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Knowledge, attitude, and practice of nutritional support and immune-related adverse events among patients undergoing immunotherapy for liver cancer: a cross-sectional study

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Knowledge, attitude, and practice of nutritional support and immune-related adverse events among patients undergoing immunotherapy for liver cancer: a cross-sectional study

Running title: KAP of irAEs and nutrition and lifestyle

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ABSTRACT

Objectives: No study specifically examined the knowledge, attitude, and practice (KAP) toward immune-related adverse events (irAEs) and nutritional support in patients with liver cancer (LC), nor have they explored their lifestyle. This study aimed to address that issue.

Design: This cross-sectional study

Setting: This cross-sectional study was conducted at Haikou People's Hospital from December 2022 to April 2023.

Participants: patients undergoing immunotherapy for LC.

Primary and secondary outcome measures: The mean knowledge, attitude, practice, and lifestyle scores.

Results: The study included 402 participants. The mean knowledge, attitude, practice, and lifestyle scores were 6.60±3.51 (/10, 66.00%), 41.26±5.06 (/50, 82.52%), 30.74±4.20 (/40, 76.85%), and 42.37±6.04 (/55, 77.04%). Attitude positively influenced practice (β=0.381, P<0.001) and lifestyle (β=1.928, P<0.001). The place of residence positively influenced attitude (β=1.242, P=0.013). The residential status positively influenced attitude (β=1.619, P=0.044). The number of immunotherapy lines positively influenced lifestyle (β=1.928, P<0.001). Gender positively influenced lifestyle (β=1.431, P=0.023).

Conclusion: Patients with LC and immunotherapy had moderate KAP toward irAEs and nutritional support. They also displayed moderate lifestyle scores. Urban residents, people not living alone, females, and those having received two or more immunotherapy treatments positively influence attitude, while attitude positively influences practice and lifestyle.

Keywords: knowledge, attitude, practice; liver cancer; nutritional support; immune-related adverse events (ir AEs); lifestyle; cross-sectional study

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Strengths and limitations of this study

1. While a cross-sectional design is useful for capturing data at a single time point, it limits the ability to establish causality or infer temporal relationships between variables.
2. Conducting the study at a single hospital may introduce selection bias and limit the generalizability of the findings to other settings or populations.
3. The reliance on self-reported measures for assessing knowledge, attitude, practice, and lifestyle introduces the potential for response bias and social desirability bias, impacting the accuracy of the results.
4. Although the study identifies certain factors influencing attitudes and lifestyle, there may be other unmeasured confounding variables that could affect the outcomes.
5. While the study assesses KAP towards irAEs and nutritional support, and lifestyle factors, it may not capture all relevant aspects influencing patient care and outcomes during immunotherapy for LC.

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INTRODUCTION

The estimated worldwide incidence of liver cancer in 2020 was 905,677 new cases, and mortality was 830,180 [1]. Most liver cancers are hepatocellular carcinoma (HCC), a highly lethal invasive carcinoma [2, 3]. The worldwide age-standardized annual mortality rates of liver cancer are 13.9 per 100,000 in men and 4.9 per 100,000 in women [1]. The most important risk factors for LC are preexisting liver cirrhosis and hepatitis B infection (due to both direct oncogenic effect and risk of cirrhosis) [2-5]. Risk factors for liver cirrhosis (and therefore risk factors for LC) include hepatitis C infection, alcohol use, and nonalcoholic steatohepatitis [2-5]. The incidence of LC is higher in men and generally follows the geographical distribution of hepatitis B virus and hepatitis C [2, 4, 5]. LC management is multidisciplinary and involves surgery (when possible), chemotherapy, targeted therapy, radiotherapy, and immunotherapy [2, 4, 5]. Despite optimal treatments, the 5-year survival is 18%, or 31% for localized disease, 11% for regional disease, and 2% for metastatic disease [6].

Immunotherapy is a recent paradigm in treating cancers, including LC [7-9]. Cancer cells can escape the immune system through the PD-1/PD-L1 pathway [10, 11], and drugs targeting PD-1 or PD-L1 have been developed to restore the immunosurveillance of cancer cells and their destruction [7-9]. Still, the PD-1/PD-L1 usually plays roles in immune tolerance and preventing autoimmune reactions [10, 11], and inhibiting the PD-1/PD-L1 pathway can lead to immune-related adverse events (irAEs). The pathogenesis of irAEs is still poorly understood, but they involve inflammatory reactions of normal tissues that can be bothersome but also life-threatening [12-14].

Adequate nutrition is also essential in patients with LC to ensure optimal outcomes, and nutritional support can be necessary in patients with inadequate nutrition due, for example, to gastrointestinal adverse events (AEs) from therapies [15, 16]. The management of irAEs and nutrition involves healthcare providers. It can involve medical interventions (e.g., management

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of irAEs, enteral nutrition, and hospitalization). Still, they also involve patient self-management in taking proper preventive measures and knowing when to consult, for example [17]. A knowledge, attitude, and practice (KAP) survey is a tool that provides quantitative and qualitative data about gaps, misconceptions, and misunderstandings that constitute barriers toward the optimal performance of a given task or set of tasks in a specific group of individuals [18, 19]. A systematic review showed that the eating habits of Chinese patients with cancer and chemotherapy were poor, but no data are available for immunotherapy specifically [20]. A study showed that Chinese patients with cancer had a basic understanding of irAEs [21], but the study was not specific to LC and did not evaluate attitudes and practices.

