



# A Study of Symptom Experience of Hepatocellular Carcinoma Patients After Hepatic Arterial Infusion Chemotherapy Surgery

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**Abstract:** Background: Hepatocellular carcinoma is the 2nd leading cause of cancer death among Chinese residents. Patients with cancer simultaneously experience multiple symptoms. Most of the current studies on patients with advanced hepatocellular carcinoma focus on the treatment effect, or focus on a single symptom, with less attention to the management of symptom clusters in patients. Objectives: The aim of this research is to explore the symptom experience of hepatocellular carcinoma patients after hepatic arterial infusion chemotherapy surgery and the Relationship between each symptom experience and total number of patient symptoms. Methods: A symptom Assessment Questionnaire for Patients undergoing Hepatic Arterial Infusion Chemotherapy (HAIC) was administered to a sample of 278 patients with hepatocellular carcinoma at advanced stages. Data were analyzed using descriptive statistics, Pearson correlation, and regression analyses. Results: The most striking result to emerge from the data is that the most severe symptoms in patients after HAIC surgery were Poor sleep and Decreased appetite. And presence of psychological suffering, pain, gastrointestinal discomfort, and bad mood may cause patients to develop more symptoms. Conclusions: Patients with hepatoma after HAIC surgery concurrently experienced multiple symptoms of discomfort. We should pay more attention to the symptomatic experience of these patients. A further study with more focus on the management of the most common and comorbid multiple symptoms to reduce symptoms and improve quality of life in patients with hepatocellular carcinoma is therefore suggested.

**Keywords:** Hepatic Arterial Infusion Chemotherapy, Hepatocellular Carcinoma, Symptom Experience

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## 1. Introduction

Hepatocellular carcinoma is the 2nd leading cause of cancer death among Chinese residents [1]. The prognosis of patients with hepatocellular carcinoma is poor, with a median survival time of only 20.8 months [2]. About 25%-70% of HCC patients in China are diagnosed at advanced stages, with only six months of survival under natural conditions [3, 8, 13]. For advanced hepatocellular carcinoma patients with non-metastatic hepatocellular carcinoma with macrovascular infiltration, hepatic arterial infusion chemotherapy (HAIC) is the main choice for their treatment [6]. In recent years, a large number of clinical research trials have shown that hepatic arterial infusion chemotherapy (HAIC) can significantly

improve the prognosis of patients with advanced hepatocellular carcinoma, prolong the survival period, and even achieve tumor downstaging and obtain the opportunity of radical surgery [4, 5]. However, most of the current studies on patients with advanced hepatocellular carcinoma focus on the treatment effect, or focus on a single symptom, with less attention to the management of symptom clusters in patients. Symptom clusters are defined as the simultaneous appearance of two or more related symptoms that form a stable cluster and are relatively independent of other symptom clusters [11].

As early as 2001, Dodd et al [10] suggested that symptom clusters may have common underlying mechanisms that adversely and 2 synergistically affect patients. Available studies have shown that patients with advanced hepatocellular

carcinoma after HAIC often have multiple symptoms, which are particularly pronounced during perfusion chemotherapy, mainly including abdominal pain, fatigue, fever, vomiting, and diarrhea [5, 7]. Patients with stage III hepatocellular carcinoma may experience about 8.89 symptoms simultaneously [9]. The superposition of various uncomfortable symptoms will increase the pain of patients and greatly affect their body function and survival quality [14]. Patients with advanced hepatocellular carcinoma undergoing HAIC-FOLFOX regimen need to receive sequential treatment every 3-4 weeks [5, 12]. Whether the core symptom clusters of patients after HAIC change with their treatment cycles is clinically important for the prognosis and subsequent treatment of patients. Therefore, this study intends to explore the core symptom clusters and their stability or changing trends in patients with advanced hepatocellular carcinoma after HAIC and to discuss the impact of symptom clusters on patients' prognosis.

