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ORIGINAL ARTICLE

Prognostic association of demographic and clinical factors with the change rates of symptoms and depression among patients with hepatocellular carcinoma

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Abstract

Purpose To identify the predictive value of demographic and clinical factors for determining changes in physical and depressive symptom among hepatocellular carcinoma (HCC) patients over time.

Methods We performed a prospective cohort study of 128 patients newly diagnosed with HCC in Taiwan. Each patient had four time-point data after the follow-up. Patients' physical symptoms were evaluated with the Edmonton Symptom Assessment System (ESAS). Psychological symptoms were evaluated with the Hospital Anxiety and Depression Scale (HADS). Clinical factors and demographic characteristics were predictors of physical and psychological symptoms, as estimated by a generalized estimating equation (GEE).

Results We found that patients who had a smoking habit and Barcelona Clinic Liver Cancer (BCLC) Stage B disease underwent radiofrequency ablation therapy (RFA) or liver resection, and those who had higher alanine aminotransferase (GPT) level reported more symptoms from baseline to 1 month. Symptoms increased from baseline to 3 months in elderly patients and patients with higher GPT levels. Additionally, patients who had jobs, underwent liver resection, and had BCLC Stage C disease had increased symptoms of depression from baseline to 1 month; in particular, BCLC Stage D disease had negative long-term effects on depression scores from baseline to four-time points following therapy.

Conclusion Advanced BCLC stage and undergoing RFA or liver resection were most closely associated with worsening physical and psychological symptoms over time. Clinical professionals should pay attention to these factors that affect physical and psychological symptoms during treatment.

Keywords Hepatocellular carcinoma (HCC) · Symptom management theory (SMT) · Symptom · Depression

Introduction

Hepatocellular carcinoma (HCC) has become one of the most common cancers and is the third leading cause of cancer-related death worldwide [1, 2]. HCC is also prevalent in East Asian countries [3–5]. In Taiwan, which exhibits an increased standardized incidence rate (31.79% per 100,000 people) and standardized mortality rate (22.46% per 100,000) compared with other cancers, HCC exhibits the fourth highest incidence rate and the second highest mortality rate among ten major cancers [6].

Unfortunately, HCC is difficult to diagnose during the early stages and is usually diagnosed late in the course of the disease. Although research is producing increasingly hopeful insight into the causes of and cures for cancer, efforts to manage the side effects of the disease and its treatments have not kept pace [7]. When HCC patients receive treatment, they experience many acute and chronic physical and psychological symptoms that may impact their quality of life [8, 9]. These symptoms may further decrease patients' treatment compliance, potentially prompting them to refuse to complete the treatment [10]. These symptoms are present throughout the

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cancer trajectory and are associated with the disease itself, the cancer treatment, or comorbidities [11], and these symptoms may change and vary over time [12, 13]. However, some longitudinal studies found that several factors were associated with changes in symptoms over time, such as age, diagnosis status [10], pretreatment fatigue, and sleep disturbance [14]. Brant et al. further indicated that advanced disease and an increased number of comorbidities predicted higher fatigue at baseline, and the symptom trajectories were highly variable in patients undergoing initial treatment [11]. Nevertheless, the inferences of these studies are limited by the fact that the samples included different types of cancer and confounding comorbidities. The association of the outcome with changes of symptoms in HCC patients still requires further examination.

In addition to physical symptoms, cancer patients also suffer from psychological problems, such as depression, which is the most common form of emotional distress among patients [15, 16]. A meta-analysis indicated that the overall prevalence of depression was significantly higher among patients with cancer compared with those without cancer (54.90% vs. 17.50%) [17], and approximately 27–38% of cancer patients had subsyndromal depression [18]. Moreover, patients with persistent or recurrent depressive symptoms had a 2.04-fold increased risk of earlier death [19]. These results revealed that the depressive symptoms changed over time and the factors that affected the depressive symptoms longitudinally are worthy of exploration. Although several factors were associated with depressive symptoms, such as stage of disease, greater number of comorbidities, and type of treatment received [19–21], these studies included a diverse group of cancer patients. No studies have examined the predictors of depressive symptoms in patients with HCC over time.

