be improved by adding quality-of-life data.

Patients and methods

Patients

We performed a pooled analysis of two RCTs of patients with HCC in a palliative setting.

The FFCD 9403 trial evaluated the survival benefit of adding tamoxifen to best supportive care. In this trial, 420 eligible patients from 78 French institutions were randomized [23]. Inclusion criteria were HCC not eligible for surgical resection, liver transplantation, percutaneous ablation, or transarterial chemoembolization. Diagnosis of HCC was either cytologically or histologically confirmed, or made by the association of a diagnosis of cirrhosis: demonstrated by ultrasonography, and/or computed tomography (CT) scan, and/or an manetic resonance imaging (MRI) showing a space-occupying lesion having an image consistent with the diagnosis of HCC and persistent alphafetoprotein (AFP) values above 500 μg/l. Exclusion criteria were renal failure (serum creatinine >130 μmol/l), advanced liver disease (Child-Pugh class C), World Health Organization (WHO) performance status (PS) greater than 2, and prior treatment with tamoxifen.

The FFCD 9402 trial evaluated the survival benefit of adding transarterial lipiodol chemoembolization to tamoxifen alone. In this trial, 122 eligible patients from 15 French institutions were randomly assigned [24]. Inclusion criteria were HCC not eligible for surgical resection, liver transplantation or percutaneous ablation. All patients were cirrhotic (cirrhosis diagnosis was histologically proven or based on clinical and biological parameters). Diagnosis of HCC was based on biopsy, or persistently elevated AFP levels (>400 μg/l) with one typical imaging finding (ultrasonography or CT scan or MRI, or normal AFP levels with 2 concordant imaging findings). Exclusion criteria were advanced liver disease (Child-Pugh class C), advanced HCC (Okuda stage III), portal vein thrombosis (trunk and primary branches) or arteriovenous shunting, extrahepatic metastases, renal failure (serum creatinine level >120 μmol/l or creatinine clearance <80 ml/min), platelet count $<50 \times 10^9$/l, prothrombin activity <50%, and cardiac ejection fraction <35%.

These two trials failed to demonstrate any superiority of the investigated treatments [23–24].

In the 9403 trial, four patients, for whom more than 60% of the data were missing, were excluded and in the 9402 trial, one patient, who had a WHO PS of 4, was excluded. Finally, 122 patients in the 9402 trial and 416 patients in the 9403 trial were retained and pooled ($n = 538$).

We further selected patients who had completed the quality-of-life questionnaire at baseline, that is before randomization.

Quality-of-life assessment

Quality of life (QoL) was evaluated before randomization by the Spitzer QoL Index [25–27], which is a global cancer-specific QoL score. A score of 0 (worst) to 10 (best) was calculated following the assessment of five dimensions related to activity, daily life, health perceptions, social support, and behavior. Each area was assessed by one item rated on a three-point Likert scale. The QoL questionnaire was completed by the patients in the two trials [23–24]. However, in the 9402 trial, to prevent missing QoL data, when patients were unable to complete the questionnaire

due to progression of the cancer and/or poor health status, clinicians were allowed to assess QoL on their behalf.

Prognostic classifications

Table 1 presents definitions of Okuda, CLIP, and BCLC prognostic scores. Furthermore, the Child-Pugh score, required to calculate CLIP, was based on ascites, encephalopathy, total bilirubin, prothrombin rate, and albumin.

Collected variables and reconciliation

The following baseline variables were retained to calculate the prognostic classification, to explore their prognostic value, and to determine whether they could improve staging systems: Spitzer QoL Index, age, sex, date and modality of HCC diagnosis, date of death or of last information on vital status, presence of cirrhosis and its aetiology, clinical parameters (weight, oedema of the lower limbs, jaundice, hepatomegaly, hepatalgia, ascites, encephalopathy), serological parameters (total bilirubin, prothrombin rate, creatinine, albumin, AFP serum levels), tumor characteristics (site of the principal tumor, maximum tumor diameter, number of tumor sites in the liver, tumor extension, portal vein thrombosis, extrahepatic metastases), and WHO performance status.

Biological parameters were dichotomized according to usual reports in the literature and age according to the median.

Portal vein thrombosis in the two trials was reported according to different criteria. The data were reconciled by the principal investigators.

"Small HCC" was defined according to the Milan Criteria [28], that is, 1 nodule <50 mm or 2–3 nodules <30 mm.

