Received: 20 June 2017 | Accepted: 18 January 2018

DOI: 10.1111/liv.13711

ORIGINAL ARTICLE

WILEY Liver INTERNATIONAL

FACT-Hep increases the accuracy of survival prediction in HCC patients when added to ECOG Performance Status

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Funding information
This work was supported by the Swiss Foundation against Liver Cancer and the Bern Krebsliga.

Handling Editor: Morris Sherman

Abstract

Background and aim: The Eastern Cooperative Oncology Group Performance Status (ECOG PS) is a strong predictor of survival for patients with hepatocellular carcinoma (HCC), and is used with liver function and tumour burden in the Barcelona Clinic Liver Cancer (BCLC) staging system. This work assesses whether the health-related quality of life (HRQL), measured by the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire, discriminates HCC patients in terms of survival and adds prognostic information to ECOG PS.

Methods: A total of 242 patients participating in the prospective Bern HCC Cohort at the University Hospital Bern were analysed. The relationship between FACT-Hep and sociodemographic and clinical factors, including survival, were assessed. An analysis on treatment subgroups was performed using Kaplan-Meier curves and Long-Rank test. Additionally, the ability to predict overall survival was compared between the ECOG PS and FACT-Hep total and subscales using Nagelkerke pseudo-R^2.

Results: FACT-Hep subscales were significantly worse in females and in patients with limited liver function. FACT-Hep total and all subscales, except the social/family well-being subscale showed significant differences between ECOG PS groups and were significant predictors of survival. ECOG PS groups, followed by the functional well-being subscale, were the best at predicting survival. In the resection subgroup, significant differences in OS regarding to HRQL were found. When adding the functional well-being subscale to ECOG PS, the accuracy of the survival prediction was significantly increased.

Conclusion: HRQL assessed by the FACT-Hep questionnaire is a reliable prognostic predictor of survival for patients with HCC and it adds prognostic information to the ECOG PS.

KEYWORDS

liver cancer, performance status, prognosis, quality of life

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; EASL-EORTC CPG, European Association for the study of the liver-European Organisation for Research and Treatment of Cancer clinical practice guidelines; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EWB, Emotional well-being; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-Hep, Functional Assessment of Cancer Therapy-Hepatobiliary; FWB, Functional well-being; HCC, Hepatocellular carcinoma; HCS, Hepatobiliary Cancer Subscale; HR, Hazard ratio; HRQL, Health-related quality of life; OS, Overall survival; PWB, Physical well-being; SWB, Social/family well-being.

1 | INTRODUCTION

The most used staging system for hepatocellular carcinoma (HCC) is the Barcelona Clinic Liver Cancer (BCLC) staging system, which includes prognostic variables related to tumour burden (size, number, vascular invasion, extrahepatic localisation), liver function (Child-Pugh classification) and performance status (PS), defined by the Eastern Cooperative Oncology Group (ECOG) scale.[1] The aim of the BCLC staging system is to allocate treatment modalities according to staging and to estimate life expectancy.[2,3] There are five different stages—0, A, B, C and D—and they lead to either curative or palliative therapy recommendations. The BCLC staging system uses the ECOG PS to measure the patient's actual level of function and capability of self-care. ECOG PS is a single-item rating scale determined by the physician and ranges from Grade 0, fully active without symptoms, to Grade 5, dead.[4] The PS is widely used in oncology trials to assess functional capability of patients as they undergo treatment. It was shown that ECOG PS has a strong prognostic influence on survival and facilitates physician decision-making in the choice of treatment.[5]

Health-related quality of life (HRQL) research in patients with cancer has grown impressively in recent years, as patient outcomes including HRQL are a priority for cancer treatment decisions. Hepatobiliary cancers, including HCC, are associated with poor prognosis and poor survival, particularly in patients diagnosed at an advanced stage.[2] For patients with HCC who will not be cured of their disease and are undergoing palliative treatment, it is particularly important to ameliorate symptoms without compromising HRQL.