However, the efforts to manage the symptoms of cancer and its treatments have not kept pace with new advances in cures for cancer [22], and symptom management has been recognized as a priority for cancer patients [23]. In addition, individuals with particular long-term trajectory patterns may suffer a disproportionate amount of negative consequences [24]. Further research is needed to identify the specific characteristics that increase the risk of self-reported physical and psychological symptoms among cancer patients.

Although most previous studies have focused on comparing symptoms with the varying effectiveness of different types of treatments [25–27], most studies employed a cross-sectional design, and symptoms were measured at a single point in time [11]. Haberman suggested that researchers define the symptom experience as a multidimensional, dynamic process of deriving meaning from subjective perceptions [28], and changes in the severity and distress associated with symptoms is a clinical reality [29]. Therefore, we employed a modified version of the Symptoms Experience Model [30] to examine the association between the antecedents and symptoms experienced in HCC patients over time. The antecedents include demographic characteristics and clinical factors. We considered both physical and psychological symptoms as the symptom experience, and this model could account for the dynamic nature of symptoms that develop over time and the interaction between antecedents and symptom experience.

The purpose of this study was to examine the change in these symptoms over time and to identify the prognostic factors affecting the changes in symptoms and depression scores over time in patients with newly diagnosed HCC. Once these specific prognostic factors are identified, clinical professionals will be able to more effectively manage these factors and symptoms in high-risk patients with different specific characteristics.

Methods

Patients

This prospective cohort study recruited 128 patients at two hospitals in Taiwan from March 2014 to September 2016. Patients who were newly diagnosed with HCC, older than 20 years old, and were able to communicate with the research staff were eligible for this study. To control confounding comorbidities, patients who had a history of mental illness or comorbidity with other cancer were excluded. The sample size of this study fulfilled the minimum number of 105, which was estimated with G*Power Version 3.1 based on the following conditions: the α level was 0.05, power was 0.85, effect size was 0.15, and a 50% rate of loss to follow-up.

When patients first visited the clinic, the clinical professionals elaborated the purpose and procedures of the study and the right of patients. After the detailed explanation, patients who agreed to participate in the study signed a consent form and completed a questionnaire that included demographic characteristics. In addition, we also collected patients' laboratory measurements, including hepatitis B virus (HBV), hepatitis C virus (HCV), liver cirrhosis, BCLC stage, alpha-fetoprotein level (AFP level), aspartate aminotransferase level (AST level, GOT level), alanine aminotransferase level (ALT level, GPT level), and treatment types. Treatment types were classified as transarterial chemoembolization (TACE), transcatheter arterial embolization (TAE), radiofrequency ablation therapy (RFA), and liver resection.

Healthcare professionals provided appropriate treatment based on the Barcelona Clinic Liver Cancer (BCLC) staging system, tumor features, and the overall functional status of patients. In general, patients with early stage disease (BCLC 0 or BCLC A) received liver resection or radiofrequency ablation therapy (RFA). Patients with intermediate-stage disease (BCLC B) underwent transarterial chemoembolization (TACE) or transcatheter arterial embolization (TAE). The

tyrosine-kinase inhibitor sorafenib was used to treat patients with advanced-stage disease (BCLC C). Patients with end-stage disease (BCLC D) were provided supportive care [31]. In Taiwan, the average length of hospital stay was approximately 5 days of TACE and TAE and approximately 10 days for liver resection. Additionally, patients who received sorafenib therapy were not hospitalized and the treatment course was approximately 2 weeks.

Data were collected at four time periods, including baseline (newly diagnosed, time 1), 1 month (time 2), 3 months (time 3), and 6 months (time4) after patients completed the treatment. The time interval between the new diagnosis and treatment was from one to 12 days (mean = 3.2) in this study. Because the nationwide health insurance covers the main cost of cancer treatment in Taiwan, most patients received the treatment within 1 week and the course of treatment was also completed in 1 week. Twenty-six patients died and 19 patients were relocated at the end of follow-up. All procedures performed in this study involving human participants were approved by the Institutional Review Board of Mackay Memorial Hospital (No: 13MMHIS231).