Table 1 Definitions of the Okuda, CLIP, and BCLC classifications

Okuda	Scores	
	0	1
Ascites	Absent	Present
Tumor size	≤50%	>50%
Bilirubin (μmol/l)	≤50	>50%
Albumin (g/l)	≤30	>30

CLIP	Scores		
	0	1	2
Child-Pugh	A	B	C
Tumor morphology	Uninodular and extension ≤50%	Multinodular and extension ≤50%	Massive or extension >50%
AFP (ng/dl)	≤400	>400	
Portal vein thrombosis	No	Yes	

BCLC	Scores						
	A1	A2	A3	A4	B	C	D
Performance status (PST)	0	0	0	0	0	1–2	3–4
Tumor stage	Single	Single	Single	3 tumors <3 cm	Multinodular	Vascular invasion or extrahepatic spread	Any
Okuda	I	I	I	I–II	I–II	I–II	II
Liver functional status	No portal hypertension and normal bilirubin	Portal hypertension and normal bilirubin	Portal hypertension and abnormal bilirubin	Child-Pugh A-B	Child-Pugh A-B	Child-Pugh A-B	Child-Pugh

Okuda stages: I = 0 points; II = 1–2 points; III = 3–4 points

CLIP: Cancer of the Liver Italian Program scoring system

BCLC: Barcelona Clinic Liver Cancer staging classification; stages A and B all criteria should be fulfilled; stage C at least one criterion PST 1–2 or vascular invasion or extrahepatic spread; stage D at least one criterion PST 3–4 or Okuda stage III/Child-Pugh C

Statistical analyses

All statistical analyses were performed on the pooled data base stratified by trial to take into account differences between the trials. Per-trial analyses were then performed and these enabled us to check the robustness of our results.

Baseline variables are given as means (standard deviation, SD), or frequencies and percentages. The Spitzer QoL Index is shown as mean (SD) and median (minimum–maximum) and the results for the two trials were compared using the Mann–Whitney test.

Overall survival is defined as the time between the date of inclusion and the date of death (all causes) or the date of the last follow-up for living patients. Survival was estimated using the Kaplan–Meier approach and was compared using the stratified log-rank test. Median survival was calculated with its 95% confidence interval (CI).

For prognosis purposes, the Spitzer QoL Index was treated as a continuous ordered variable. However, to represent survival graphically, we divided the Spitzer Index into three subgroups (0–7 versus 8 versus 9 and 10).

Monotonicity of the gradients according to the Spitzer QoL Index score was checked by comparing median survival times. Patients with a better prognosis should have higher median values than patients with a poor prognosis. A significant log-rank for trend was considered to reflect this monotonicity.

Univariate and multivariate Cox analyses stratified by trial were performed to estimate hazard ratios (HR) and its 95% confidence intervals (95% CI). We performed univariate Cox analyses of all potential baseline predictors including the variables constituting each score. We tested a multivariate model including all variables with univariate $P < 0.10$, including bilirubin, which had a P-value close to 0.10. The final multivariate model was constructed with a backward procedure among these variables to select variables likely to improve each scoring system. Internal validity of this model has been explored using bootstrapping (100 replications).

Finally, multivariate Cox model analyses were performed for each score. The best models were built with forward and backward procedures among baseline variables pertinent to improve each score. In order to retain the best prognostic variable to add to each score, from the final model we compared the Akaike information criterion (AIC), the likelihood ratio (LR), and Harrell's C statistic [29]. A smaller AIC value or a higher LR indicated that the model was more informative regarding the prognosis of overall survival. Harrell's C statistic estimates the proportion of correct predictions, i.e., the proportion of patients with a better prognostic stage who have better survival. Bootstrapping (100 replications) was applied for internal validity to calculate optimism-corrected C-statistics. The results of Harrell's C-index varied from 0.5 (no discrimination) to 1 (perfect discrimination).

Harrell's C-index was also calculated for the Spitzer QoL Index score alone.

All data analyses were performed using Stata V10. A P-value less than 0.05 was considered significant.

Results

Patients' characteristics

Among the 538 patients of the pooled database, 489 patients had available QoL scores at baseline: 93 (76%) in the 9402 trial and 396 (95%) in the 9403 trial. Their baseline clinical characteristics were similar to those of the whole population (Table 2). In the 9402 trial all QoL questionnaires were completed by the patients while clinicians were allowed to assess QoL on behalf of the patients when they were unable to complete the questionnaire.

Patients' baseline characteristics are described in Table 2. Males were predominant (88%), as were patients aged $\geq$65 years (63%). All patients in the 9402 trial were cirrhotic (inclusion criteria), and 91% patients of the 9403 trial were cirrhotic. Among them, 454 patients (78%) had alcoholic cirrhosis. WHO PS 0 was more frequent (50.3%). Finally, patients in the 9402 trial had a better clinical, biological, and tumor status (Table 2). Due to the inclusion criteria, the majority of patients were Child-Pugh class A or B, Okuda I and II, CLIP 1–3, and BCLC B or C.

The mean QoL at baseline differed significantly (Wilcoxon $P \leq 0.0001$) by trial; it was 8.6 (SD 1.3) and 7.6 (SD 1.8) in the 9402 and 9403 trial, respectively, resulting in a clinical difference of 10% in the theoretical score range. A majority of patients had a Spitzer score between 7 and 10.

Overall survival

At the time the databases were closed, 459 (94%) patients had died and only 30 patients (6%) were alive. The median survival was 5.26 months (95% CI: 4.4–6.0).

Overall survival differed significantly by trial (log-rank test: $P < 0.0001$) and thus required stratified analyses (Table 3). Median survival was longer in the 9402 trial: 13 months (8.2–16.8) versus 4.3 months (3.8–5.0).

