

# Qualitative Study on Nutrition and Immune-Mediated Adverse Events in Patients with Hepatocellular Carcinoma Immunotherapy in Hainan Province

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*Abstract:* Objective To gain an in-depth understanding of the nutritional and immune adverse event perceptions and needs of immunotherapy patients with hepatocellular carcinomain Hainan province, with the aim of providing a basis for developing a model for thefull management of adverse event symptoms and nutrition in immunotherapy patients with hepatocellular carcinoma. Methods Using the phenomenological research method in qualitative research, 13 immunotherapy patients with hepatocellular carcinoma were interviewed in depth in asemi-structured manner, and the interview data were analyzed by the Colaizzi's 7-stepmethod on phenomenological data with the Nvivo10 software. Result Four themes were summarized: multiple factors to undernutrition; adverse event of immune; ignorance the correlation of immune adverse event and nurtrition; the way to acquiring nutrition and immune adverse event of immunotherapy patients with hepatocellular carcinoma, we should pay attention to the nutritional needs and the treatment of adverse immune events in physiological, social, psychological and environmental asperc, to achieve a multi-form educational intervention mode with self-management and establish a feasible high-quality, efficient and sustainable whole-course management mode. *Keywords:* Hepatocellular Carcinoma; Immunotherapy; Nutrition; Immune-Mediated Adverse Events; Qualitative Study

#### Introduction

In China, liver cancer is mostly secondary to chronic viral cirrhosis and alcoholic liver disease, which can cause serious impairment of liver function and impair protein synthesis and degradation, directly affecting the metabolism of nutrients in the body and leading to malnutrition in patients, who are often accompanied by gastrointestinal symptoms such as nausea, vomiting and loss of appetite, resulting in weight loss and wasting, further aggravating malnutrition in patients. Immunotherapy is currently an effective method of palliative and translational treatment <sup>[11]</sup>. Studies have shown that albumin and prognostic nutritional indices decreased significantly in patients in the immunotherapy disease progression group, suggesting that immunotherapy can alter the nutritional and metabolic status of patients with advanced hepatocellular carcinoma and that nutritional indices are significantly correlated with prognosis, therefore, attention should be paid to the nutritional and metabolic status of patients with immunotherapy <sup>[2-3]</sup>. The long-term benefits of immunotherapy in patients with hepatocellular carcinoma are accompanied by the risk of malnutrition and the occurrence of immune-related adverse events. In a Meta-analysis, the common immune-related adverse events in 425 patients were rash 47 (11%), hypothyroidism 35 (8.2%), hepatitis 24 (5.6%), hyperthyroidism 21 (4.9%), adrenal insulin deficiency 17 (4%), pneumonia 15 (3.5%) and colitis 11 (2.6%) <sup>[4]</sup>, while severe immune adverse reactions require different nutritional and symptom management depending on the degree of gastrointestinal symptoms and liver and renal function of the patient, in addition to hormonal

therapy and adjustment of the dose of immune agent drugs.

As there is still a lack of research on immune adverse events and nutritional support for immunotherapy patients with hepatocellular carcinoma in China and abroad, and the new challenge of immunotherapy is when to initiate nutritional support, what nutritional agents to choose and how to develop nutritional regimens to mitigate immune responses, and there is a lack of research on the knowledge and needs of immune adverse events and nutritional-related factors among immunotherapy patients with hepatocellular carcinoma. Therefore, this paper uses a qualitative study to understand the immune adverse events and nutritional knowledge and beliefs of immunotherapy patients in Hainan Province, with a view to providing a reference for the development of a model for the management of nutrition and immune adverse events in immunotherapy patients with liver cancer.