Assessment of symptoms

The assessment of symptoms included two dimensions. First, the physical symptoms were assessed with the Edmonton Symptom Assessment System (ESAS). Second, for the psychological dimension, we utilized the Hospital Anxiety and Depression Scale (HADS) to measure depressive symptoms.

The ESAS is a self-reporting questionnaire of symptom intensity for cancer patients that is well established in terms of its feasibility, reliability, and validity [32, 33]. The Chinese version of ESAS also had satisfied acceptable internal consistency (Cronbach $\alpha = 0.72$) and validity [34]. The ESAS also allows the researcher to add items to make the questionnaire more comprehensive; hence, we modified the Chinese version of the ESAS for the common symptoms of HCC patients in Taiwan.

The modified ESAS includes 14 symptoms HCC patients experience, such as nausea, insomnia, pain, fatigue, dyspnea, appetite, difficult defecation, restlessness, appearance, ascites, fever, jaundice, edema, and urination. The severity of each symptom is rated from 0 to 10, and the total score represents the level of distress caused by symptoms. Higher scores indicate a higher level of distress. Cronbach's α of this study was 0.86–0.93.

Depressive symptoms

Patients' depression was assessed by the depression subscale of the Hospital Anxiety and Depression Scale (HADS), which was developed by Zigmond and Snaith (1983); this scale is commonly used by clinical professionals to evaluate the levels of depression experienced by patients [35]. The Chinese version of HADS and the original scale are both reliable scales for screening for clinical depression and exhibit satisfactory reliability and validity [36, 37]. Higher scores represent increased depression scores, whereas a score of 11 or greater indicates depression [38]. In the current study, Cronbach's α was 0.76.

Statistical analysis

Descriptive statistics were used to analyze the demographic and clinical factors by the percentage, mean, and standard error (SE) among patients. The prevalence of possible case of depression was estimated by a clinical HADS cut-off score greater than 11 [38]. Based on statistical power calculations, we used a cut-off point of 60 years old to classify age into two groups. Univariate analysis was performed to examine the association between demographic, clinical factors, and physical and psychological symptoms independently. All of the demographic and clinical factors were included in the multivariate analysis. We used generalized estimating equation (GEE) models to estimate the longitudinal association between demographic and clinical factors and the changes over time in physical symptoms and depression scores over 6 months. The GEE was suitable to analyze the longitudinal data measured at different points and focused on estimating the average response overpopulation. The GEE accommodated the missing data of subjects and increased the effectiveness of the sample, especially in the longitudinal study. Robust SE and their 95% confidence intervals were also calculated by GEE models; hence, the statistical inference was not restricted to the compound symmetry. We also explored potential interactions between the two outcome variables and demographic characteristics and laboratory measurements in relation to changes over time. The significance level was 0.05, and all statistical significance was examined with a two-tailed test. SPSS Statistics Version 22.0 (IBM, Armonk, NY, USA) software was used for all analyses.

Results

Baseline patient characteristics

In this study, the mean age of the patients was 60.41 years (SE = 1.07) and the majority were male ($n = 89$, 69.5%), employed ($n = 59$, 46.1%), and consumed alcohol ($n = 75$, 58.6%). Forty-nine had a habit of smoking (38.3%) and 45 (35.2%) had liver cirrhosis. Fifty-two patients were infected with HBV (40.6%) and 41 had HCV infection (32%). The distribution of patients' BCLC stages were as follows: 16 (12.50%) had BCLC Stage 0 disease; 45 (35.20%) had BCLC Stage A disease; 27 (21.10%) had BCLC Stage B disease; 34 (26.60%) had BCLC Stage C disease; and 6

(4.70%) had BCLC Stage D disease. Thirty-three (26%) patients received TAE/TACE treatment, 31 (24%) received RFA treatment, and 32 (25%) underwent liver resection.