In the past few decades, major efforts were made to develop quality of life questionnaires for cancer patients.[6] Besides generic measures of quality of life that provide global and domain-specific (eg physical, emotional, social) quality of life indicators, disease-specific measures have also been developed and validated.[7] One of the most widely used instruments to assess HRQL in patients with cancer is the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire.[8] The FACT-G was adapted into a disease-specific measure for patients with HCC, which gave rise to the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire.[9] The FACT-Hep is a reliable and valid 45-item self-report questionnaire, consisting of the 27-item FACT-G and the 18-item Hepatobiliary Cancer Subscale (HCS). It assesses HRQL in patients with hepatobiliary cancer including HCC.[9-11] The FACT-Hep additionally evaluates specific issues, such as jaundice, itching and indigestion.[8,9] The FACT-Hep was evaluated to capture changes in clinical indicators that reflect disease progression and response to treatment.

Despite the existence of these HRQL questionnaires, there are limited data on HRQL in HCC patients. In general, it has been shown that HCC has a negative impact on patients' HRQL, mainly on physical, emotional and functional well-being, whereas social/family well-being seems unaffected.[6] In addition, medical variables such as disease stage, treatment, liver function and symptoms play an important role in determining HRQL.[6]

Key points

- Quality of life was prospectively assessed in 242 HCC patients participating in the prospective Bern HCC Cohort.
- Quality of life assessed by the FACT-Hep questionnaire was a significant predictor of survival.
- When adding the functional well-being subscale to the ECOG performance status, the accuracy of the survival prediction was significantly increased.
- FACT-Hep subscales were significantly worse in females and in patients with limited liver function

With respect to the association between performance status and HRQL, all the FACT-G subscales except for the social/family well-being subscale have shown differences in self-reported performance status.[9] Compared with the general population, patients diagnosed with HCC had worse HRQL, but better social and family well-being.[12] Furthermore, people diagnosed with HCC reported higher rates of sexual problems than the general population and those who had increased rates of sexual problems, also reported worse HRQL.[13] HRQL, by FACT-Hep subscales, has also been assessed to determine the impact of different treatments.[14-16]

The aim of this study was to evaluate the HRQL of patients diagnosed with HCC and to assess HRQL with respect to sociodemographic and clinical factors. In addition, this study investigates whether the FACT-Hep questionnaire discriminates patients in terms of survival and whether FACT-Hep has the ability to add information to ECOG PS with regard to survival.

2 | PATIENTS AND METHODS

We used a prospective cohort of HCC patients based at the University Hospital Bern, Switzerland. The diagnosis of HCC was established following the European Association for the study of the liver-European Organisation for Research and Treatment of Cancer clinical practice guidelines (EASL-EORTC CPG).[2] All patients aged 18 years and over were invited to participate in the study and all enrolled patients signed an informed consent. The study was approved by the local ethics committee (Kantonale Ethikkommission Bern, Bern, Switzerland). In this manuscript, we analysed the baseline questionnaires which were filled out before the therapeutic management was discussed. Follow-up visits took place every 3 months. Patients filled out the FACT-Hep questionnaires at baseline. At inclusion, 136 variables were gathered for each patient covering demographic, clinical, laboratory, radiological, treatment and HRQL data.

To assess HRQL, the FACT-Hep questionnaire was used.[9] Physical (PWB), social/family (SWB), emotional (EWB) and functional well-being (FWB) subscales from the FACT-G questionnaire and the HCS for symptom-specific HRQL were completed by patients. All items used a five-point scale ranging from "not at all" (0) to "very much" (4). The following characteristics were evaluated: energy, nausea, needs of family, pain, side effects, illness, time in bed by the PWB subscale; closeness to friends, support from family, support from friends, acceptance of the illness by their families, communication about the illness, closeness with support person, satisfaction with sex life by the SWB subscale; sadness, satisfaction with coping, loosing hope, nervousness, worry about dying, worry about condition worsening by the EWB; ability to work, fulfilment of the work, ability to enjoy life, acceptance of the illness, quality of sleep, enjoyment of things, contentment with quality of life at the moment by the FWB; and additional concerns such as diarrhoea, appetite, chills, itching by the HCS. The PWB, SWB, EWB and FWB were combined to generate the FACT-G total score. The sum of the FACT-G total and HCS scores generated the FACT-Hep total score.