According to the Spitzer QoL Index, median overall survival varied significantly from 2.17 for a Spitzer 3 to 8.93 months for a Spitzer 10 (log-rank test for ordered groups: $P < 0.0001$) (Table 3). Figure 1 shows survival curves according to the Spitzer score subgroups.

Harrell's C statistic, which reflects discriminatory capability, was 0.63 for the Spitzer QoL Index alone.

Table 2 Baseline characteristics of patients with HCC with or without available QoL data

	Patients with available QoL data						All patients	
	9402		9403		Total		Total	
	N	%	*N*	%	*N* = 489	%	*N* = 538	%
Spitzer QoL Index								
0	0	0.00	1	0.25	1	0.20		
1	0	0.00	0	0.00	0	0.00		
2	0	0.00	1	0.25	1	0.20		
3	0	0.00	8	2.02	8	1.64		
4	0	0.00	19	4.80	19	3.89		
5	1	1.08	27	6.82	28	5.73		
6	6	6.45	46	11.62	52	10.63		
7	12	12.90	58	14.65	70	14.31		
8	16	17.20	94	23.74	110	22.49		
9	32	34.41	82	20.71	114	23.31		
10	26	27.96	60	15.15	86	17.59		
Sex								
Male	81	87.10	354	89.39	435	88.96	478	88.85
Age (years)								
≥65	45	48.39	261	65.91	306	62.58	337	62.64
Cirrhosis								
Present	93	100.00	361	91.16	454	92.84	498	92.57
Alcoholic cirrhosis								
Yes	75	80.65	307	77.53	382	78.12	414	76.95
Jaundice								
Yes	6	6.45	77	19.44	83	16.97	93	17.29
Hepatomegaly								
Yes	61	65.59	307	77.53	368	75.26	401	74.54
Hepatalgia								
Yes	19	20.43	103	26.01	122	24.95	131	24.35
Involved liver volume								
>50%	13	13.98	122	30.81	135	27.61	144	26.77
Extrahepatic metastases								
Yes	0	0.00	67	16.92	67	13.70	70	13.01
Portal vein thrombosis								
Yes	25	26.88	155	39.14	180	36.81	197	36.62
Alpha-fetoprotein serum level (μg/l)								
≥200	35	37.63	209	52.78	244	49.90	265	49.26
Total bilirubin (μmol/l)								
≥20	43	46.24	223	56.31	266	54.40	296	55.02
Prothrombin rate (%)								
≥80	46	49.46	171	43.18	217	44.38	241	44.80
Albumin (g/l)								
≥35	64	68.82	175	44.19	239	48.88	260	48.33
Creatinine (μmol/l)								
≥80	44	47.31	202	51.01	246	50.31	270	50.19
Small HCC								
Yes	20	21.51	36	9.09	56	11.45	65	12.08
WHO PS								
0	37	39.78	75	18.94	112	22.90	123	22.86

Table 2 continued

	Patients with available QoL data						All patients	
	9402		9403		Total		Total	
	N	%	*N*	%	*N* = 489	%	*N* = 538	%
1	50	53.76	196	49.49	246	50.31	276	51.30
2	6	6.45	125	31.57	131	26.79	139	25.84
Child-Pugh								
Child-Pugh A	67	72.04	208	52.53	275	56.24	304	56.51
Child-Pugh B	26	27.96	171	43.18	197	40.29	217	40.33
Child-Pugh C	0	0.00	17	4.29	17	3.48	17	3.16
Okuda stage								
I	62	66.67	133	33.59	195	39.88	221	41.08
II	30	32.26	229	57.83	259	52.97	279	51.86
III	1	1.08	34	8.59	35	7.16	38	7.06
CLIP score								
0	10	10.75	17	4.29	27	5.52	32	5.95
1	32	34.41	82	20.71	114	23.31	125	23.23
2	29	31.18	109	27.53	138	28.22	155	28.81
3	16	17.20	107	27.02	123	25.15	132	24.54
4	6	6.45	59	14.90	65	13.29	72	13.38
5–6	0	0.00	22	5.56	22	4.50	22	4.09
BCLC stage								
A	10	10.75	3	0.76	13	2.66	14	2.60
B	20	21.51	42	10.61	62	12.68	68	12.64
C	62	66.67	310	78.28	372	76.07	411	76.39
D	1	1.08	41	10.35	42	8.59	45	8.36

Analyses of prognostic factors

Univariate Cox analyses stratified by trial showed that the following variables were significantly associated with lower overall survival (Table 4): alcoholic cirrhosis, jaundice, hepatomegaly, hepatalgia, ascites, involved liver volume greater than 50%, tumor localization, portal vein thrombosis, AFP serum level $\geq$200 µg/l, total bilirubin $\geq$20 µmol/l, and WHO PS >0. An increase of one unit of the Spitzer QoL Index was significantly associated with longer survival [HR = 0.81 (0.77–0.86)]. Likewise, albumin $\geq$35 g/l, prothrombin activity $\geq$80%, and small HCC improved survival.

In multivariate analysis including the above variables and those with univariate $P \leq 0.10$ (age, other cirrhosis aetiology, and oedema of the lower limbs) the following remained significant independent baseline predictors: jaundice, hepatomegaly, hepatalgia, ascites, portal vein thrombosis, AFP level, albumin level, small HCC, and Spitzer QoL Index.