The mean scores of symptoms during follow-up were 20.05 (SE = 1.63), 19.68 (SE = 1.96), 19.86 (SE = 2.76), and 16.17 (SE = 2.26) at the four time points. The mean scores of depressive symptoms were 13.41 (SE = 0.44), 13.39 (SE = 0.47), 12.70 (SE = 0.54), and 12.67 (SE = 0.54) at four time points, respectively. No significant differences in symptoms ($F = 0.60$, $p = 0.62$) and depressive symptoms ($F = 0.66$, $p = 0.58$) were noted among the four time points. Fifty-nine percent of the patients had a clinically relevant score of 11 or higher on the HADS at baseline. The results of other laboratory measurements at baseline were as follows: AFP (mean = 29,656.90, SE = 25,723.74), GOT (mean = 78.45, SE = 6.93), and GPT (mean = 59.70, SE = 4.98).

Associations among outcome variables, demographic characteristics, and clinical factors in the univariate regression

Table 1 displays the associations between total symptom and depression symptom score and demographic and clinical factors. The findings showed that patients with a habit of smoking and those infected with HCV exhibited higher symptom scores compared with those who did not smoke and those without HCV infection, respectively. Those who had worse BCLC stages were more likely to report fewer symptoms. AFP level, GOT level, and GPT level were associated with slight increases in the patients' symptom scores. Patients who underwent liver resection reported lower symptoms scores than those who received TAE/TACE. However, patients who underwent RFA experienced more symptoms compared with those who received TAE/TACE.

The results regarding depressive symptom indicated that patients who were older, consumed alcohol, had an early BCLC stage, and had elevated GOT and GPT levels exhibited slightly increased depression scores. Patients who underwent liver resection had higher depression scores compared with those who received RFA, and those who received RFA exhibited a slightly increased depression score compared with those who received TAE/TACE.

Predictors of symptoms in the multivariable regression

Table 2 shows that patients' symptoms were improved from baseline to 1 month, 3 months, and 6 months following treatment. Patients with BCLC Stage B or C had more symptoms than did those with BCLC Stage 0. Patients who underwent liver resection had more symptoms than those who received RFA, and those who received RFA had fewer symptoms than those who received TAE/TACE.

The results of the interaction analysis indicated that patients with a habit of smoking, with BCLC Stage B compared with those with BCLC Stage 0, who received RFA or liver resection compared with TAE/TACE, and who had higher GPT levels reported more symptoms from baseline to 1 month. Older patients reported increased symptoms from baseline to 3 months and 6 months. GPT level had a slightly negative effect on symptoms from baseline to 3 months.

Predictors of depression scores in the multivariable regression

The association between the predictors and depression scores is presented in Table 3. The results of the main effect were similar to symptoms. The patients' depression scores improved from baseline to 1 month, 3 months, and 6 months. Patients with BCLC Stage C or D exhibited improved depression scores compared with those with BCLC Stage 0 disease. Patients who underwent liver resection had improved depression scores compared with those who received RFA, and those who received RFA had 3.65-fold-reduced depression scores compared with those who underwent TAE/TACE. AFP levels also had a very slight effect on depression scores.

The results of interaction terms indicated that patients with jobs had increased depression scores from baseline to 1 month and 3 months. Patients with BCLC Stage C or D had higher depression scores from baseline to 1 month compared with those with BCLC Stage 0 disease. The negative effects were continued from baseline to 3 months and 6 months among patients with BCLC Stage D disease compared to those with BCLC Stage 0 disease. We also found that patients who underwent liver resection vs. TAE/TACE reported higher depression scores from baseline to 1 month. AFP level also slightly increased depression scores during the follow-up.

Discussion

In this prospective cohort study, we found that both total and depressive symptoms exhibited significant improvements in mean change rates compared with baseline during the follow-up. In addition, our results also supported the modified version of the Symptom Experience Model, and our study revealed that age, smoking status, BCLC Stage, types of treatment, AFP levels, and GPT levels predicted changes in symptoms and depression scores over time.