## 1. Subjects and methods

## 1.1 Study subjects

A purposive sampling method was used to select inpatients from a tertiary care hospital in Hainan Province from April to June 2022 as interview subjects. Inclusion criteria: (1) age  $\geq 18$  years old; (2) liver cancer patients receiving immunotherapy; (3) literacy level primary school or above; (4) clarity of their condition; (5) informed consent. Exclusion criteria: (i) severe confusion, confusion, cognitive impairment; (ii) inability to communicate verbally. The sample was determined on the basis of "saturation" and "adequacy" of the data. A total of 13 patients were interviewed, coded P1-P13, aged 48-74 years, with a mean age of  $61.07\pm7.68$  years; see Table 1 for details.

| Number | Gender | Age | Education level                   | Home location | Monthly income (RMB) | How medical expenses are paid    |
|--------|--------|-----|-----------------------------------|---------------|----------------------|----------------------------------|
| P1     | Men    | 55  | Junior/Junior High<br>School      | City          | ≥5000                | Public funding/medical insurance |
| P2     | Men    | 64  | Bachelor's degree<br>and above    | City          | ≥5000                | Public funding/medical insurance |
| Р3     | Female | 68  | Bachelor's degree<br>and above    | City          | ≥5000                | Public funding/medical insurance |
| P4     | Men    | 60  | Bachelor's degree<br>and above    | City          | ≥5000                | Public funding/medical insurance |
| Р5     | Female | 62  | Junior/Junior High<br>School      | City          | 1000-3000            | Public funding/medical insurance |
| P6     | Men    | 68  | Specialties                       | County        | 1000-3000            | Public funding/medical insurance |
| P7     | Female | 74  | Junior/Junior High<br>School      | City          | 1000-3000            | Public funding/medical insurance |
| P8     | Female | 64  | High School /<br>Secondary School | City          | 3000-5000            | Self-financed                    |
| Р9     | Men    | 68  | High School /<br>Secondary School | Rural         | <1000                | Rural cooperative medical care   |
| P10    | Female | 48  | Junior/Junior High<br>School      | County        | 1000-3000            | Public funding/medical insurance |
| P11    | Female | 50  | Junior/Junior High<br>School      | Rural         | 1000-3000            | Rural cooperative medical care   |
| P12    | Men    | 58  | Specialties                       | City          | 3000-5000            | Public funding/medical insurance |
| P13    | Men    | 55  | High School /<br>Secondary School | County        | 3000-5000            | Public funding/medical insurance |

Table 1 General information of the interviewed patients (n=13)

# **1.2 Methodology**

## 1.2.1 Study design

A semi-structured interview was used to collect data, using the phenomenological research method in qualitative research as the methodological basis. An interview outline was drawn up before the interview, focusing on the perception of immune adverse events and nutrition-related factors in immune patients with hepatocellular carcinoma, and two patients were pre-interviewed to revise the interview outline, which was finalised to include: ① What kind of adverse effects do you currently know about immunotherapy? ②What do you think are the causes of nutritional deficiencies? ③What do you think is the relationship between immune adverse events and nutrition? ④What would you do if you encountered nutritional problems? ⑤What would you do in the event of an immune adverse event? ⑥ What kind of help would you like to receive from medical staff regarding adverse immune events and nutrition?

#### **1.2.2 Method of data collection**

Through one-to-one interviews, the study participants were informed of the purpose, method and content before the interview, and the need for field notes and recordings was explained; they undertook to sign the informed consent form with code instead of name and confidentiality of information; the three researchers underwent rigorous training before the interview and established good cooperation to ensure a reasonable division of labour in listening, questioning and recording; the researchers had good interviewing skills to The location was the meeting room of each department, in a relaxed, quiet and comfortable environment. The interviews were conducted in a relaxed, quiet and comfortable environment, avoiding the busy hours of the departments and were conducted between 16:00 and 17:00 daily.

#### **1.2.3 Data analysis and quality control**

After the interviews were completed, the audio recordings were transcribed verbatim in a timely manner and the non-verbal behaviour of the interviewees and the basic personal information they provided were recorded. Each interviewee's transcript was sequenced in order from P1-P13 and a separate file was created. The analysis of the data was carried out throughout the data collection and the two were inseparable at the same time. During the analysis of the interview material, Colaizzi's 7-step method for analysing phenomenological material was used, and the material was imported and managed with the help of NVivo 10.0 software. During the analysis of the material, the researcher repeatedly listened to and read the original transcripts of the conversations to identify the commonalities that were the subject of this study.