Therefore, this study aimed to investigate the KAP-lifestyle (KAP-L) of patients with LC and immunotherapy patients regarding nutritional support and irAEs. The results can provide crucial information to design educational interventions to improve patient self-management and outcomes.

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MATERIALS AND METHODS

Study design and participants

This cross-sectional study was conducted at Haikou People's Hospital from December 2022 to April 2023 and enrolled patients undergoing immunotherapy for LC. This study was approved by the Institutional Review Board of Haikou People's Hospital (2022-Ethical Review-231). All participants signed the informed consent form before completing the survey.

The inclusion criteria were: 1) Aged 18-90 years old; 2) Pathologically confirmed locally advanced or unresectable liver cancer. The exclusion criteria were: 1) Surgical patients; 2) Simultaneously suffering from other malignant tumors; 3) Before or planned liver transplantation; 4) Active autoimmune diseases; 5) Ambiguous consciousness, unable to fill out by oneself or with assistance; 6) Withdrawal during the filling process.

Questionnaire and quality control

A self-designed questionnaire consisting of five dimensions was developed based on the relevant literature [12, 15, 16, 20-22]. After the questionnaire design, modifications were made by incorporating insights from 15 experts in nutrition in oncology and medical oncology, removing similar or redundant questions, and refining questions with unclear phrasing.

The final questionnaire encompassed 1) participants' demographic information (including age, gender, residential area, education level and income level, et.al), 2) knowledge dimension (10 items, with a score of 1 assigned for correct answers and 0 for incorrect or uncertain responses), 3) attitude dimension (10 items, scored using a 5-point Likert scale, ranging from "strongly positive" (5 points) to "strongly negative" (1 point)), 4) practice dimension (eight items, scored using a 5-point Likert scale, ranging from "always" (5 points) to "never" (1 point)), and 5) lifestyle dimension (11 items, also scored using a 5-point Likert scale, ranging from "always" (5 points) to "never" (1 point)). Higher scores correspond to better knowledge, more positive attitudes, and more proactive practices.

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Before the official distribution, a small-scale pilot test (70 participants) was conducted, yielding a Cronbach's α coefficient of 0.853, indicating strong internal consistency. An online questionnaire was developed using the WeChat-based Wenjuanxing platform. A QR code was generated for data collection via WeChat. The participants accessed and completed the questionnaire by scanning the QR code received via WeChat. In order to ensure the quality and completeness of the questionnaires, all items were made mandatory. The research team members reviewed the integrity, internal consistency, and rationality of all collected questionnaires. A given IP address could be used to submit a questionnaire only once. Questionnaires that took <110 s to complete were excluded. Questionnaires completed using all the same options (e.g., the first option) were deemed invalid.

Statistical analysis

The statistical analysis software was SPSS 26.0 (IBM, Armonk, NY, USA). Quantitative variables were described as means ± standard deviations (SD), while group comparisons were conducted using Student's t-test or analysis of variance (ANOVA). Categorical variables were presented as n (%). Pearson's correlation analysis explored the relationships between knowledge, attitude, and practice scores. The study used a structural equation modeling (SEM) analysis to validate various causality hypotheses empirically. These hypotheses encompassed 1) knowledge has a direct impact on attitudes, practices, and lifestyles, 2) attitudes have a direct influence on practices and lifestyles, 3) residential area and status have direct influences on attitudes, 4) gender has direct influences on attitudes and lifestyles, and 5) assessing the direct association between the number of immunotherapy medication usage and lifestyles. All statistical tests were two-tailed, and P-values <0.05 were considered statistically significant.

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RESULTS

Characteristics of the participants

The study included 419 respondents. After removing the following cases: 1) 1 respondent with abnormal height and weight, 2) 9 respondents answered with logical errors, and 3) 7 respondents with a completion time of less than 110 seconds, a total of 402 valid questionnaires were included in the analysis. The participants were 56.84±11.93 years old. Most participants were male (71.89%), had a BMI of 18.5-23.9 kg/m^2 (60.95%), were living in rural areas (55.97%), were not living alone (89.30%), were married (90.05%), had high school or technical secondary school education (34.08%), had an income of 2000-5000 RBM/months (48.76%), had health insurance (99.50%), had gastrointestinal symptom (50.75%), did not experience irAEs (89.80%), received one line of immunotherapy (54.23%), and were not familiar with the name of their immunotherapy (65.17%) (Table 1).

Knowledge

The mean knowledge score was 6.60±3.51 (/10, 66.00%). No significant differences were observed according to the characteristics of the participants. The knowledge item with the lowest score was K1 (50.75%; "Adverse reactions can occur during immunotherapy, but they are normal occurrences that do not require excessive attention."), while the item with the highest score was K9 (72.39%; "Prompt identification and timely reporting of symptoms of malnutrition and immune-related events to healthcare professionals are not only beneficial for immunotherapy and ameliorating immune-related adverse symptoms and nutritional status but also increase the likelihood of continuing immunotherapy.") (Table 2).