Our study revealed a significant interaction between time and age; elderly patients reported more symptoms from baseline to 3 and 6 months. This finding might be attributed to the fact that elderly patients exhibited increased rates of morbidity and mortality compared with younger patients [39]; hence, they reported more symptoms during treatment. Our results were consistent with prior research that indicated significantly

Table 1 Risk factors for symptoms and depression at baseline

	ESAS				HADS-depression			
	B	SE	95% CI	*p* value	*B*	SE	95% CI	*p* value
Demographic characteristics								
Age (ref: < 60)	1.28	1.62	− 1.91–4.46	0.43	0.95	0.36	0.25–1.66	0.01*
Gender (ref: female)	0.96	1.76	− 2.50–4.23	0.59	− 0.49	0.39	− 1.26–0.29	0.22
Job status (ref: no)	− 3.35	1.68	− 6.6–− 0.04	0.05	0.18	0.37	− 0.54–0.91	0.62
Smoking status (ref: no)	5.48	1.64	2.56–8.71	< 0.001***	0.14	0.37	− 0.60–0.87	0.72
Alcohol intake (ref: no)	1.64	1.66	− 1.62–4.90	0.32	− 1.15	0.37	− 1.86–− 0.43	0.002**
Clinical characteristics								
Hepatitis B (ref: no)	− 2.49	1.65	− 5.73–0.74	0.13	0.26	0.37	− 0.47–0.98	0.49
Hepatitis C (ref: no)	3.85	1.73	0.45–7.25	0.03*	0.37	0.39	− 0.40–1.13	0.35
Liver cirrhosis (ref: no)	− 0.49	1.73	− 3.89–2.90	0.78	− 0.76	0.38	0.02–1.51	0.05
BCLC stage								
0 vs. D	28.76	3.89	21.11–36.40	< 0.001***	2.15	0.96	0.26–4.03	0.03*
A vs. D	27.06	3.43	20.32–33.80	< 0.001***	2.89	0.87	1.18–4.60	0.001**
B vs. D	20.14	3.57	13.13–27.16	< 0.001***	1.52	0.90	− 0.26–3.29	0.09
C vs. D	9.86	3.50	2.99–16.74	0.005**	0.83	0.89	− 0.91–2.57	0.35
AFP level	< 0.001	< 0.001	Not detected	0.02*	< 0.001	< 0.001	Not detected	0.84
GOT level	0.75	0.01	0.06–0.09	< 0.001***	0.006	0.002	0.001–0.01	0.02*
GPT level	0.06	0.01	0.03–0.08	< 0.001***	0.009	0.003	0.002–0.02	0.002**
Treatment								
Liver resection vs. TAE/TACE	− 5.35	1.81	− 8.92–− 1.78	0.003**	0.80	0.48	− 0.13–1.74	0.09
Liver resection vs. RFA	2.93	1.85	− 0.70–6.57	0.11	1.95	0.48	1.00–2.90	< 0.001***
RFA vs. TAE/TACE	8.28	1.88	4.59–11.97	< 0.001***	1.15	0.48	0.21–2.09	0.02*

B, coefficient estimated by univariable regression; *SE*, standard error; *CI*, confidence interval; *ref.*, reference category in the analysis

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

more complications after treatment in elderly patients [40, 41]. Moreover, smoking had similar effects on symptoms, and a prospective cohort study reported a negative impact of smoking on the overall survival of HCC patients [42]. The negative effects of smoking might also increase the symptoms of HCC patients.

We also found that BCLC stage and GPT levels were risk factors for symptoms. BCLC stage and GPT levels are indicators for evaluating the severity of HCC; a worse BCLC stage or higher GPT levels represent a more advanced prognosis. Hansen et al. demonstrated that patients with advanced HCC reported more symptoms including pain and lack of energy [13]. Thus, we considered that the changes in the BCLC stage and GPT levels were important factors for symptom management during treatment.