## 2. Results

## 2.1 Theme 1: Factors associated with undernutrition are multiple

Most patients perceived malnutrition as a result of physical discomfort caused by the disease itself and reduced eating, or as a result of worsening chronic illnesses such as high blood glucose, hypertension and lipids due to fear of not eating properly. p1: "Mainly liver and gallbladder disease causing fear of eating more, poor appetite after immunotherapy, and slightly reduced appetite during the last fever. " P6: "Because of diabetes, I don't know how to control my diet, my wife will only cook me good food according to my preference. p8: "Diabetes, afraid to eat anything, once I eat, I get high." P10: "High blood pressure and blood lipids, and high blood sugar. Taking medicines to lower blood pressure, blood lipids and blood sugar, I can't eat for meals. You can only drink porridge, and when you drink porridge, your blood sugar is high again." P11: "I don't dare to eat when my blood pressure is high." P12: "Individuals do not absorb well." P13: "Abdominal pain doesn't want to eat."

Psychological aspects Patients also perceived negative emotions such as anxiety and resistance due to the tumour as a cause of malnutrition. p5: "The condition is stressful and I don't want to eat because I don't feel well." P10: "Don't like to eat, don't want to eat."

Environmental aspects Different generations, geographical areas and changes in the eating environment can have an impact on malnutrition. p2: "I am from Guizhou and the food in or around the canteen is not good. Your canteen is light, but there is a lot of soy sauce and there is no way to choose too much in terms of food variety, which does not suit my appetite, and I don't want to eat even more when the weather is sultry." P5: "I don't want to eat in the canteen." P9: "People of our era experienced hunger and hardship in the 1960s, when there was not enough to eat and malnutrition. Now times are better and there is a big change from the old life, yet we can't eat because of illness. People in the countryside don't have as much knowledge, they don't eat scientifically, they eat whatever they want according to their appetite, and they can't do with a light diet."

Social support As a result of social policies, a large proportion of patients are now cared for by only children or chaperones. p5: "The children are busy with work and the chaperones they hire do not take good care of them." P10: "The food the child cooks is not to their liking."

## 2.2 Theme 2: Immune adverse events and nutritional correlates not

#### attended

Nutrition is important for health P9: "It is important to supplement nutrition when people are old and have high blood lipids that block the blood vessels in the brain and cause paralysis in one limb." P10: "Apart from the disease itself, it is the effect of immunotherapy drugs. If you have bad nutrition, you will be in poor health."

Belief that malnutrition is not related to adverse immunotherapy events P2: "Not knowing what the adverse immune reactions are, let alone how to tell, if there are adverse immune events and malnutrition, it is the medication that is causing them." P7: "Malnutrition is caused by the disease itself and has nothing to do with immunotherapy." P11: "I don't know what immunotherapy adverse events are and I don't care about nutrition, we Hainan people are different from you, we locals think that if you are sick you can't eat hairy food, hairy food is seafood, fish, beef and mutton, etc., just have some thin porridge."

## 2.3 Theme 3: Inconsistent approaches to proactive access to knowledge

#### about immune adverse events and nutrition

Correct way of acquiring knowledge about immunotherapy adverse events and nutrition Some patients with high literacy level would acquire knowledge about immunotherapy adverse events and nutrition through books, newspapers, etc. P1: "We read the newspapers Health News and Hainan Medical News by ourselves." P3: "We often read books dedicated to nutrition, the most interesting ones are newspapers: there are Life Times, Hainan Daily, Haikou Daily, Hainan Special Zone Newspaper, Happy Elderly, Happy Elderly, etc., all about how to see a doctor and what to eat. Read the nutritional knowledge yourself and don't be deceived by the outside health care products and some advertisements that cheat the elderly. Immunotherapy adverse events on the red spots that grow on the body, at first I don't know thought it was some skin disease, looking for dermatology said it was capillary hyperplasia.

Prefer a more visual and imaginative way of acquiring knowledge Most prefer a more visual and imaginative way of acquiring knowledge through mobile phones such as Baidu, TV and videos. p2: "Check mobile phones." P7: "Will look up which foods are suitable for liver cancer patients' diet online." P8: "Directly Baidu, including nutrition and condition, and then ask the doctor what can and cannot be eaten." P6: "What I like most is watching TV." P13: "TV, videos, the more direct kind of understanding."