Attitude

The mean attitude score was 41.26±5.06 (/50, 82.52%). Higher attitude scores were observed in urban dwellers (P=0.010), those not living alone (P=0.035), and those with higher income (P=0.005) (Table 1). The attitude item with the lowest score was A1 (64.52%; "I

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consider nutritional support to be highly significant throughout the entire course of immunotherapy."), while the item with the highest score was A10 (93.28%; "I believe that maintaining a positive mindset and quality sleep are important during immunotherapy.") (Table 2).

Practice

The mean practice score was 30.74±4.20(/40, 76.85%). Higher practice scores were observed in females (P=0.027), widows (P=0.031), and with more than one immunotherapy line (P=0.001) (Table 1). The practice item with the lowest score was P6 (39.53%; "If required, I am prepared to receive enteral feeding through nasogastric/nasoenteric tubes."), while the item with the highest score was P1 (86.07%; "I am capable of cooperating with medical personnel for comprehensive treatment monitoring and follow-up.") (Table 2).

Lifestyle

The mean lifestyle score was 42.37±6.04 (/55, 77.04%). Higher lifestyle scores were observed in females (P=0.027), widows (P=0.031), and with more than one immunotherapy line (P=0.001) (Table 1). The lifestyle item with the lowest score was L11 (30.35%; "Citrus fruits (grapefruit, pomelo, honey pomelo, etc.).)"), while the item with the highest score was L2 (83.84%; "Alcohol consumption") (Table 2).

Correlations

The knowledge scores were correlated to the attitude scores (r=0.105, P=0.035). The attitude scores were correlated to the practice (r=0.460, P<0.001) and lifestyle (r=0.486, P<0.001) scores. The practice scores were correlated to the lifestyle scores (r=0.269, P<0.001).

Structural equation modeling

As shown in Table 3 and Figure 1, attitude positively influenced practice (β=0.381, P<0.001) and lifestyle (β=1.928, P<0.001). The place of residence positively influenced attitude (β=1.242, P=0.013). The residential status positively influenced attitude (β=1.619,

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P=0.044). The number of immunotherapy lines positively influenced lifestyle (β=1.928, P<0.001). Gender positively influenced lifestyle (β=1.431, P=0.023). Table S1 shows that the SEM analysis had a good fit.

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DISCUSSION

No study specifically examined the KAP toward irAEs and nutritional support in patients with LC. This study aimed to address that issue. Therefore, this study aimed to investigate the KAP of patients with LC and immunotherapy patients regarding nutritional support and irAEs and their lifestyle. The results suggest that patients with LC and immunotherapy had moderate KAP toward irAEs and nutritional support. They also displayed moderate lifestyle scores. Urban residents, people not living alone, females, and those having received two or more immunotherapy treatments positively influence attitude, while attitude positively influences practice and lifestyle.

Self-management is a critical component of cancer care. Indeed, the patients must remain aware of the signs and symptoms that should prompt consultation. At home, they are also responsible for maintaining lifestyle habits that could improve their prognosis or, at least, not worsen it [17]. A previous systematic review revealed poor KAP toward good eating habits among Chinese patients on chemotherapy for various types of cancers [20]. That previous study supports the present one, which showed poor lifestyle scores for several foods in patients with LC and immunotherapy. Increasing evidence indicates that a healthy diet can improve the outcomes of immunotherapy [23, 24]. Although the knowledge about which food can improve immunotherapy outcomes is lacking, it appears, for now, that a healthy diet, in general, improves the response to immunotherapy. Hence, good lifestyle habits should be promoted among patients on immunotherapy.

For example, in this study, 30 (7.46%) participants were still regularly smoking, 17 (4.23%) participants were still drinking alcohol, 32 (7.96%) participants were not avoiding unhealthy cooking methods, 40 (9.95%) participants were not avoiding high oil, high salt, spicy, 43 (10.69%) participants were not consuming high-protein foods, 57 (14.18%) participants were not consuming light and easily digestible foods, 42 (10.45%) participants

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were not eating foods rich in vitamins, 55 (13.68%) participants were eating stimulant foods, and 28 (6.97%) participants were eating sugary beverages. Of importance, most participants (72.64%) did not eat probiotics, and 50.99 were not eating citrus fruits. Probiotics are important in the management of gastrointestinal side effects of cancer treatments [25].

Therefore, the healthy lifestyle of the study population was not ideal. Especially, smoking and alcohol consumption are independent risk factors for confirmed liver cancer [2-5], and they affect liver function and immunotherapy efficacy [26].

Recent data also suggests that probiotics should be encouraged to prevent irAEs [27]. Indeed, regulation of the gut microbiome appears crucial in preventing irAEs [28]. The gut microbiota was also shown to modulate the response to immunotherapy, with distinct responses to immunotherapy according to the composition of the microbiome [29]. Gut dysbiosis can even lead to resistance to immunotherapy [29]. Hence, administering specific bacteria could be used to improve the response to immunotherapy and prevent irAEs [30].