Different treatments were accompanied by different symptoms, and the symptoms changed over time. The results of the interaction terms showed that patients who underwent liver resection ($B = 13.16$, $p = 0.01$) or RFA ($B = 11.39$, $p = 0.02$) suffered from more symptoms than those who received TAE/TACE from baseline to 1 month. This finding might be attributed to the fact that liver resection requires a more prolonged recovery [39] and had a higher rate of postoperative complications [40] because treatment increases symptoms in patients.

Another important finding of the present study is that patients who underwent liver resection had higher depression scores than those who received TAE/TACE from baseline to 3 months. As mentioned above, patients who underwent liver resection required a more prolonged recovery and had more symptoms and postoperative complications that might also affect their function. One longitudinal study also revealed that the trends of change in patients' functioning significantly predicted a patient depression status 1 year later [42]. Due to the side effects of treatment, the depression scores increased over time. On the other hand, this increase might also be attributed to the fact that patients who underwent liver resection (mean = 13.53; SE = 0.20) had higher depression scores than those who received TAE/TACE (mean = 12.73; SE = 0.35) at baseline; however, no significant difference was noted between the two groups ($t = -1.59$, $p = 0.11$).

Table 2 Predictors of patients' symptoms as estimated by generalized estimating equations (GEE)

	B	SE	95% CI		Wald χ^2	*p* value
Intercept	17.50	8.89	0.07	34.93	3.87	0.05
Time						
2 vs. 1	− 23.73	7.36	− 38.15	− 9.32	10.41	< 0.001***
3 vs. 1	− 45.56	13.05	− 71.14	− 19.99	12.20	< 0.001***
4 vs. 1	− 43.96	12.51	− 68.49	− 19.44	12.34	< 0.001***
Age (ref: < 60)	− 3.35	3.69	− 10.58	3.88	0.82	0.36
Gender (ref: female)	− 7.24	4.56	− 16.18	1.70	2.52	0.11
Job status (ref: no)	3.40	4.61	− 5.62	12.43	0.55	0.46
Smoking status (ref: no)	− 0.71	3.76	− 8.09	6.67	0.04	0.85
Alcohol intake (ref: no)	− 2.57	3.31	− 9.07	3.92	0.60	0.44
Hepatitis B (ref: no)	3.15	4.49	− 5.65	11.95	0.49	0.48
Hepatitis C (ref: no)	3.20	4.73	− 6.07	12.48	0.46	0.50
Liver cirrhosis (ref: no)	− 0.47	3.53	− 7.38	6.44	0.02	0.89
BCLC stage						
A vs. 0	6.75	3.68	− 0.46	13.96	3.37	0.07
B vs. 0	11.00	4.71	1.76	20.23	5.45	0.02*
C vs. 0	19.50	5.54	8.64	30.36	12.38	< 0.001***
D vs. 0	14.76	7.42	0.22	29.30	3.96	0.05
Treatment						
Liver resection vs. TAE/TACE	− 5.60	4.28	− 13.98	2.78	1.72	0.19
Liver resection vs. RFA	9.08	4.36	0.53	17.63	4.33	0.04*
RFA vs. TAE/TACE	− 14.68	4.89	− 24.26	− 5.10	9.02	0.003**
AFP level	–	–	–	–	5.28	0.02*
GOT level	0.07	0.03	0.01	0.13	4.80	0.03*
GPT level	− 0.07	0.06	− 0.18	0.04	1.59	0.21
Interaction[a]						
Time 3* age (ref: < 60)	15.13	4.84	5.64	24.62	9.76	0.002**
Time 4* age (ref: < 60)	15.01	4.74	5.71	24.31	10.01	0.002**
Time 2* smoking status (ref: no)	10.30	3.85	2.75	17.85	7.15	0.01*
Time 2* BCLC stage (D)	17.17	7.39	2.68	31.66	5.39	0.02*
Time 2* RFA[b]	13.16	5.23	2.91	23.40	6.34	0.01*
Time 2* liver resection[b]	11.39	5.07	1.46	21.32	5.05	0.02*
Time 2* GPT level	0.13	0.06	0.02	0.25	5.46	0.02*
Time 3* GPT level	0.17	0.05	0.07	0.27	10.31	0.001**