The final multivariate model was constructed with a backward procedure based on these variables plus total bilirubin, whose multivariate *P* values were nearly 0.10. This final multivariate model retained the following significant prognostic factors (Table 4): jaundice, hepatomegaly, hepatalgia, ascites, portal thrombosis, AFP, total bilirubin, albumin, small HCC, and Spitzer QoL Index. Internal validity of this model assessed by bootstrapping showed the following 95% CI: jaundice ([0.93–1.99]; $P = 0.108$), hepatomegaly ([1.18–1.91]; $P = 0.001$), hepatalgia ([1.09–1.89]; $P = 0.011$), ascites (minimal vs. no [1.03–1.80]; $P = 0.03$, abundant vs. no [0.65–2.17]; $P = 0.571$), portal thrombosis ([1.18–1.77]; $P \leq 0.0001$), AFP ([1.34–2.23]; $P \leq 0.0001$), total bilirubin ([0.97–1.62]; $P = 0.085$), albumin ([0.56–0.93]; $P = 0.011$), small HCC ([0.40–0.80]; $P = 0.001$), and Spitzer QoL Index ([0.80–0.90]; $P \leq 0.0001$).

The three scores investigated could thus be improved with the following eligible variables which are not included in the corresponding score (Table 5):

- For CLIP: jaundice, hepatalgia, hepatomegaly, and Spitzer QoL Index.
- For Okuda: hepatomegaly, hepatalgia, portal vein thrombosis, AFP serum level, small HCC, and Spitzer QoL Index.
- For BCLC: hepatomegaly, jaundice, hepatalgia, AFP serum level, and Spitzer QoL Index.

Table 3 Overall survival related to the staging systems, Spitzer QoL Index, and WHO PS at inclusion (trial stratification)

	Overall survival						
	Log-rank	*P* value	Median (months)	95% CI	1 year (%)	2 years (%)	3 years (%)
Trial	28.99	<0.0001					
9402			12.97	[8.37;16.83]	0.53	0.27	0.12
9403			4.33	[3.77;5.03]	0.22	0.08	0.03
Spitzer QoL Index	165.30	<0.0001					
0			1.23	[;]	0.00	0.00	0.00
1				[;]	0.00	0.00	0.00
2			0.33	[;]	0.00	0.00	0.00
3			2.17	[0.60;5.90]	0.00	0.00	0.00
4			2.27	[1.33;3.07]	10.53	0.00	0.00
5			2.27	[1.47;2.60]	3.73	0.00	0.00
6			3.30	[2.40;5.17]	17.09	4.27	4.27
7			3.10	[2.43;4.37]	22.86	6.86	1.71
8			5.60	[4.27;7.90]	29.26	6.57	3.29
9			7.67	[5.80;10.50]	36.50	19.97	7.71
10			8.93	[6.77;11.73]	38.06	22.64	10.26
WHO PS	60.86	<0.0001					
−0			11.53	[8.67;16.13]	49.62	21.50	12.51
−1			4.73	[4.10;5.80]	24.74	11.59	3.52
−2			2.43	[2.13;3.07]	14.04	3.90	1.56
Child-Pugh	53.68	<0.0001					
Child-Pugh A			7.50	[5.90;8.93]	35.17	15.19	7.64
Child-Pugh B			3.43	[2.60;4.23]	18.78	7.84	2.10
Child-Pugh C			1.57	[0.37;2.87]	5.88	0.00	0.00
Okuda	165.4331	<0.0001					
Okuda I			11.40	[8.53;14.00]	46.59	21.89	10.30
Okuda II			4.00	[3.43;4.97]	16.86	5.47	1.82
Okuda III			1.43	[0.90;1.80]	0.00	0.00	0.00
CLIP	147.8784	<0.0001					
CLIP 0			23.03	[16.23;26.17]	77.78	42.99	12.90
CLIP 1			12.97	[11.10;17.97]	54.92	28.18	14.28
CLIP 2			4.33	[3.70;5.73]	15.22	3.30	1.65
CLIP 3			4.60	[3.57;5.53]	19.67	3.27	2.18
CLIP 4			2.13	[1.37;2.60]	6.28	3.14	0.00
CLIP 5–6			1.73	[1.10;2.50]	4.55	4.55	0.00
BCLC	114.2513	<0.0001					
BCLC A			21.37	[13.77;40.43]	76.92	46.15	30.77
BCLC B			16.10	[11.37;18.80]	60.71	22.71	11.65
BCLC C			4.67	[4.10;5.57]	23.10	10.00	3.61
BCLC D			1.53	[0.93;1.90]	2.38	0.00	0.00

Internal validity of these models assessed by bootstrapping showed the following 95% CI:

- For CLIP: jaundice ([1.13–2.16], $P = 0.007$]), hepatalgia ([0.99–1.90]; $P = 0.061$), hepatomegaly ([0.99–1.59]; $P = 0.059$), and Spitzer QoL Index ([0.80–0.91]; $P \leq 0.0001$).
- For Okuda: hepatomegaly ([1.18–1.82]; $P = 0.001$), hepatalgia ([1.04–1.82]; $P = 0.026$), portal vein thrombosis ([1.09–1.84]; $P = 0.008$), AFP serum level ([1.35–2.16]; $P \leq 0.0001$), small HCC ([0.46–0.91]; $P = 0.013$), and Spitzer QoL Index ([0.80–0.90]; $P \leq 0.0001$).