Citrus fruits are rich in vitamins and antioxidants and play roles in maintaining the integrity of immunological barriers and in supporting immune cells [31]. On the other hand, citrus fruits are rich in active ingredients, such as furacoumarin, naringin, and bergamot, that can inhibit the activity of metabolic enzymes (mainly UGT1A3 or UGT2B7) [32]. UGT1A3 is involved in the metabolic elimination of many aromatic hydrocarbons, amines, non-steroidal anti-inflammatory drugs, and statins [33]. UGT2B7 participates in drug glucuronidation reactions, including anticancer drugs, gemcitabine, etc. It can also bind many endogenous substances, such as bile acids, androgens, and estrogen [34]. When certain drugs metabolized by UGT1A3 or UGT2B7 enzymes are taken together with pomelo, it may affect the metabolism and excretion of the drugs, leading to increased adverse reactions. Therefore, in the future, intervention research on the impact of fruits such as grapefruit on medication can be strengthened.

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IrAEs can be simply bothersome but also life-threatening [12-14]. Still, irAEs appear to be related to the efficacy of immunotherapy [35, 36]. Therefore, the patients have to maintain a good attitude and practice toward the management of irAEs and know when to consult and how to deal with them. A study showed that Chinese patients with cancer had a basic understanding of irAEs [21] but that there were several gaps in knowledge, as observed in the present study. In particular, the patients should be educated on the nature of irAEs and their manifestations.

People living in urban areas and not living alone often enjoy a higher socioeconomic status, and it is well-known that higher socioeconomic status is associated with better health literacy [37]. In the present study, the knowledge scores were only correlated to the attitude scores, while the attitude scores were correlated to the practice and lifestyle scores. Although knowledge did not influence attitude in the SEM, improving knowledge could translate into attitude, practice, and lifestyle improvements. Healthcare providers are a primary source of information for the patients, but previous studies revealed relatively poor KAP toward cancer nutritional support [22, 38] and irAEs [39] among healthcare providers. Future studies should examine the KAP toward irAEs and nutritional support among healthcare providers. Educational interventions should be designed for the patients and maybe also for the healthcare providers.

This study has limitations. It was a single-center study. Even though 402 patients with LC and immunotherapy represent a relatively large sample size, it is still too small to derive correlations and recommendations regarding the KAP-L in patients with LC. The study was cross-sectional in design, preventing the analysis of causality. Still, a SEM analysis was performed to infer causality, but it must be remembered that the causality is purely statistical and remains to be confirmed. In addition, the data represent a single point in time. Still, the results could serve as a historical baseline to evaluate the effect of future interventions. Future

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studies should examine the impact of health education on the KAP-L of patients with LC and immunotherapy. The questionnaire was designed by local investigators based on local practice, policies, and reality, limiting generalizability. Finally, all KAP studies are at risk of the social desirability bias, in which some participants might be tempted to answer what they know they should do instead of what they are actually doing [40, 41].

It is recommended to expand the scope of the survey and include hospitals in different regions and levels to validate the results of this study. Clinical intervention research should be performed on the knowledge, attitude, behavior, and lifestyle level of nutrition and irAEs in patients with LC and immunotherapy and evaluate the effectiveness of the intervention. The impact of good sleep and moderate exercise (as good lifestyles) in relation to nutrition and irAEs should also be examined.

In conclusion, patients with LC and immunotherapy had moderate KAP toward irAEs and nutritional support. They also displayed moderate lifestyle scores. Urban residents, people not living alone, females, and those having received two or more immunotherapy treatments positively influence attitude, while attitude positively influences practice and lifestyle.

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Declarations

Ethics approval and consent to participate

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved by the Institutional Review Board of Haikou People's Hospital (2022-Ethical Review-231). All participants signed the informed consent form before completing the survey.

The Patient and Public Involvement statement

No patient or public involved in this study.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this article and it's supplementary materials.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Wen Wen and Fangqing Gao carried out the studies, participated in collecting data, and drafted the manuscript. Yingshuang Chen and Liling Tong performed the statistical analysis and participated in its design. Wen Wen and Yingshuang Chen participated in acquisition, analysis, or interpretation of data and draft the manuscript. All authors read and approved the final manuscript.

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Figure 1. Structural equation modeling (SEM).

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Table 1. Characteristics of the participants and KAP scores.

Variables	n (%)	Knowledge		Attitude		Practice		Lifestyle	
		Mean±SD	P	Mean±SD	P	Mean±SD	P	Mean±SD	P
Total Score	402	6.60±3.51		41.26±5.06		30.74±4.27		42.37±6.04	
Gender			0.385		0.694		0.384		0.027
Male	289 (71.89)	6.69±3.39		41.32±4.63		30.86±3.98		41.95±6.24	
Female	113 (28.11)	6.35±3.79		41.10±6.05		30.45±4.78		43.43±5.36	
Age (years)	56.84±11.93								
Body mass index (kg/m²)			0.550		0.687		0.406		0.570
<18.5	55 (13.68)	6.16±3.68		41.69±4.57		30.05±4.17		43.07±6.99	
18.5-23.9	245 (60.95)	6.61±3.44		41.09±5.13		30.90±4.37		42.36±5.78	
≥24	102 (25.37)	6.80±3.59		41.41±5.16		30.75±3.78		42.00±6.12	
Residential area			0.061		0.010		0.347		0.274
Rural	225 (55.97)	6.31±3.53		40.68±4.89		30.57±4.16		42.08±5.51	
City	177 (44.03)	6.97±3.46		41.99±5.19		30.97±4.25		42.74±6.65	
Residential status			0.560		0.035		0.084		0.136