B, coefficient estimated by GEE; SE, standard error; CI, confidence interval

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

[a] The interaction term was only present the significant difference

[b] TAE/TACE was the reference group

A similar situation was noted for job status. Patients with jobs (mean = 12.62; SE = 0.27) exhibited higher depression scores than those without jobs (mean = 12.44; SE = 0.24), but a significant difference was noted between the two groups ($t = 0.50$, $p < 0.001$). The significant difference in job status might not affect the inferences of this study because we included the job status in the GEE model. Hence, any confounding effect due to job status might be minimized, but this notion needs further confirmation in additional studies. In addition, the side effects of treatment may affect performance at work. One large cross-sectional survey was conducted involving 63,949 cancer patients and revealed that patients with a greater number of side effects missed more work days [43]. The missed work days might lead to salary cuts and

Table 3 Predictors for depression scores as estimated by generalized estimating equations (GEE)

	B	SE	95% CI		Wald χ^2	*p* value
Intercept	19.57	2.90	13.89	25.26	45.55	< 0.001***
Time						
2 vs. 1	− 10.69	3.18	− 16.92	− 4.46	11.32	0.001**
3 vs. 1	− 15.08	4.01	− 22.93	− 7.23	14.18	< 0.001***
4 vs. 1	− 12.87	4.21	− 21.13	− 4.61	9.33	0.002**
Age (ref: <60)	0.57	1.13	− 1.65	2.79	0.25	0.61
Gender (ref: female)	− 0.85	1.44	− 3.67	1.97	0.35	0.55
Job status (ref: no)	− 2.34	1.33	− 4.95	0.28	3.07	0.08
Smoking status (ref: no)	0.32	1.21	− 2.05	2.69	0.07	0.79
Alcohol intake (ref: no)	− 0.39	1.12	− 2.58	1.80	0.12	0.73
Hepatitis B (ref: no)	0.24	1.27	− 2.25	2.74	0.04	0.85
Hepatitis C (ref: no)	− 1.05	1.44	− 3.87	1.76	0.54	0.46
Liver cirrhosis (ref: no)	0.47	1.02	− 1.54	2.48	0.21	0.65
BCLC stage						
A vs. 0	− 0.93	1.51	− 3.90	2.03	0.38	0.54
B vs. 0	− 2.07	1.92	− 5.82	1.69	1.16	0.28
C vs. 0	− 4.57	1.80	− 8.09	− 1.05	6.46	0.01*
D vs. 0	− 10.01	2.17	− 14.26	− 5.76	21.28	< 0.001***
Treatment						
Liver resection vs. TAE/TACE	− 3.34	1.33	− 5.95	− 0.73	6.31	0.01*
Liver resection vs. RFA	0.31	1.43	− 2.50	3.11	0.05	0.95
RFA vs. TAE/TACE	− 3.65	1.44	− 6.48	− 0.82	6.38	0.01*
AFP level	< 0.001	< 0.001	< 0.001	< 0.001	40.92	< 0.001***
GOT level	< 0.001	0.01	− 0.02	0.02	0.15	0.70
GPT level	− 0.02	0.01	− 0.05	0.01	2.18	0.14
Interaction[a]						
Time 2* job status (ref: no)	4.52	1.50	1.59	7.46	9.10	0.003**
Time 3* job status (ref: no)	4.67	1.80	1.14	8.20	6.72	0.01*
Time 2* BCLC stage (C)	10.90	2.48	6.05	15.76	19.37	< 0.001***
Time 2* BCLC stage (D)	13.17	2.96	7.36	18.98	19.73	< 0.001***
Time 3* BCLC stage (D)	10.57	3.06	4.57	16.57	11.94	0.001**
Time 4* BCLC stage (D)	9.74	2.77	4.32	15.16	12.39	< 0.001***
Time 2* liver resection[b]	3.49	1.74	0.09	6.90	4.04	0.04*
Time 2* AFP level	< 0.001	< 0.001	< 0.001	< 0.001	44.55	< 0.001***
Time 3* AFP level	< 0.001	< 0.001	< 0.001	< 0.001	32.98	< 0.001***
Time 4* AFP level	< 0.001	< 0.001	< 0.001	< 0.001	30.49	< 0.001***

B, coefficient estimated by GEE; SE, standard error; CI, confidence interval

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

[a] The interaction term was only present the significant difference

[b] TAE/TACE was the reference group

increase the risk of patients being laid off. Additionally, the majority of patients were male ($n = 89$, 69.5%) in this study, and the main source of family income generally depends on males in Taiwan. Thus, patients with jobs had increased depression scores compared with those without jobs.