## 2. Methods

### 2.1. Study Population and Settings

This was a descriptive correlation study, that included 278 HCC patients who underwent HAIC at Sun Yat-sen University Cancer Center (Guangzhou, China) between October 2021 and December 2022. The inclusion criteria were as follows: 1) Diagnosed with primary liver cancer in the pathology report and meet the indications of hepatic artery perfusion chemotherapy; 2) Age  $\geq 18$  years old; 3) With elementary school education or above; 4) Knowing their own cancer diagnosis; 5) Agreeing to take part in this study, and able to cooperate with the completion of the questionnaire. Exclusion criteria: 1) history of mental illness; 2) tumor recurrence or distant metastasis; 3) primary hepatocellular carcinoma undergoing radiotherapy at the same time; 4) history of malignant tumors other than primary hepatocellular carcinoma; 5) serious complications such as severe systemic infection, severe anemia, and malignant fluid. The study was approved by the Ethics Committee of Sun Yat-sen University Cancer Center, and the protocol was in accordance with the ethical standards outlined in the Helsinki Declaration.

### 2.2. Instruments

#### 2.2.1. Demographic and Medical Characteristics

Medical data were obtained from the patients' medical records. The patients independently completed a demographic questionnaire to collect information on Sex, age, education, occupational status, marital status, and whether it was the first hepatic artery perfusion chemotherapy.

#### 2.2.2. Symptom Assessment Questionnaire for Patients Undergoing Hepatic Arterial Infusion Chemotherapy (HAIC)

Since no symptom assessment scale has been developed and revised for patients with advanced hepatocellular carcinoma after hepatic artery perfusion chemotherapy, this

study designed the Symptom Assessment Questionnaire for Patients with Advanced Hepatocellular Carcinoma after Hepatic Artery Perfusion Chemotherapy based on consultation with relevant nursing experts and administrators with reference to various literatures and related scales. The questionnaire consisted of 10 core symptom severity items (ie, Adverse emotions, the feeling of stiffness, numbness, sweating; Gastrointestinal discomfort; Irritability; aches and pains; Tiredness; Suffering; Difficulty with prolonged lower limb bracing; Poor sleep; Decreased appetite) And the factors of Anxiety (including Gastrointestinal reactions; Poor sleep; Pain; Postural bracing; Difficulty with toileting; Therapeutic effect) The options score were 0~4, "The Cronbach's alpha coefficient of the comfort level questionnaire was 0.781, which was considered to be a good agreement between the items. Five experts from the School of Nursing of Sun Yat-sen University, the Department of Interventional Medicine and the Department of Hepatobiliary Surgery of the Affiliated Cancer Prevention and Control Center of Sun Yat-sen University were invited to screen the entries and test the content validity of the questionnaires, which was 0.870, and one-on-one interviews were conducted to find out about the smoothness of the questionnaire's phrases, its comprehensibility, the degree of difficulty in filling out the questionnaires, and the time it took to complete the questionnaires. The results showed that the patients took about 5 minutes to complete the questionnaire, and all reflected that the semantic expression of the comfort care scale was clear and easy to understand.

### 2.3. Procedures

The questionnaire method was used in this study. Referring to Gorsuch's [3] method to estimate the sample size, which is 5-10 times the number of entries of the independent variable, the number of questionnaire entries used in this study is 25 entries, the maximum sample size of 250 was selected for this study, and a total of 287 were required at 15% missing value. A total of 287 questionnaires were distributed in this study, out of which 278 questionnaires were valid, with a valid recovery rate of 97.54%. The questionnaires were explained to those who met the inclusion criteria and followed the principle of voluntariness, and after obtaining consent, the questionnaires were distributed and self-completed anonymously. Uniform instructions were used to explain the method of filling out the questionnaires and the precautions to be taken to the study participants, and they were collected on the spot by the researcher.

## 3. Statistical Analyses

All data were statistically analyzed using SPSS 26.0. Depending on the nature of the information, frequency, percentage (categorical information), and mean and standard deviation (measurement information) were used for statistical description. Pearson correlation coefficients were calculated to analyze the relationships among symptoms. Linear regression analysis was used to analyze the relationship of symptoms with total symptoms.