Acquiring relevant knowledge through non-professional channels Some patients did not take an active approach or the pathway came from non-professional sources such as information networks and advertisements which may lead to biased knowledge. p5: "Advertisements, health products, taking nutrients, nutritional powders and so on every day." P12: "Haven't bothered to find out. Relying on common sense, have tried to look up information from my phone but didn't do it and felt

that the knowledge online was not always suitable for me." P9: "People in rural areas don't have that much knowledge and don't eat scientifically." P11: "Just eat less, don't eat greasy, just eat simple, used to eat everything, now they are afraid to eat."

## 2.4 Theme 4: Desire for timely, professional, quantitative and continuing

#### guidance

Trust in medical staff Patients were mostly willing to accept and trust interventions from medical people regarding the amount and structure of their diet during their stay in hospital. p1: "I did not have surgery because I was old. Doctors and nurses would advise to eat small meals and easy to digest foods and hopefully advise what you can and cannot eat." P9: "I definitely listened to the doctor during my stay in hospital, I quit smoking when the doctor told me to do so. Eat whatever the doctor says, eat a diet low in fat and light, no chicken, duck, pork skin or offal. Red meat: less beef, lamb and pork, chicken, duck and goose is more white meat." P12: "There were told to eat a light diet and not to eat greasy, spicy or stimulating foods, but not so stereotypically precise as to how much, and if there was a basis for a nutritional plan developed after the experiment, would definitely follow their instructions."

Not receiving long-term guidance A minority of patients felt that the disease was a long-term process and did not need dietary guidance. P8: "What is there to guide on diet, even if you get guidance in the hospital, you still have to do it yourself after discharge, the nurses in your old home can come to your home, Hainan does not, you still have to come to the hospital to adjust your medication and infusion."

Health education can improve patient satisfaction There is high satisfaction with various forms of health education in the unit. P4: "We came here to listen to the leaders' lectures at least 2 times, after we got up in the afternoon, this time is more free for everyone to go over and listen. The leaders give us lectures on what to pay attention to and what nutritious food to eat for oncology patients, and also what to pay attention to for hepatobiliary disease. I thought this was very good, and I could also ask any questions I wanted to ask. You can sit and chat with the director about the disease, about nutrition, and you can explain and answer questions freely. If there is a recipe for the week, what is the best thing to eat for breakfast and dinner. Nowadays the patients are somewhat literate, even if they are not, the children know and will explain to the patients what to eat and what not to eat."

Simple content of in-hospital preaching The workload of medical staff, little time for preaching, generalised content, lack of attention and policies prevented patients from receiving timely, accurate, professional and quantitative nutritional guidance. P2: "The doctor thinks nutrition is okay, so he talks less about it." P5: "We all look it up online and then we can ask the doctor. The doctors and nurses are busy flying, so we will go by our knowledge and hopefully make nutrition charts that tell us what to eat and how much to eat." P6: "The doctor will tell to eat some fish and beef. Eat better in the morning, drink milk and eat bread, eat rice at lunchtime, eat more vegetables, no sweets or porridge, and control blood sugar." P7: "The doctor would also tell us about diet and recovery, that we had to eat meat, and that it was all nutrition if we could eat it anyway so that the protein could keep up." P11: "Just eat less, no greasy food, just simple food, I used to eat it all, but now I don't dare to eat it." P13: "I hope to spread knowledge of what an immune adverse event is, preferably with a diagram we can read and understand, how to go about self-care and then tell us the amount and structure of food we need to eat."

#### 3. Discussion

## 3.1 Multidimensional focus on immune adverse events and

## nutrition-related factors in immunotherapy patients with liver cancer in

#### **Hainan Province**

The average level of dietary knowledge and attitudes among Chinese adults is low and correlates with urban-rural differences, literacy, age and work status <sup>[5]</sup>. In recent years, many guidelines for nutritional support of oncology patients have been issued at home and abroad, giving recommendations on nutritional screening, nutritional interventions and immune nutrients, etc. The European Society for Clinical Nutrition and Metabolism (ESPEN) published a guideline on cancer Nutrition guidelines for patients state that psychosocial support, nutritional screening, increased calorie intake, increased protein intake and enhanced immune nutrition for oncology patients may improve their overall survival and reduce complications. Early identification of immune-related adverse events and corresponding management decisions need to be actively explored to achieve a state of immune homeostasis in the body [7], whereas in this study, patients were not sufficiently concerned about immune adverse events and malnutrition, and similarly did not focus on immunotherapy adverse events and nutritional correlates, and the study yielded nutritional correlates including physical, psychological, environmental and social support. This suggests that clinical staff should pay attention to the nutritional status of patients, care for their eating experience, correct unhealthy eating behaviours, assess patients as a whole in terms of their physiological, psychological, environmental and social support domains, and instruct patients on the prevention and management of adverse immune therapy events, in addition to educating them on the nutritional aspects of adverse immune therapy events and improving interventions. Monitor changes in patient knowledge, behaviour and attitudes to improve adverse event symptoms and nutritional status and improve quality of life.