FACT-Hep was scored according to the Functional Assessment of Chronic Illness Therapy manual.[17] Overall survival (OS) was defined as the time from the date of diagnosis of HCC to the time of death, last follow-up evaluation or the date of data censoring. FACT-Hep total and subscale scores were stratified by baseline characteristics, and the Kruskal-Wallis test applied. Kaplan-Meier curves and the Log-Rank test were used to assess the OS difference between low/high scores on FACT-Hep scales and subscales (mean value was used as cut-off) with a subgroup analysis on treatment groups were patient number was sufficient (resection, n = 54; TACE, n = 84). Cox proportional hazard regressions were used to estimate hazard ratio (HR) of the FACT-Hep total and subscales on OS. Nagelkerke pseudo-R2[18] was used to evaluate the predictive reliability of the FACT-Hep total and subscales on OS. All analyses were conducted using R version 3.1.1[19] and a *P* value of less than .05 was considered statistically significant.

3 | RESULTS

From 1 August 2010 to 27 November 2015, a total of 242 patients were enrolled in the study. Table 1 shows the baseline characteristics of the sample, which comprised a greater proportion of males than females, and in which the median (range) age was 63.7 (45-85) years. The main aetiologies of HCC were alcoholic steatohepatitis, non-alcoholic steatohepatitis, hepatitis C and hepatitis B. Cirrhosis occurred in 81.7% patients, whereby about two-thirds of patient were classified into Child-Pugh class A. The majority of patients was classified ECOG PS 1 or PS 0, and most were BCLC stage A or B. The most common treatments patients had received were transarterial chemoembolisation and liver resection, with only a small proportion having received radiofrequency ablation or microwave ablation.

TABLE 1 Baseline characteristics of 242 patients with hepatocellular carcinoma[a]

Variable	No. of patients[b]	%
Total	242	100
Age		
Median (range), years	63.7 (45-85)	
Sex		
Female	36	14.9
Male	206	85.1
Aetiology[c]		
ASH	104	43.7
NASH	74	31.1
HH	17	7.2
Hepatitis C	49	20.7
Hepatitis B	72	30.1
Cirrhosis		
Yes	196	81.7
No	44	18.3
Child-Pugh Score[d]		
A	131	67.2
B	56	28.7
C	8	4.1
BCLC		
0	12	5.1
A	84	35.7
B	82	34.9
C	43	18.3
D	14	6.0
ECOG PS		
0	9	38.2
1	105	44.1
2	30	12.6
3	11	4.6
4	1	0.4
Treatment		
TACE/TAE	85	35.1
Liver resection	54	22.3
Liver transplantation	25	10.3
SIRT	21	8.7
RFA/MWA	13	5.4
Sorafenib	30	12.4
Palliative	14	5.6

[a]There is missing data for Cirrhosis, Child-Pugh Score, BCLC, ECOG PS.
[b]Data are n (%) unless otherwise stated.
[c]More than 1 aetiology is possible.
[d]Child-Pugh was only calculated for cirrhotic patients.
ASH, alcoholic steatohepatitis; BCLC, Barcelona Clinic Liver Cancer; ECOG, PS, Eastern Cooperative Oncology Group Performance Status; HH, haemochromatosis; MWA, microwave ablation; NASH, non-alcoholic steatohepatitis; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolisation; TAE, transarterial embolisation.

3.1 | Baseline characteristics

Median (range) FACT-G score was 84 (36.2-108), HCS score was 60.0 (36-72) and FACT-Hep total score was 144.7 (82-179). Median (range) scores for the FACT-Hep subscales were as follows: PWB 20 (4-28), SWB 28 (0-28), EWB 18 (5-24) and FWB 19 (1-28). Table 2 shows the differences in HRQL stratified by baseline characteristics. For EWB, females showed significantly worse scores than men (P = .018), with no significant differences recorded for other FACT-Hep subscales by gender. In cirrhotic patients with Child-Pugh A, scores for PWB (P = .013), FWB (P = .017), FACT-G (P = .035), the HCS (P = .041) and FACT-Hep total score (P = .036) indicated better HRQL than those with other Child-Pugh classification. Patients consuming alcohol showed significant better PWB (P = .028) than patients who were abstinent. There were no significant differences in HRQL in patients with or without diabetes, nor in smokers and non-smokers.