## 4. Results

### 4.1. Demographic and Medical Characteristics of the Study Population

Table 1 shows the demographic and medical characteristics of the study population. The mean (SD) age was 52.5 years, and 245 patients (88.13%) were male. 28.78% of patients were First time to do the HAIC surgery.

**Tables 1.** Demographics and Medical Characteristics of the Study Population (N=278).

Variable	N	(%)
Sex		
Male	245	88.13
Female	33	11.87
Marital status		
Married	264	94.96
Divorced	8	2.88
Widowed	2	0.72
Unmarried	4	1.44
Educational attainment		
Elementary and below	45	16.19
Junior High School	113	40.65
High School/Middle School	73	26.26
College	43	15.47
Undergraduate and above	4	1.44
Medical insurance		
New rural medical insurance	44	15.83
Urban Medical Insurance	204	73.38
Self-funded	7	2.52
Public Fee	27	9.71
First time to do the HAIC		
Yes	80	28.78
No	198	71.22

### 4.2. Symptom Severity and d Interference Factors of Anxiety in HC Patients After HAIC

From this data, we can see that Table 2 resulted in the highest value of Symptom Severity was Decreased appetite

(2.66±1.15), secondly is Poor sleep (2.47±1.11); And thirdly is Difficulty with prolonged lower limb braking (1.87±0.98). The factor that caused the most anxiety in patients was the Therapeutic effect (1.88±1.13).

**Table 2.** Symptom Severity and Factors of Anxiety in HCC Patients after HAIC (N=278).

Symptom Item	Mean	SD
Symptom severity		
Adverse emotions	0.96	0.900
The feeling of stiffness, numbness, sweating	1.19	0.954
Gastrointestinal discomfort	1.33	1.011
Irritability	1.33	0.949
aches and pains	1.44	0.920
Tiredness	1.54	1.049
Suffering	1.71	1.103
Difficulty with prolonged lower limb braking	1.87	0.987
Poor sleep	2.47	1.107
Decreased appetite	2.66	1.144
Factors of Anxiety		
Gastrointestinal reactions	1.53	1.029
Poor sleep	1.59	1.094
Pain	1.66	1.024
Postural braking	1.65	0.978
Difficulty with toileting	1.61	1.088
Therapeutic effect	1.88	1.128

### 4.3. Relationships Between Symptoms Severity and Total Symptoms

Total symptoms were significantly correlated with all

symptom's severity, except for Decreased appetite, and Poor sleep. It is apparent from Table 3 that Poor sleep was irrelevant to Gastrointestinal; Tiredness; Bad mood and Suffering.

**Table 3.** Relationships between Symptoms Severity and Total Symptoms (N=278).

	Decreased appetite	Prolonged braking difficulties	Pain	Stiffness / numbness / sweating	Irritability	Gastrointestinal discomfort
Decreased appetite	1	0.053	0.204 <sup>a</sup>	0.263 <sup>a</sup>	0.282 <sup>a</sup>	0.212 <sup>a</sup>
Prolonged braking difficulties	0.053	1	0.339 <sup>a</sup>	0.199 <sup>a</sup>	0.359 <sup>a</sup>	0.174 <sup>a</sup>
Pain	0.204 <sup>a</sup>	0.339 <sup>a</sup>	1	0.448 <sup>a</sup>	0.305 <sup>a</sup>	0.162 <sup>a</sup>
Stiffness / numbness / sweating	0.263 <sup>a</sup>	0.199 <sup>a</sup>	0.448 <sup>a</sup>	1	0.395 <sup>a</sup>	0.221 <sup>a</sup>
Irritability	0.282 <sup>a</sup>	0.359 <sup>a</sup>	0.305 <sup>a</sup>	0.395 <sup>a</sup>	1	0.407 <sup>a</sup>
Gastrointestinal discomfort	0.212 <sup>a</sup>	0.174 <sup>a</sup>	0.162 <sup>a</sup>	0.221 <sup>a</sup>	0.407 <sup>a</sup>	1
Poor sleep	0.256 <sup>a</sup>	0.184 <sup>a</sup>	0.147 <sup>b</sup>	0.124 <sup>b</sup>	0.175 <sup>a</sup>	0.054
Tiredness	0.244 <sup>a</sup>	0.307 <sup>a</sup>	0.229 <sup>a</sup>	0.259 <sup>a</sup>	0.423 <sup>a</sup>	0.274 <sup>a</sup>
Bad mood	0.190 <sup>a</sup>	0.262 <sup>a</sup>	0.296 <sup>a</sup>	0.257 <sup>a</sup>	0.463 <sup>a</sup>	0.320 <sup>a</sup>
Suffering	0.152 <sup>b</sup>	0.326 <sup>a</sup>	0.339 <sup>a</sup>	0.171 <sup>a</sup>	0.363 <sup>a</sup>	0.214 <sup>a</sup>
Total Symptoms	0.352 <sup>a</sup>	0.310 <sup>a</sup>	0.497 <sup>a</sup>	0.460 <sup>a</sup>	0.576 <sup>a</sup>	0.463 <sup>a</sup>