Physiologically: With the gradual spread of immunotherapy for hepatocellular carcinoma, nutritional management is important for active support and symptomatic treatment of the immune phase, while nutritional support for drug non-response is beginning to receive attention: ① Diarrhoea is one of the most common manifestations of irAE, especially after anti-CTLA-4 monotherapy, and some patients may also be combined with other GI symptoms such as abdominal pain, blood in stool, vomiting and even intestinal perforation. In addition to hormonal therapy and dose adjustment of ICI medication, nutritional management needs to be tailored to the degree of gastrointestinal symptoms. (ii) Immune-related hepatitis is also one of the common immune adverse events. If abnormal liver function occurs, patients are advised to follow a light diet and monitor liver function and bilirubin indicators. (iii) Endocrine system disorders (e.g. changes in thyroid function, pituitary inflammation, type 1 diabetes) require appropriate dietary modification according to the altered nutritional metabolism caused by endocrine hormone disorders. ④ Cardiotoxic reactions, for patients who develop cardiotoxic reactions such as heart failure, arrhythmias and myocarditis, patients need to be finely monitored and fluid intake managed according to their cardiac function and fluid in/out balance management requirements. Patient-reported outcomes [8-9] have been shown to better reflect patient experience and perceptions and facilitate improved reporting and treatment of adverse events. The psychometric characteristics of the tool, the intended purpose of the study, and the impact characteristics of the intervention should be weighed <sup>[10]</sup>, and a tool containing patient history combined with nutritional status should be used to assess current needs for immunotherapy patients with hepatocellular carcinoma and those who have experienced adverse events for nutrients, such as protein, energy, vitamins, minerals, etc., to develop inpatient recipes for matters

Psychologically: we take the initiative to provide psychological counselling, understand the needs, disease burden and concerns of patients, provide health education, especially on diet, and help patients to change their loss of appetite due to the disease, so as to avoid their psychological care being taken lightly and affecting the outcome of the disease; environmentally: Hainan Province is the only island in China with a tropical marine monsoon climate, where islanders are exposed to high temperature, high humidity, strong ultraviolet light and high thyroid secretion all year round. The islanders are always in a state of high temperature, high humidity, strong ultraviolet rays and thyroid secretion, with high labour intensity and energy consumption. Providing an inpatient environment with appropriate temperature and humidity for immunotherapy patients with liver cancer improves the inpatient experience, while the backward level of knowledge related to immunotherapy and nutrition among some local Hainan residents, coupled with the limitations of the hospital meal preparation system, affects the way patients eat and their experience. Therefore, there is a need to expedite the establishment of hospital meal allocation centres and a la carte meal service systems that meet the realities of Hainan Province, making every effort to offer a variety

of types of cuisine and provide food choices with good organoleptic properties to meet the needs of patients with different dietary habits and promote their dietary health and development. At the same time, under the guidance of the medical staff, patients with non-Hainanese dietary habits are encouraged to allow their families to prepare daily meals according to their dietary preferences, improve their nutritional levels and give immune nutrition when necessary<sup>[11]</sup>.

Social support: Combine nutrition, psychology, public health, health promotion and other multidisciplinary collaboration to set up a nutrition support and symptom management group for liver cancer patients, providing them with professional, individualised guidance on nutrition knowledge, immune adverse event self-care and emergency management to improve their early warning of adverse events and malnutrition. Establish effective family and social support systems using the environment, peer support, community, health care institutions, social groups, government and media campaigns.