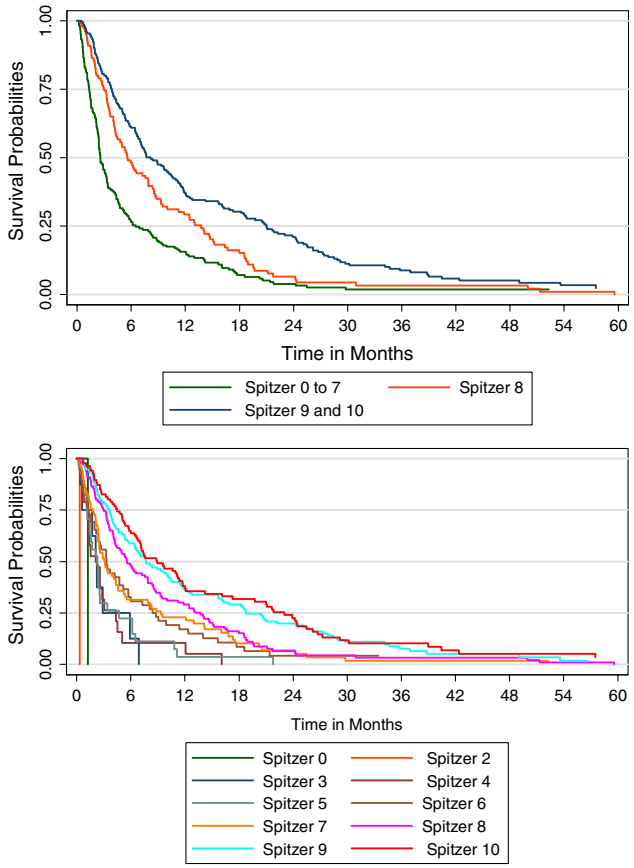

Fig. 1 Overall survival according to the Spitzer QoL Index (four subgroups) using Kaplan-Meier estimation, $n = 489$

– For BCLC: hepatomegaly ([1.24–2.03]; $P \leq 0.0001$), jaundice ([0.95–1.93]; $P = 0.092$), hepatalgia ([1.09–1.90]; $P = 0.009$), AFP serum Level ([1.48–2.21]; $P \leq 0.0001$), and Spitzer QoL Index ([0.81–0.93]; $P = 0.001$).

AIC and LR statistics highlighted the fact that the Spitzer QoL Index was the most informative variable to be added to the CLIP and Okuda (Table 5). Prognostic information of the BCLC could be improved by adding AFP or the Spitzer QoL Index even though the BCLC included WHO PS (Table 5).

According to Harrell's C-index, the discriminating value of CLIP plus the Spitzer QoL Index ($C = 0.71$) was better than that of Okuda plus the Spitzer QoL Index ($c = 0.69$) and BCLC ($C = 0.68$). Furthermore, the discriminatory capability of Okuda ($c = 0.64$) and BCLC ($C = 0.62$) alone were closer to QoL alone ($c = 0.63$) while, with a Harrell's C-index of 0.67, the discriminatory capability of CLIP alone was best. The optimism-corrected C-statistics and its 95% CI confirmed these results, as shown in Table 5.

Discussion

Our results highlighted the fact that QoL assessed by the Spitzer Index was a strong and independent prognostic factor of overall survival time for French patients with advanced HCC following mainly alcoholic cirrhosis. Furthermore, the Spitzer QoL Index was the most informative variable to add in order to improve the discriminating power of the existing staging systems. After adjusting for the prognostic score, the Spitzer QoL Index as well as other variables remained associated with overall survival, suggesting that prediction of the prognosis could be improved. Nevertheless, patient-reported baseline QoL provides additional prognostic information that supplements traditional clinical factors, and should be considered a complementary prognostic tool for survival in patients with advanced HCC.

This positive correlation between QoL data and survival time has already been reported in various cancer sites and more specifically in advanced cancer [9, 30–32]. These sites include the breast [33–35], lung [36–39], oesophagus [40–42], head and neck [43], colon [44], malignant melanoma [45], multiple myeloma [46], ovary [47], and malignant glioma [48]. Even though few studies have been carried out in HCC patients, our results are in agreement with a recent study from Yeo et al. [49], which showed that role and emotional functioning and appetite loss of QLQ-C30 were associated with survival time. However, our study is the first to assess the QoL score as a prognostic factor in a population with mainly alcoholic HCC aetiology, which is associated with older age at diagnosis, poor living conditions, and other complications due to alcoholism. The independent prognostic value of QoL for these patients suggests that a better Spitzer QoL score reflects better physical and emotional functioning (e.g., because of certain personality characteristics and/or social circumstances) within a group of patients with similar disease characteristics (advanced HCC and cirrhosis). In our opinion one of the first therapeutic goal, in the aim to improve overall survival, could be to preserve or improve QoL by controlling impact of disease and maybe alcoholic dependency on physical and emotional functioning.