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Living alone	43 (10.70)	6.30±3.56		39.72±4.76		29.70±4.68	41.07±6.00	
Living with others	359 (89.30)	6.63±3.50		41.44±5.07		30.87±4.13	42.52±6.03	
Marital Status			0.918		0.148		0.153	0.031
Unmarried	22 (5.47)	6.14±3.76		40.36±4.75		29.91±4.20	39.09±6.45	
Married	362 (90.05)	6.64±3.50		41.32±5.09		30.75±4.26	42.49±5.99	
Divorced	8 (1.99)	6.25±3.49		38.25±5.47		29.50±5.07	42.38±5.15	
Widowed	10 (2.49)	6.50±3.81		43.40±3.53		33.30±3.66	45.20±5.55	
Education			0.426		0.449		0.310	0.233
Junior high school and below	79 (19.65)	6.56±3.60		40.96±5.89		30.01±4.85	42.67±5.95	
High school/technical secondary school	137 (34.08)	6.33±3.60		41.72±4.61		31.25±3.66	42.81±5.69	
College	112 (27.86)	6.92±3.36		40.72±5.05		30.71±3.94	42.12±6.04	
Bachelor's degree	68 (16.92)	6.82±3.46		41.35±5.03		30.56±4.88	41.99±6.39	
Postgraduate and above	6 (1.49)	4.67±3.27		43.33±3.33		31.67±2.25	37.33±9.61	

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Average monthly income, RMB			0.500	0.005	0.276	0.094
<2000	86 (21.39)	6.13±3.70	39.66±5.88	30.05±4.83	42.19±5.97	
2000-5000	196 (48.76)	6.81±3.39	41.87±4.58	31.04±3.90	42.64±5.93	
5001-10,000	83 (20.65)	6.52±3.64	40.90±5.39	30.69±4.20	42.98±5.89	
10,001-20,000	23 (5.72)	6.30±3.50	41.87±3.86	30.22±3.63	39.26±6.88	
>20,000	14 (3.48)	7.50±3.16	43.50±3.46	32.07±3.27	41.21±6.55	
Types of health insurance						
Urban Employee Basic Medical Insurance	134 (33.33)	6.94±3.37	41.70±4.90	30.93±4.11	42.82±5.96	
New Rural Cooperative Medical Insurance	207 (51.49)	6.24±3.57	40.87±5.16	30.76±4.15	41.91±6.08	
Urban Resident Basic Medical Insurance	53 (13.18)	7.11±3.46	42.06±4.72	30.75±3.95	43.66±5.73	
Commercial Insurance	6 (1.49)	6.33±4.56	40.33±6.25	29.67±5.75	38.17±7.11	
Self-payment	2 (0.50)	8.00±1.41	33.00±1.41	20.00±8.49	38.00±4.24	

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GI Symptoms						
Loss of appetite	113 (28.11)	6.09±3.45	41.15±4.33	30.44±4.65	40.89±6.72	
Nausea and vomiting	54 (13.43)	6.80±3.20	40.89±4.90	29.81±5.5	39.52±7.87	
Constipation	53 (13.18)	6.25±3.59	40.72±5.26	29.70±4.2	40.13±6.30	
Diarrhea	34 (8.46)	7.41±2.84	40.88±3.67	30.00±4.7	41.15±6.63	
Oral ulcers	18 (4.48)	6.94±3.46	41.89±4.17	31.56±4.0	39.89±8.63	
Dry Mouth	45 (11.19)	6.11±3.49	41.07±4.86	30.24±4.7	41.91±6.78	
Altered taste perception	27 (6.72)	5.37±3.56	40.44±4.97	30.81±5.58	41.59±8.02	
Altered smell perception	8 (1.99)	4.75±3.45	41.13±3.72	29.13±6.13	41.00±8.64	
Swallowing Difficulties	13 (3.23)	6.38±3.64	40.08±6.49	29.31±5.99	41.38±7.09	
Feeling of fullness	48 (11.94)	5.65±3.44	41.65±4.35	31.40±4.34	43.33±6.57	
Pain	66 (16.42)	6.39±3.71	42.29±4.04	30.56±3.89	43.06±6.00	
None	198 (49.25)	6.80±3.52	40.98±5.45	30.88±4.07	43.28±5.18	
IrAEs		0.527	0.276	0.122	0.954	
Yes	41 (10.20)	6.27±3.78	42.07±4.42	29.78±4.18	42.32±6.60	
No	361 (89.80)	6.63±3.48	41.16±5.13	30.85±4.20	42.37±5.98	