## 3.2 A multiform educational intervention model targeting self-management

Patients in this study were proactive in acquiring knowledge about adverse immune events and nutrition, but some patients lacked professionalism and accuracy in the way they acquired knowledge. Patients were eager to receive professional and quantitative guidance. Therefore, health workers can organise multi-modal health education, such as lectures on relevant knowledge, watching health education video clips, distributing health education booklets, using interactive online information, "317 nursing"<sup>[11]</sup> and telephone follow-up monitoring. The content of the education was repeated to emphasise the importance in order to improve patient compliance, focusing on the skills training of health care workers while strengthening the ability of patients and carers to care for themselves. Given that healthcare workers' instruction has a direct impact on patient compliance, healthcare workers should take the initiative to carry out education on immunological adverse events and nutrition and incorporate this into their routine work. Teaching should be intuitive, vivid, visual and easy to understand, and should continue throughout the hospital stay rather than being a formality. Evidence-based, structured treatment and education models for patient self-management can be used to improve patients' knowledge, attitudes and behaviours <sup>[12-13]</sup> and to adopt the right approaches, methods and methods for addressing health problems in the context of adverse immunotherapy events and nutrition.

## 3.3 Establishing a model for full symptom and nutritional management

Patients undergoing immunotherapy for liver cancer are also at risk of malnutrition, immunotoxic reactions and concomitant symptoms such as nausea, vomiting and abdominal pain, which severely affect their quality of life. Most patients in this study mentioned that they did not know how to eat due to co-morbidities such as hypertension, hyperglycaemia and hyperlipidaemia, and were afraid to eat more, which could aggravate their risk of malnutrition. At the same time, hospitals lack uniform standards in the management of symptoms and nutrition of immunotherapy patients with liver cancer. The establishment of a health management model involving hospitals, patients, families and communities should be accelerated, information technology should be introduced, self-management health electronic files should be established using big data, and refined service modules for immune-related adverse events and nutritional interventions for immunotherapy patients with liver cancer should be developed with the help of information platforms to form self-management and The information platform will be used to develop a module for the refinement of immune-related adverse events and nutritional interventions for immunotherapy patients with liver cancer.

Therefore, based on the three-level diagnosis of hepatocellular carcinoma malnutrition<sup>[15]</sup> and patient-reported outcomes, a full nutrition and symptom management programme for immunotherapy patients with hepatocellular carcinoma was constructed, with comprehensive nutrition knowledge education and symptom intervention guidance implemented in the four segments of screening and assessment, diagnosis, support and monitoring and follow-up, based on the multi-team collaboration of doctors, dieticians and pharmacists, and with reference to the five-step treatment protocol for malnutrition<sup>[16]</sup> and the China Clinical Society of Oncology (CSCO) Guidelines for the Management of Toxicity Associated with Immune Checkpoint Inhibitors 2021 <sup>[17]</sup>, especially for patients with adverse immune reactions, consult with oncologists and

dietitians to form a specialist immunotherapy care and nutrition support plan, observe quantitative outcomes such as physical examination, laboratory data and ancillary tests, and also combine patient-reported outcomes to understand patients' quality of life and symptoms, etc The qualitative results of the main complaints, prevention-oriented, optimised prevention and control strategies, promotion, disease prevention and control management system, with the goal of effectively controlling health risk factors, thus improving the nutritional status of patients with mid- to late-stage immunotherapy, early detection of adverse symptoms, improving patients' clinical outcomes, reducing medical costs, improving the quality of care, and promoting effective clinical practice of immunotherapy for liver cancer.

## 4. Summary

Improving the quality of life of liver cancer patients has now become one of the three major endpoint goals (survival, treatment toxicity, and healthy quality of life) for evaluating cancer outcomes. This study used a qualitative study to understand immune adverse events and nutritional perceptions and needs of liver cancer immunotherapy patients through in-depth interviews. It is suggested that the management in hospitals should not only focus on symptom management of immune adverse events in immunotherapy patients with liver cancer, but also focus on the nutritional needs of this group of patients in the region in a multidimensional way, including physical, social, psychological, environmental and health promotion, with a multiform educational intervention model aimed at achieving self-management to advance oncology rehabilitation <sup>[18]</sup> and the construction and management practices of nutrition clinics and wards in order to improve the level of medical services in the FCT.

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