3.2 | Association of HRQL with PS and OS

A comparison between median scores across different ECOG PS groups and the FACT-G, the HCS and the FACT-Hep total score showed significant differences (P < .001) among the ECOG PS groups (Figure 1). Furthermore, all the FACT-Hep subscales were significant in different ECOG PS groups (P < .001), except for the SWB subscale (P = .622) (Table 2).

Most of the FACT-Hep scores were significantly associated with OS: PWB (HR 0.907 [95% CI: 0.876-0.939] P < .001), EWB (HR 0.905 [95% CI 0.862-0.949] P < .001), FWB (HR 0.910 [95% CI 0.882-0.938] P < .001), FACT-G (HR 0.966 [95% CI 0.954-0.978] P < .001) HCS (HR 0.955 [95% CI 0.934-0.976] P < .001), FACT-Hep total (HR 0.976 [95% CI 0.967-0.985] P < .001). Only SWB was not significant (HR 1.007 [95% CI 0.968-1.047] P = .732). The PS was also significantly associated with the OS (HR: 2.215 [95% CI 1.818-2.698] P < .001). The value of the, Nagelkerke R^2 was 0.21 for PWB, 0.12 for EWB, 0.251 for FWB, 0.211 for FACT-G total score, 0.127 for HCS, 0.208 for FACT-Hep total score and 0.390 for ECOG PS. Combining the two best predictors of OS (FWB and ECOG PS), the R^2 was 0.440. Compared with the ECOG PS alone, by adding the FWB subscale, there was a 5% increase in the predicted variance. The likelihood ratio test showed a significant difference between the model including ECOG PS only and the model including ECOG PS and FWB (P = .002).

Moreover, patients were analysed in subgroups according to their treatment, surgical resection (n = 54) and TACE (n = 84). In the resected patients, the PS was not associated with the OS (P = .356), but the dichotomised FACT-Hep total and FACT-G scales (low/high) were both associated with the OS (FACT-Hep total P = .010, FACT-G P = .003, Figure 2). In the patients who underwent TACE neither the PS (P = .050) nor the FACT-Hep total and FACT-G scales (P = .675 and P = .680, respectively) were associated with the OS.

In a multivariate Cox regression model, the FWB subscale remained significant when adjusted for age (HR 0.898 [95% CI: 0.868–0.928] P < .001), for gender (HR 0.898, 95% CI: 0.868–0.928) P < .001), for ECOG PS (HR 0.936 [95% CI: 0.901-0.973] P = .001), for Child-Pugh (HR 0.909 [95% CI: 0.880-0.939] P < .001), for diabetes (HR 0.901 [95% CI: 0.872-0.931] P < .001), for alcohol consumption (HR 0.901 [95% CI: 0.872-0.932] P < .001) and for smoking (HR 0.904 [95% CI: 0.874-0.935] P < .001).

4 | DISCUSSION

These results based on a large prospective cohort show that HRQL, assessed by the FACT-Hep questionnaire, has the ability to discriminate patients with HCC in terms of survival. Quality of life is an independent predictor of survival and when combined with ECOG performance status it adds prognostic information.