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Symptoms you experienced					
Capillary Proliferation Syndrome	9 (2.24)	4.89±3.95	41.11±3.37	31.00±2.65	42.78±7.66
Other skin reactions (rash, papules, itching, vitiligo, etc.)	18 (4.48)	6.89±3.41	40.94±4.32	30.83±3.76	41.67±7.04
Gastrointestinal reactions (diarrhea, colitis, abdominal pain, nausea, vomiting, etc.)	16 (3.98)	6.75±3.24	41.75±4.30	30.00±4.76	40.25±6.22
Hepatic reactions	7 (1.74)	5.14±3.39	43.29±3.99	30.43±3.99	43.86±7.24
Endocrine reactions (hypothyroidism, hyperthyroidism,	2 (0.50)	9.50±0.71	40.00±8.49	26.00±8.49	35.00±11.31

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adrenal insufficiency, etc.)						
Pneumonia	1 (0.25)	9.00	40	29	30	
Cardiac reactions	0	0	0	0	0	
Renal toxicity (nephritis)	0	0	0	0	0	
Muscle or joint pain, muscle weakness	13 (3.23)	5.85±3.74	41.92±4.82	30.08±5.38	44.92±2.99	
Other	4 (1.00)	7.50±4.36	39.75±5.06	27.75±5.44	41.00±9.56	
Number of immunotherapy medication		0.736	0.529	0.620		0.001
1	218 (54.23)	6.65±3.50	41.11±5.04	30.84±3.71	41.45±5.88	
>1	184 (45.77)	6.53±3.52	41.43±5.09	30.63±4.73	43.46±6.06	

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Familiar with the specific names of the immunotherapy drugs		0.990	0.724	0.806	0.884	
Yes	140 (34.83)	6.60±3.62	41.38±5.03	30.81±4.[illegible]	42.43±6.71	
No	262 (65.17)	6.60±3.45	41.19±5.09	30.71±4.[illegible]	42.34±5.66	

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Table 2. Knowledge, attitudes, and practices

Statement	Accuracy, n (%)
K1. Adverse reactions can occur during immunotherapy, but they are normal occurrences that do not require excessive attention.	204 (50.75)
K2. Skin toxicities (rashes, dermatitis, capillary proliferation), endocrine toxicities (hypothyroidism, hyperthyroidism, adrenal insufficiency), hepatic toxicities, cardiac toxicities, gastrointestinal toxicities (abdominal pain, diarrhea), pneumonia, renal toxicity (immune nephritis leading to proteinuria), etc., might emerge during the immunotherapy process.	247 (61.44)
K3. The liver is engaged in digestion, synthesis, and metabolic processes of various nutrients; impaired liver function significantly elevates the incidence of malnutrition in liver cancer patients.	245 (60.95)
K4. Tumor progression and immunotherapy can exacerbate malnutrition due to deteriorating liver function, which, in turn, affects the prognosis of liver cancer patients, leading to a vicious cycle.	231 (57.46)
K5. Liver cancer patients undergoing treatment should undergo nutritional screening and assessment, followed by personalized nutritional interventions based on their nutritional status.	281 (69.90)
K6. Nutritional risk screening and assessment include disease status, dietary surveys, weight changes, anthropometric measurements, laboratory examinations, etc.	290 (72.14)

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K7. Nutritional support encompasses dietary guidance, oral supplements, enteral nutrition, and parenteral nutrition.	283 (70.40)
K8. Appropriate and effective nutritional interventions can optimize the intake structure and quantity of nutrients, improve nutritional status and liver function, enhance tolerance to surgery or other treatments, enhance immune conditions, reduce complications during treatment, elevate quality of life, and extend survival time.	290 (72.14)
K9. Prompt identification and timely reporting of symptoms of malnutrition and immune-related events to healthcare professionals are not only beneficial for immunotherapy and ameliorating immune-related adverse symptoms and nutritional status but also increase the likelihood of continuing immunotherapy.	291 (72.39)
K10. Liver cancer patients receiving immunotherapy should be managed comprehensively throughout the cycle, from screening and assessment to diagnosis, supportive treatment, monitoring, and follow-up, focusing on nutritional and adverse event management.	290 (72.14)

Attitude	**Strongly Agree**	**Agree**	**Neutral**	**Disagree**	**Strongly Disagree**
A1. I consider nutritional support highly significant throughout the entire course of immunotherapy.	230 (27.21)	150 (37.31)	16 (3.98)	2 (0.50)	4 (1.00)
A2. I believe that targeted nutritional interventions can enhance the efficacy of immunotherapy.	196 (48.76)	175 (43.53)	25 (6.22)	2 (0.50)	4 (1.00)