**Table 3.** Continued.

	Poor sleep	Tiredness	Bad mood	Suffering	Total Symptoms
Decreased appetite	0.256 <sup>a</sup>	0.244 <sup>a</sup>	0.190 <sup>a</sup>	0.152 <sup>b</sup>	0.352 <sup>a</sup>
Prolonged braking difficulties	0.184 <sup>a</sup>	0.307 <sup>a</sup>	0.262 <sup>a</sup>	0.326 <sup>a</sup>	0.310 <sup>a</sup>
Pain	0.147 <sup>b</sup>	0.229 <sup>a</sup>	0.296 <sup>a</sup>	0.339 <sup>a</sup>	0.497 <sup>a</sup>
Stiffness/numbness/ sweating	0.124 <sup>b</sup>	0.259 <sup>a</sup>	0.257 <sup>a</sup>	0.171 <sup>a</sup>	0.460 <sup>a</sup>
Irritability	0.175 <sup>a</sup>	0.423 <sup>a</sup>	0.463 <sup>a</sup>	0.363 <sup>a</sup>	0.576 <sup>a</sup>
Gastrointestinal discomfort	0.054	0.274 <sup>a</sup>	0.320 <sup>a</sup>	0.214 <sup>a</sup>	0.463 <sup>a</sup>
Poor sleep	1	0.041 <sup>b</sup>	0.081	0.101	0.151 <sup>b</sup>
Tiredness	0.041	1	0.317 <sup>a</sup>	0.223 <sup>a</sup>	0.467 <sup>a</sup>
Bad mood	0.081	0.317 <sup>a</sup>	1	0.323 <sup>a</sup>	0.524 <sup>a</sup>
Suffering	0.101	0.223 <sup>a</sup>	0.323 <sup>a</sup>	1	0.485 <sup>a</sup>
Total Symptoms	0.151 <sup>b</sup>	0.467 <sup>a</sup>	0.524 <sup>a</sup>	0.485 <sup>a</sup>	1

<sup>a</sup>  $P < 0.01$ .<sup>b</sup>  $P < 0.05$ .

#### 4.4. Multiple Linear Regression Analysis of Total Symptoms

Table 4 presents the estimated logistic regression coefficients. In this study, multiple logistic regression modeling shows that suffering, pain, gastrointestinal discomfort, and bad mood played the most significant role in the regression models.