In this study, consistent with Steel et al.[12] the median SWB score is remarkably high (SWB, 28 in this study; SWB, 22 in Steel et al.). In comparison to all the other FACT-Hep subscales, SWB obtains the highest median. Furthermore, the SWB subscale was not significantly associated with survival in Cox regression, unlike the other subscales. It is plausible that patients diagnosed with HCC or other type of cancer may receive more care and support from their families and friends, as a cancer diagnosis is a drastic event which may bring them together. Our findings showed that the HRQL, specifically the EWB of FACT-Hep, is significantly worse in females than in males. A similar trend was also shown in the HCS and the FACT-G. This finding may be due to the fact that women with HCC are more likely to be stigmatised since this tumour is often perceived as being associated with alcoholism and/or drug consumption. An alternative explanation may be that women have a different perception of the disease and struggle more with the diagnosis than men. HCC patients with increasing severity of liver disease based on the Child-Pugh classification showed significantly worse HRQL in the FACT-Hep, FACT-G, the HCS, and the PWB and FWB subscales in this study. This was to be expected, as increasing severity of liver disease has a strong impact on physical condition. FACT-Hep total and all subscales, except the SWB subscale, showed significant differences across ECOG PS groups, which indicates a strong relationship between HRQL and PS. Based on our findings, ECOG PS determines the degree of health status competently.

One aim of the study was to evaluate if the FACT-Hep questionnaire, as a disease-specific instrument measuring HRQL, is predictive of survival. In Cox regression analysis, patients reporting a high level of HRQL in the FACT-G, the HCS and the FACT-Hep questionnaires were found to have longer survival. Additional subscales of the FACT-Hep, including the PWB, the FWB and the EBW were also significantly associated with survival. These results are consistent with previous findings that quality of life measures in cancer patients are predictors of survival.[20,21] Patients with HCC are affected by side effects of their disease; hence, HRQL is lower as complications increase in advanced disease. Our findings demonstrate a strong relationship between HRQL and survival in patients with HCC. Three studies reported similar results. Yeo et al.[22] suggested that HRQL baseline could be applied as a new prognostic marker for survival in

TABLE 2 Kruskal-Wallis test for each component of FACT-Hep with ECOG PS, gender, Child-Pugh, alcohol consumption, diabetes and smoking

	PWB	*P*	SWB	*P*	EWB	*P*	FWB	*P*	FACT-G total	*P*	HCS	*P*	FACT-Hep total	*P*
ECOG PS		<.001		.622		<.001		<.001		<.001		<.001		<.001
PS0	152.7		115.2		137.7		147.1		145.8		148.1		147.8	
PS1	114.8		116.8		117.9		116.6		115		115.7		114.1	
PS2	66.6		130.1		82.0		81.8		76.7		75.6		74	
PS3	33.7		127.6		72.9		30.7		41.7		48.1		41.5	
PS4	1.0		148.0		33.5		15		13		15.0		11.5	
Gender		.065		.761		.018		.236		.053		.077		.051
Male	124.5		120.1		124.6		123.7		123.7		124.8		123.7	
Female	101.3		123.0		95.3		108.8		99.4		102.5		99.3	
Child Pugh[a]		.013		.260		.075		.017		.035		.041		.036
A	105.7		95.7		102.73		105.4		103.5		104.5		103.4	
B	82.0		96.7		87.8		86.0		84.05		87.5		84.6	
C	72.3		121.0		67.1		61.7		69.31		69.3		67.8	
Alcohol Consumption		.028		.144		.486		.440		.344		.062		.241
Yes	142.0		105.1		125.2		126.9		127.5		138.7		130.0	
No	114.1		119.5		116.3		117.1		115.3		115.1		114.9	
Diabetes		.752		.915		.950		.198		.550		.197		.366
Yes	115.5		117.5		116.6		109.8		112.7		109.8		110.8	
No	118.5		116.8		117.2		122.0		118.3		122.0		119.3	
Smoking		.512		.127		.827		.164		.588		.779		.659
Yes	113.8		126.3		119.6		109.0		113.6		117.0		114.4	
No	120.3		114.8		117.4		122.9		119.0		119.7		118.7	

[a]Calculated among cirrhotic patients.

ECOG, PS, Eastern Cooperative Oncology Group Performance Status; EWB, emotional well-being; FACT-G: Functional Assessment of Cancer Therapy-General; FACT-Hep, Functional Assessment of Cancer Therapy-Hepatobiliary; FWB, functional well-being; HCS, Hepatobiliary Cancer Subscale; PWB, physical well-being; SWB, social/family well-being.