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A3. I deem continuous monitoring of adverse immune events to be essential.	208 (51.74)	160 (39.80)	32 (7.96)	0	2 (0.50)
A4. I would be concerned about adverse reactions following immunotherapy.	169 (42.04)	183 (45.52)	36 (8.96)	6 (1.49)	8 (1.99)
A5. I find it necessary to monitor nutrition-related indicators comprehensively.	188 (46.77)	172 (42.79)	30 (7.46)	6 (1.49)	6 (1.49)
A6. I think consuming high-quality proteins, abundant dietary fiber, and appropriate carbohydrates is crucial.	216 (53.73)	158 (39.30)	23 (5.72)	3 (0.75)	2 (0.50)
A7. I wish to acquire further knowledge about nutritional support through professional channels.	200 (49.75)	163 (40.55)	32 (7.96)	2 (0.50)	5 (1.24)
A8. I desire to gain more insights through professional channels regarding self-management, emergency responses, and precautions for managing adverse events during immunotherapy.	193 (48.01)	175 (43.53)	27 (6.72)	4 (1.00)	3 (0.75)
A9. I am confident in maintaining a relatively favorable nutritional status.	179 (44.53)	165 (41.04)	45 (11.19)	7 (1.74)	6 (1.49)

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A10. I believe that maintaining a positive mindset and quality sleep are important during immunotherapy.	214 (53.23)	161 (40.05)	19 (4.73)	3 (0.75)	5 (1.24)

Practice	**Always**	**Frequently**	**Sometimes**	**Occasionally**	**Never**
P1. I can cooperate with medical personnel for comprehensive treatment monitoring and follow-up.	216 (53.73)	130 (32.34)	43 (10.70)	6 (1.49)	7 (1.74)
P2. I will regularly monitor nutrition-related indicators such as body weight, body mass index, grip strength, albumin, and prognostic nutritional index.	177 (44.03)	140 (34.83)	55 (13.68)	22 (5.47)	8 (1.99)
P3. If a physician recommends it, I will take medication to enhance appetite, digestion, and absorption.	192 (47.76)	132 (32.84)	53 (13.18)	18 (4.48)	7 (1.74)
P4. I will proactively seek relevant knowledge about immunotherapy nutrition and adverse reactions through professional channels such as healthcare providers, health promotion columns, books, and television.	172 (42.79)	126 (31.34)	64 (15.92)	27 (6.72)	13 (3.23)

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P5. I will undergo oral nutritional supplementation, including branched-chain amino acids, omega-3 fatty acids, and vitamin D if necessary.	162 (40.30)	118 (29.35)	60 (14.93)	31 (7.71)	31 (7.71)
P6. If required, I am prepared to receive enteral feeding through nasogastric/nasoenteric tubes.	133 (33.08)	38 (6.45)	46 (11.44)	36 (8.96)	149 (37.06)
P7. If necessary, I am open to receiving parenteral nutrition support (intravenous administration).	123 (30.60)	43 (10.70)	52 (12.94)	56 (13.93)	128 (31.84)
P8. I will maintain moderate physical exercise to improve my overall physical condition.	176 (43.78)	122 (30.35)	55 (13.68)	34 (8.46)	15 (3.73)
Lifestyle	**Never**	**Occasionally**	**Sometimes**	**Frequently**	**Always**
In your daily lifestyle habits, what is your eating frequency for the following types:					
L1. Smoking	272 (67.66)	38 (9.45)	27 (63.72)	35 (8.71)	30 (7.46)
L2. Alcohol consumption	285 (70.90)	52 (12.94)	27 (6.72)	21 (5.22)	17 (4.23)
L3. Cooking methods involving frying, smoking, baking, pickling, etc.	223 (55.47)	100 (24.88)	47 (11.69)	19 (4.73)	13 (3.23)

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L4. High-fat, high-salt, spicy foods (such as chili peppers, onions, ginger, raw garlic, and pepper)	212 (52.74)	100 (24.88)	50 (12.44)	27 (6.72)	13 (3.23)
L5. High-quality protein sources (legumes, eggs, meat, fish, shellfish, dairy products, etc.)	22 (5.47)	21 (5.22)	37 (9.20)	224 (55.72)	98 (24.38)
L6. Light and easily digestible foods (egg custard, millet porridge, lotus root powder, Chinese yam)	15 (3.73)	42 (10.45)	61 (15.17)	213 (52.99)	71 (17.66)
L7. Foods rich in vitamins (fresh vegetables and fruits, such as spinach, cabbage, kiwi, tomatoes, etc.)	8 (1.99)	34 (8.46)	42 (10.45)	217 (53.98)	101 (25.12)
L8. Stimulants like coffee, chocolate, and strong tea	247 (61.44)	70 (17.41)	30 (7.46)	38 (9.45)	17 (4.23)
L9. Probiotics	202 (50.25)	90 (22.39)	51 (12.69)	37 (9.20)	22 (5.47)
L10. Sugary beverages	215 (53.48)	114 (28.36)	45 (11.19)	20 (4.98)	8 (1.99)
L11. Citrus fruits (grapefruit, pomelo, honey pomelo, etc.)	93 (23.13)	112 (27.86)	75 (18.66)	92 (22.89)	30 (7.46)

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Table 3. SEM, including lifestyle

			β	P
Attitude	<---	Gender	-0.457	0.407
Attitude	<---	Residential area	1.242	0.013
Attitude	<---	Knowledge	0.128	0.069
Attitude	<---	Residential status	1.619	0.044
Lifestyle	<---	Knowledge	-0.048	0.565
Practice	<---	Knowledge	0.011	0.841
Lifestyle	<---	Attitude	0.222	<0.001
Practice	<---	Attitude	0.381	<0.001
Lifestyle	<---	Number of immunotherapy	1.928	<0.001
Lifestyle	<---	Gender	1.431	0.023