We found that patients with advanced BCLC stage disease, such as Stage C and Stage D, exhibited increased depressive symptoms from baseline to 1 month compared with BCLC Stage 0 disease. Moreover, patients with BCLC Stage D disease reported higher depression scores from baseline to

3 months and 6 months. These results were consistent with previous studies, in which patients with advanced stages of disease had a higher risk of depression than those with earlier stage disease [18]. When patients are diagnosed with HCC, it may impact their life. We further analyzed depression scores among BCLC stages at baseline. Although the mean depression scores were smaller in BCLC Stage A compared with BCLC Stage 0 disease (11.44 vs. 12.19, $p = 0.80$), the mean of depression scores was increased in advanced BCLC stages (Stage B = 12.81, Stage C = 13.50, Stage D = 14.33) compared with Stage 0, but there was no significant difference in a posteriori comparisons. The more advanced the stage of disease is, the more patients worry about the efficacy of treatment and the survival rate. We suggest that clinical professionals should pay attention to changes in the BCLC stage and provide emotional consultation for patients and their families to decrease depression scores.

AFP levels had very slight positive effects on depression scores despite the strong significant difference value ($p < 0.001$) during the follow-up. AFP was used to evaluate prognosis and monitor recurrence following treatment [9]. Changes in AFP levels might suggest the progression of the pathological grade, which was also measured by BCLC stage in this study. Patients with increased AFP levels had higher depression scores when the pathological grade worsened.

However, some limitations should be noted. First, a recall bias might be present because data were reported by patients. However, patients rated their symptoms based on the subjective experiences of symptoms, and assessments of symptoms and the depression scores have improved over time. This might not affect the inference of this study. Second, we used a prospective design. Therefore, many patients were lost to follow-up or died. We did not have sufficient patients to perform further analysis to draw detailed conclusions; consequently, larger samples are needed in future studies. Third, HCC progresses quickly, and patients developed advanced stage disease in a short time, which might have increased their symptoms during treatment. This feature might also restrict the interpretation of results. Despite these limitations, we believe that the present study still revealed useful information for patients and clinical staff to fill the knowledge gap by identifying factors associated with both physical and psychological symptoms.

In conclusion, the present study supported the modified version of the Symptoms Experience Model; several specific factors from the demographic and clinical characteristics predicted the changes in symptoms and the depression scores over time. According to the Symptoms Experience Model, modifiable antecedents, such as smoking status, GPT level, AFP level, and job status, had a variety of negative effects on symptom perception. If a patient's perception of a symptom was more negative they were more likely to develop negative consequences, such as quality of life and disease progression, and survival is also getting worse. Symptom management strategies should be tailored for these modifiable antecedents to improve treatment. For instance, healthcare professionals might provide a class for smoking cessation for patients with smoking habits and offer psychological consultation resources to patients with jobs to reduce their depressive intensity. Clinical characteristics, such as GPT level or AFP level, might also be controlled by medicine. For patients with early stage disease, these practices might both decrease the development of symptoms and improve their treatment effectiveness. However, patients with advanced-stage disease mainly received palliative or supportive care. Thus, symptom reduction is very relevant. These patients might experience reduced symptom distress and better relief by controlling these modifiable antecedents. It is important for clinicians involved in cancer care to be aware of patients with specific factors to decrease the intensity of symptoms, and these findings may be beneficial to design comprehensive symptom management strategies to improve the wellbeing of patients with HCC in different stages.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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