The major strengths of our study are that 80% of the QoL data were available at baseline. The clinical characteristics of these patients are similar to those of the whole population of our pooled randomized clinical trials, which limits most potential selection biases. A high standard of follow-up was applied, resulting in a minimal rate of loss to follow-up, a large number of events, and adequate overall statistical power. To complement the analyses of the prognostic value of QoL data, we used statistical methods

Table 4 Univariate and multivariate analyses of baseline prognostic factors (Cox model)

		Univariate Cox			Full multivariate Cox			Final multivariate Cox		
		HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex	(F vs. M)	0.90	[0.67;1.21]	0.4902						
Weight (kg)	[≥65 (F) and ≥75 (M) vs. <65 (F) and <75 (M)]	0.94	[0.78;1.13]	0.5089						
Age in years	(≥65 vs. <65)	0.84	[0.69;1.02]	0.0752	0.96	[0.78;1.18]	0.6842			
Cirrhosis	(yes vs. no)	1.31	[0.91;1.87]	0.1445						
Alcoholic cirrhosis	(yes vs. no)	1.27	[1.01;1.59]	0.0410	1.20	[0.93;1.53]	0.1602			
HCV cirrhosis	(yes vs. no)	0.97	[0.74;1.28]	0.8329						
HBV cirrhosis	(yes vs. no)	0.81	[0.53;1.24]	0.3376						
Other cirrhosis	(yes vs. no)	0.65	[0.42;1.03]	0.0647	1.11	[0.68;1.80]	0.6797			
Jaundice	(yes vs. no)	2.02	[1.58;2.58]	<0.0001	1.38	[1.04;1.82]	0.0265	1.36	[1.04;1.79]	0.0254
Hepatomegaly	(yes vs. no)	1.57	[1.27;1.95]	<0.0001	1.41	[1.11;1.79]	0.0055	1.50	[1.19;1.89]	0.0005
Oedemas of the lower limbs	(yes vs. no)	1.21	[0.97;1.51]	0.0840	0.90	[0.71;1.14]	0.3693			
Hepatalgia	(yes vs. no)	1.64	[1.32;2.03]	<0.0001	1.45	[1.14;1.84]	0.0024	1.43	[1.14;1.80]	0.0017
Ascites	(minimal vs. no)	2.00	[1.60;2.49]	<0.0001	1.41	[1.11;1.79]	0.0190	1.36	[1.08;1.72]	0.0325
	(abundant vs. no)	1.94	[1.37;2.75]		1.25	[0.82;1.88]		1.19	[0.80;1.76]	
Tumor localization	(left vs. right)	1.02	[0.83;1.26]	<0.0001	0.99	[0.79;1.24]	0.7862			
	(bilateral vs. right)	1.53	[1.07;2.18]		1.14	[0.78;1.67]				
Tumor morphology	(unilateral-multinodular vs. uninodular)	1.21	[0.92;1.58]	0.1374						
	(bilateral-multinodular vs. uninodular)	1.23	[1.00;1.53]							
Involved liver volume >50%	(yes vs. no)	1.59	[1.29;1.97]	<0.0001	1.22	[0.97;1.55]	0.0945			
Portal vein thrombosis	(yes vs. no)	1.76	[1.45;2.13]	<0.0001	1.40	[1.14;1.72]	0.0014	1.45	[1.19;1.77]	0.0003
Alphafetoprotein (μg/l)	(≥200 vs. <200)	1.91	[1.58;2.32]	<0.0001	1.72	[1.40;2.11]	<0.0001	1.73	[1.42;2.12]	<0.0001
Total bilirubin (μmol/l)	(≥20 vs. <20)	1.60	[1.33;1.93]	<0.0001	1.20	[0.96;1.50]	0.1177	1.25	[1.01;1.55]	0.0385
Prothrombin (%)	(≥80 vs. <80)	0.78	[0.65;0.94]	0.0075	0.91	[0.74;1.13]	0.4024			
Albumin (g/l)	(≥35 vs. <35)	0.61	[0.50;0.74]	<0.0001	0.77	[0.63;0.95]	0.0162	0.73	[0.59;0.89]	0.0019
Creatinine (μmol/l)	(≥80 vs. <80)	0.92	[0.76;1.10]	0.3478						
Small HCC	(yes vs. no)	0.66	[0.49;0.89]	0.0061	0.59	[0.43;0.81]	0.0010	0.56	[0.42;0.77]	0.0002
Spitzer QoL Index	(continuous)	0.81	[0.77;0.86]	<0.0001	0.87	[0.81;0.93]	0.0001	0.84	[0.79;0.90]	<0.0001
WHO PS	(PS 1 vs. PS 0)	1.64	[1.29;2.09]	<0.0001	1.16	[0.90;1.50]	0.2062			
	(PS 2 vs. PS 0)	2.44	[1.85;3.23]		1.36	[0.97;1.91]				