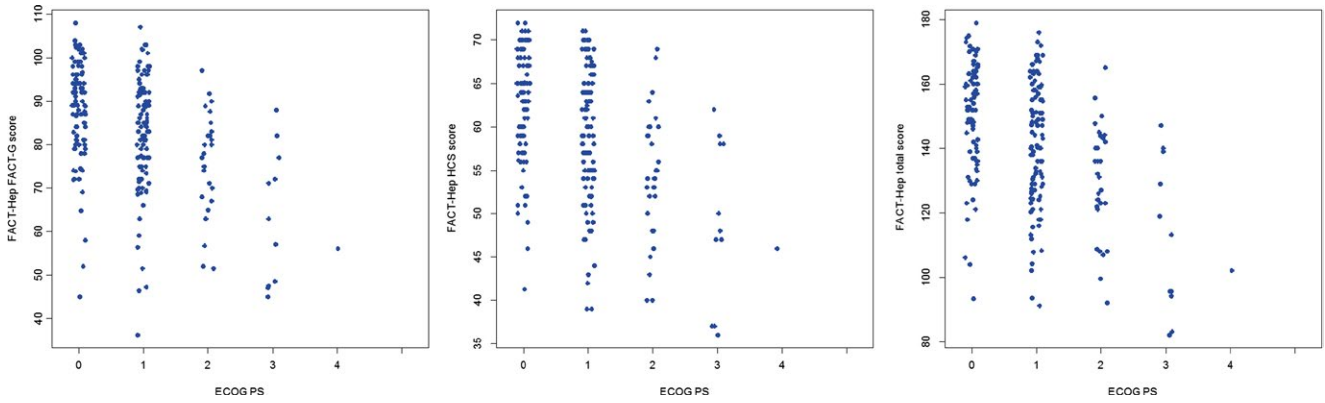

FIGURE 1 Comparison between the FACT-G, HCS and the FACT-Hep total score across different ECOG PS groups. ECOG PS, Eastern Cooperative Oncology Group Performance Status; FACT-Hep, Functional Assessment of Cancer Therapy-Hepatobiliary; FACT-G, Functional Assessment of Cancer Therapy-General; HCS, Hepatobiliary Cancer Subscale

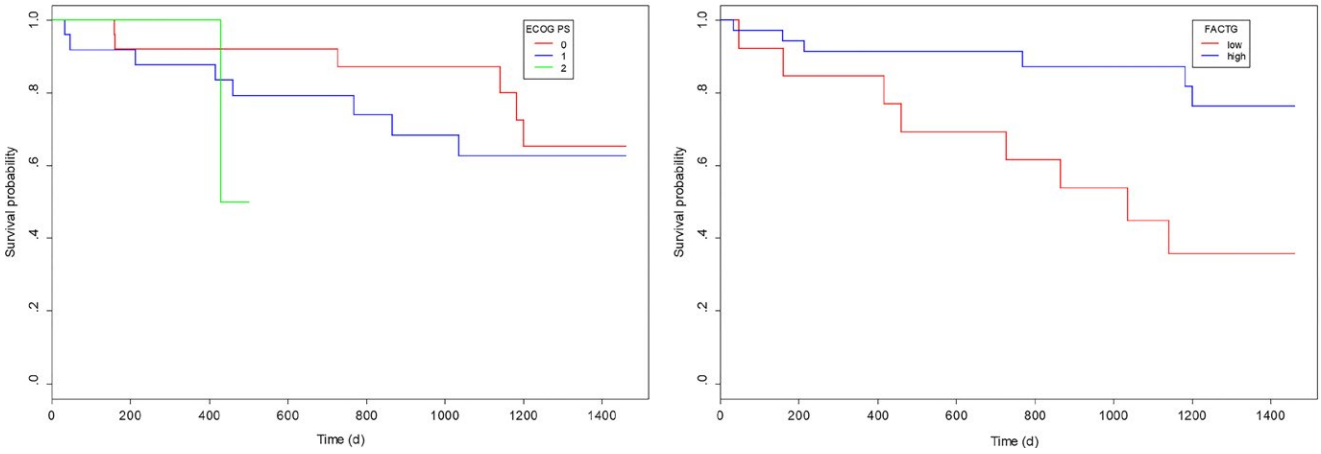

FIGURE 2 Association in the resected patients between OS and ECOG PS and OS and FACTG. OS, Overall survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FACT-G, Functional Assessment of Cancer Therapy-General