**Table 4.** Multiple Linear Regression Analysis of Total Symptoms (N=278).

<b>Multiple R=0.787, <math>P &lt; 0.001</math></b>				
<b>Covariates</b>	<b>Regression coefficients (B)</b>	<b>P</b>	<b>OR (95% confidence interval)</b>	
constant	4.874	0.000	4.371	5.378
Decreased appetite	0.091	0.030	0.014	0.290
Difficulty with prolonged limb braking	-0.039	0.380	-0.241	0.092
Pain	0.195	0.000	0.218	0.591
Stiffness, numbness, sweating	0.132	0.004	0.087	0.441
Irritability	0.149	0.003	0.101	0.500
Gastrointestinal discomfort	0.183	0.000	0.187	0.501
Poor sleep	0.011	0.775	-0.116	0.155
Tiredness	0.162	0.000	0.138	0.450
Bad mood	0.178	0.000	0.192	0.564
Suffering	0.207	0.000	0.211	0.505

## 5. Discussion

Overall, this study had 2 major findings: (1) The most severe symptoms in patients after HAIC surgery were Poor sleep and Decreased appetite. (2) It was determined that the presence of suffering, pain, gastrointestinal discomfort, and bad mood may cause patients to develop more symptoms. These findings may inform the overall assessment and management of symptoms in patients with hepatocellular carcinoma.

The results of this study showed that most patients with hepatocellular carcinoma after HAIC surgery experienced 8.37 symptoms, which is higher than the total number of coexisting symptoms in most liver cancer patients in Taiwan [16]. A systematic review of 18 studies showed that the occurrence of multiple symptoms is associated with decreased functional status and quality of life [18]. Golan-Vered Y, et al. have shown that patients with multiple symptoms are more likely to develop chemotherapy-induced neuropathic pain (CINP) [17]. Considering the negative outcomes associated with a wide range of symptoms, clinicians should emphasize a

comprehensive assessment of patient symptoms, especially in hepatocellular carcinoma patients after HAIC surgery.

According to our results, the most severe symptoms of the patients were loss of appetite and sleep disturbances, but these were not the most important factors causing anxiety about the disease. The patients were most concerned about the effectiveness of treatment, pain, and prolonged limb bracing. The above factors may further contribute to the patients' bad mood and cause an increase in symptoms over the same period. Besides, the severity of symptoms may be related to the size of the tumor, the dose, and the number of chemotherapeutic agents infused. Therefore, early steps should be taken to improve the patient's appetite loss and sleep disturbance. However, there are fewer studies on decreased appetite and sleep disorders in patients with hepatocellular carcinoma, and pharmacologic symptomatic management remains the only treatment available. Further studies are needed to address the potential role of non-drug therapies in this population [19].

Furthermore, the results showed a weak correlation between the symptoms, and the total number of symptoms is proportional to the individual symptoms, except for sleep disturbances and prolonged limb bracing difficulties. The highest regression coefficients were for psychological aspects of suffering (0.207), pain (0.195), and gastrointestinal discomfort (0.183). It may be that these three factors are also the focus and key to controlling for the coexistence of various symptoms (i.e., total number of symptoms). A Systematic Review indicates that psychological burden is high in patients with hepatobiliary cancers as reflected in high levels of depressiveness and anxiety as well as reduced quality of life [20]. Some studies also showed that Patients do not usually report pain spontaneously, but pain is important to their quality of life [21, 22]. Taken together, our findings provide insights for further research into the management of the most common and comorbid multiple symptoms to reduce symptoms and improve quality of life in patients with hepatocellular carcinoma.

Of note, the present study exhibits certain limitations. Initially, This study was limited to one medical institution and did not result in a multicenter cross-sectional survey study, and the results of the study are only applicable to patients with advanced hepatocellular carcinoma after HAIC at the local institution. Secondly, the data in this study appear to be heavily skewed in favor of male patients (88%), possibly related to the restricted study sample. A large number of patients with sufficient details are required in further study.

## 6. Conclusion

The most severe symptoms in patients after HAIC surgery were Poor sleep and Decreased appetite. And presence of psychological suffering, pain, gastrointestinal discomfort, and bad mood may cause patients to develop more symptoms. A further study with more focus on the management of the most common and comorbid multiple symptoms to reduce symptoms and improve quality of life in patients with hepatocellular carcinoma is therefore suggested.

## Conflicts of Interest

The authors declare no conflicts of interest.

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