to estimate the discrimination and the effect of adding QoL information to existing prognostic scores. These analyses were performed in order to investigate how QoL data, as a complement to the widely used and validated staging systems (CLIP, Okuda, and BCLC), could help clinicians plan clinical trials and select populations. Improving the scores is a delicate challenge. Due to the specificity of HCC, which generally develops with underlying cirrhosis, clinicians have to take into account the gravity of the hepatic disease, the extension of the tumor as well as the general status and finally QoL of the patient. In our study, the Spitzer QoL Index was associated with survival after adjustment on the CLIP score, making it a good candidate for the construction of a new score. Other variables of interest that were not reported in previous studies [16, 17, 22, 23] include the presence of jaundice, hepatomegaly or

Table 5 Evaluation of the independent contribution of retained baseline variables for each prognostic score

		Multivariate Cox model			Multivariate Cox model			
		Trial stratification			Trial stratification			C optimism-corrected [95% CI]
		HR	95% CI	*P* value	Model	AIC	LR	
CLIP	(CLIP 1 vs. CLIP 0)	1.19	[0.75;1.88]	<0.0001	Without covariates	4412.65	–	0.5
	(CLIP 2 vs. CLIP 0)	2.82	[1.79;4.45]		CLIP	4305.14	117.51	0.67 [0.64;0.69]
	(CLIP 3 vs. CLIP 0)	2.51	[1.59;3.98]		+Spitzer QoL Index	4270.42	154.22	0.71 [0.67;0.73]
	(CLIP 4 vs. CLIP 0)	4.22	[2.58;6.88]		+Jaundice	4288.52	136.13	0.68 [0.65;0.70]
	(CLIP 5–6 vs. CLIP 0)	4.36	[2.37;8.02]		+Hepatalgia	4296.06	128.59	0.69 [0.65;0.71]
Jaundice	(yes vs. no)	1.56	[1.21;2.02]	0.0007	+Hepatomegaly	4297.99	126.66	0.69 [0.66;0.70]
Hepatomegaly	(yes vs. No)	1.26	[1.00;1.58]	0.0486	Full model	4250.70	179.95	0.73 [0.70;0.75]
Hepatalgia	(yes vs. no)	1.37	[1.10;1.71]	0.0057	−Spitzer QoL Index	4276.98	151.67	0.71 [0.68;0.73]
Spitzer QoL Index	Continuous	0.85	[0.80;0.90]	<0.0001	−Jaundice	4259.33	169.31	0.72 [0.69;0.74]
					−Hepatalgia	4256.02	172.63	0.72 [0.69;0.74]
					−Hepatomegaly	4252.69	175.96	0.72 [0.69;0.74]
OKUDA	(Okuda II vs. Okuda I)	1.59	[1.29;1.97]	<0.0001	Without covariates	4412.65	–	0.5
	(Okuda III vs. Okuda I)	4.57	[3.03;6.88]		OKUDA	4321.09	95.56	0.64 [0.61;0.66]
Hepatomegaly	(yes vs. no)	1.47	[1.16;1.85]	0.0012	+Spitzer QoL Index	4289.83	128.82	0.69 [0.66;0.71]
Hepatalgia	(yes vs. no)	1.38	[1.10;1.71]	0.0046	+AFP	4293.86	124.79	0.68 [0.65;0.69]
Portal thrombosis	(yes vs. no)	1.42	[1.16;1.73]	0.0006	+Hepatalgia	4304.92	113.72	0.67 [0.64;0.68]
AFP (μg/l)	(≥200 vs. <200)	1.71	[1.40;2.08]	<0.0001	+Portal thrombosis	4307.34	111.30	0.67 [0.64;0.69]
Small HCC	(yes vs. no)	0.65	[0.48;0.87]	0.0039	+Small HCC	4313.86	104.79	0.65 [0.62;0.67]
Spitzer QoL Index	Continuous	0.85	[0.80;0.90]	<0.0001	+Hepatomegaly	4316.00	102.65	0.66 [0.63;0.68]
					Full model	4228.56	200.09	0.74 [0.70;0.75]
					−Spitzer QoL Index	4257.67	168.98	0.72 [0.69;0.74]
					−AFP	4254.57	172.08	0.72 [0.69;0.74]
					−Portal thrombosis	4238.04	188.61	0.73 [0.70;0.74]
					−Hepatomegaly	4237.55	189.10	0.73 [0.70;0.74]
					−Small HCC	4235.73	190.92	0.73 [0.70;0.75]
					−Hepatalgia	4234.28	192.37	0.73 [0.70;0.75]
BCLC	(BCLC B vs. BCLC A)	1.48	[0.76;2.89]	<0.0001	Without covariates	4412.65	–	0.5
	(BCLC C vs. BCLC A)	2.12	[1.13;3.97]		BCLC	4347.61	71.04	0.62 [0.59;0.63]
	(BCLC D vs. BCLC A)	5.21	[2.53;10.72]		+AFP	4317.31	103.34	0.67 [0.64;0.69]
Jaundice	(yes vs. no)	1.36	[1.03;1.78]	0.0285	+Spitzer QoL Index	4320.92	99.73	0.68 [0.65;0.70]
Hepatomegaly	(yes vs. no)	1.58	[1.26;1.99]	<0.0001	+Hepatomegaly	4332.15	88.50	0.65 [0.63;0.67]
Hepatalgia	(yes vs. no)	1.44	[1.16;1.80]	0.0011	+Hepatalgia	4333.70	86.95	0.64 [0.62;0.66]
AFP (μg/l)	(≥200 vs. <200)	1.81	[1.49;2.21]	<0.0001	+Jaundice	4339.87	80.77	0.64 [0.61;0.66]
Spitzer QoL Index	Continuous	0.87	[0.82;0.92]	<0.0001	Full model	4262.15	166.50	0.72 [0.69;0.74]
					−AFP	4295.03	131.61	0.70 [0.69;0.72]
					−Spitzer QoL Index	4280.55	146.10	0.71 [0.67;0.73]
					−Hepatomegaly	4276.48	150.17	0.71 [0.68;0.73]
					−Hepatalgia	4270.32	156.33	0.72 [0.69;0.74]
					−Jaundice	4264.73	161.92	0.72 [0.69;0.74]