patients with unresectable HCC in a population with chronic hepatitis B (assessed by the EORTC QLQ-C30). The EORTC QLQ-C30 baseline score in physical functioning was significantly associated with survival, as well as role functioning and appetite loss. Diouf et al.[23] reported role functioning (assessed by the EORTC QLQ-C30) as the main independent prognostic factor of survival in patients with palliative HCC. Bonnetain et al.[24] also presented a positive correlation between HRQL data (rated by Spitzer QoL Index) and survival in patients with advanced HCC with mainly alcoholic aetiology. They pointed out that HRQL data may have more prognostic power than other clinical parameters and that a staging system such as the BCLC could be improved by assessing HRQL data.[24] Unlike these three studies that assessed HRQL and survival in patients with HCC, our study is not limited to a segment of patients with HCC. Comparing the different scales and subscales in their ability to predict OS in our cohort accurately, the FWB subscale was best at predicting survival ($P < .001$). It is interesting to note that FWB is the best predictor as it is the subscale that is most similar to the ECOG PS, since the PS also evaluates the functional aspect of the patient. As the FWB subscale remained statistically significant when adjusted for age, sex, Child-Pugh score, diabetes, alcohol consumption and smoking, we can conclude that this subscale is an independent predictor for survival. It even remained statistically significant when adjusted for PS, which means that FWB adds prognostic information. This confirms the hypothesis that HRQL assessed by the FACT-Hep has the ability to add prognostic information. However, as shown ECOG PS predicts 39% of the variance of the OS, which is better than FACT-Hep total and all subscales, including 25.1% with the FWB. However, adding the FWB subscale to ECOG PS resulted in a 5% increase in the predicted variance compared with ECOG PS alone. Together, they predict 44% of the variance in OS. This gives strong evidence that adding a FACT-Hep subscale is a better model to predict survival than ECOG PS alone. In contrast to the other reported studies about HRQL as a predictor of survival, our study quantifies the added information.

Additional analysis about the association of low or high HRQL (by the dichotomised FACT-Hep total and FACT-G) with OS in treatment subgroups showed a significant difference in survival for the resected patients, whereby the PS was not associated with OS. In the TACE patient subgroup, we do not have a difference. An explanation for these findings may be that resection is the most common

first-line therapy option in patients with solitary tumours and well preserved liver function, whereas patients undergoing TACE are more likely to be in a more advanced stage disease.

The results in this study indicate that PS alone predicts survival better than HRQL alone. These findings seem surprising as ECOG PS is a subjective evaluation by the treating physician, by which patients' well-being is quantified in five categories, whereas the FACT-Hep is a self-rated 45-item questionnaire about physical and mental health, and disease-specific issues. Perhaps also the reason PS is so highly predictive is that the clinician is taking into account the clinical prognostic severity and observed survival data when rating PS, whereas patients with self-reported HRQL may report their actual functional status and not a global clinical impression.

Using the two assessment tools together, as shown, could help influence prognostic information as the patient's health status would be assessed by both the physician and the patient.

This study has some limitations. The data used in this study were collected in a single centre and the results of this study may not apply to other centres. The patients enrolled in this cohort are staged according to the BCLC staging system, which uses PS as a staging parameter and could represent a potential bias. Strengths of this study are the large sample size and that the data have been acquired prospectively.

In summary, our results showed that HRQL is a reliable predictor of survival and that FACT-Hep increases the accuracy of survival prediction in HCC patients when added to ECOG PS.

CONFLICT OF INTEREST

The authors do not have any disclosures to report.

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How to cite this article: Gmür A, Kolly P, Knöpfli M, Dufour J-F. FACT-Hep increases the accuracy of survival prediction in HCC patients when added to ECOG Performance Status. *Liver Int*. 2018;00:1–7. https://doi.org/10.1111/liv.13711