All statistics were calculated based on Cox regression with stratification per trial. LR, likelihood ratio; LR estimates loss of adjustment by calculating the difference of the deviance between models with and without the variable. AIC, Akaike information criterion. A smaller AIC value or a higher LR indicates that model is more informative regarding prognosis of overall survival. C, Harrell's C-index varies from 0.5 (no discrimination) to 1 (perfect discrimination). C optimism-corrected and its 95% CI calculated using bootstrapping (100 replications)

hepatalgia. However, these variables raise concerns due to their dependence on the clinical examination. Likewise, it is interesting to observe that QoL data seem to be have more prognostic power and are more informative than these parameters, and particularly when compared with general performance status. As an example of the benefit,

the prognostic information of the BCLC [12], which includes performance status in staging systems, could also be improved by adding QoL. First these results highlighted that QoL and performance status covered different health measurements, and secondly that QoL seems to be more informative.

On the one hand, we have demonstrated that the Spitzer QoL Index could be the most interesting data to include in existing models to better predict overall survival among patients with advanced HCC. On the other hand, the prognostic classifications contain characteristics that are part of the exclusion criteria of our trials. Variations in the classification scores are therefore reduced, which leads to lower discriminative power than that in the whole group of advanced HCC patients. In such situations, new variables such as QoL are more likely to improve the prognostic ability of the classifications. However, it is well known that the results of prognostic evaluations on the same data overestimate the performance of any new prognostic score or the prognostic value of QoL. As highlighted by Altman and Royston [50] neither internal nor temporal evaluation addresses the wider issue of the generalizability of the model. The reproducibility of a prognostic model is defined as the performance of a model on a sample of similar patients not included in the development of the model. Our results thus need to be validated in another trial. We plan to perform this external validation on patients included in the randomized FFCD CHOC trial investigating long-acting octreodid treatment versus placebo in patients with advanced HCC [51]. Furthermore, this trial used multidimensional European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 QoL assessment, which makes it possible to explore which QoL dimensions would be predictive, and finally to confirm if general health is predictive of overall survival.

One of the major limits of this pooled study is that QoL was assessed using a cancer-specific global QoL tool. On the one hand, we agree that multidimensional QoL would be more informative than global QoL regarding which parameters could predict overall survival [52]. On the other hand, in a setting of advanced HCC, it would be difficult for patients to complete a 30-item questionnaire; the process would be more time consuming and there would be a higher rate of missing scores. As suggested by Lipscomb et al., in some cases, a short simple (even single-question) patient-reported evaluation of outcome is appropriate and adequate [53]. In this way, the Spitzer QoL Index could be proposed as an acceptable alternative tool to prevent missing data due to cancer progression and/or poor health status. Furthermore, even though multidimensional measures are more informative [54–57], single-item or global tools have already demonstrated their clinical values in cancer patients.

Since the investigated patients had mainly alcoholic cirrhosis and were not eligible for curative treatments, they were exclusively in a palliative setting. Even though between 60% and 75% of all patients in France are treated in this setting [58], the patients in this study formed a rather homogeneous sample that was not representative of the whole HCC population. Therefore, the conclusions are limited to this specific population and cannot be extended to less advanced patients. The effect of QoL on survival in such patients would require a separate study.

Quality of life is a well-established end point for treatment comparisons, and this study provides further reasons for measuring QoL both in cancer research and clinical practice for patients with advanced HCC. Further research is needed to identify specific baseline QoL parameters that are relevant to these patients. However, we could suggest that global QoL scores should be components of all QoL questionnaires used in phase III trials as they may be used to measure the impact of treatments on patients' well-being as well as to predict prognosis. Lipscomb et al. [8] underlined the fact that the use of QoL as an established and accepted end point in cancer required the study of the prognostic value of QoL. Studies using different QoL tools and different cancer sites are necessary to confirm the value of QoL in determining prognosis in cancer patients.

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