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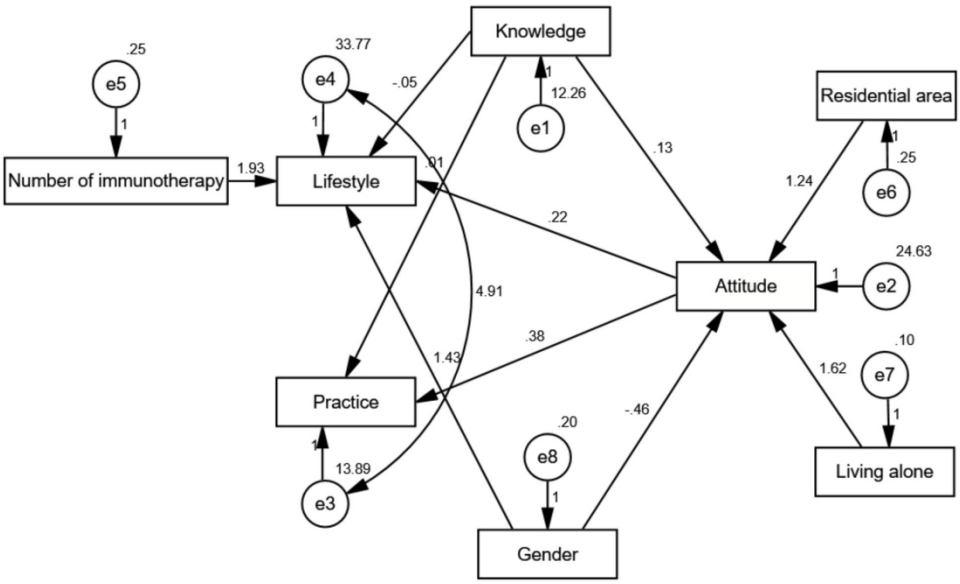

Figure 1. Structural equation modeling (SEM).

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Table S1. SEM model fit

Indicators	Reference	Results
CMIN/DF	1-3 Excellent, 3-5 Good	1.610
RMSEA	<0.08 Good	0.039
IFI	>0.8 Good	0.939
TLI	>0.8 Good	0.893
CFI	>0.8 Good	0.935

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Knowledge, attitude, and practice of nutritional support and immune-related adverse events among patients undergoing immunotherapy for liver cancer: a cross-sectional study

Running title: KAP of irAEs and nutrition and lifestyle

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ABSTRACT

Objectives: No study specifically examined the knowledge, attitude, and practice (KAP) toward immune-related adverse events (irAEs) and nutritional support in patients with liver cancer (LC), nor have they explored their lifestyle. This study aimed to address that issue.

Design: This cross-sectional study

Setting: This cross-sectional study was conducted at Haikou People's Hospital from December 2022 to April 2023.

Participants: Patients undergoing immunotherapy for LC.

Primary and secondary outcome measures: The mean knowledge, attitude, practice, and lifestyle scores using an investigator-designed questionnaire completed during immunotherapy.

Results: The study included 402 participants. The mean knowledge, attitude, practice, and lifestyle scores were 6.60±3.51 (/10, 66.00%), 41.26±5.06 (/50, 82.52%), 30.74±4.20 (/40, 76.85%), and 42.37±6.04 (/55, 77.04%). Attitude positively influenced practice (β=0.381, P<0.001) and lifestyle (β=1.928, P<0.001). The place of residence positively influenced attitude (β=1.242, P=0.013). The residential status positively influenced attitude (β=1.619, P=0.044). The number of immunotherapy lines positively influenced lifestyle (β=1.928, P<0.001). Gender positively influenced lifestyle (β=1.431, P=0.023).

Conclusion: Patients with LC and immunotherapy had moderate KAP toward irAEs and nutritional support. They also displayed moderate lifestyle scores. Urban residents, people not living alone, females, and those having received two or more immunotherapy treatments positively influence attitude, while attitude positively influences practice and lifestyle.

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Keywords: knowledge, attitude, practice; liver cancer; nutritional support; immune-related adverse events (ir AEs); lifestyle; cross-sectional study

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Strengths and limitations of this study

1. While a cross-sectional design is useful for capturing data at a single time point, it limits the ability to establish causality or infer temporal relationships between variables.

2. Conducting the study at a single hospital may introduce selection bias and limit the generalizability of the findings to other settings or populations.

3. The reliance on self-reported measures for assessing knowledge, attitude, practice, and lifestyle introduces the potential for response bias and social desirability bias, impacting the accuracy of the results.

4. Although the study identifies certain factors influencing attitudes and lifestyle, there may be other unmeasured confounding variables that could affect the outcomes.

5. While the study assesses KAP toward irAEs, nutritional support, and lifestyle factors, it may not capture all relevant aspects influencing patient care and outcomes during immunotherapy for LC.

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INTRODUCTION

The estimated worldwide incidence of liver cancer in GLOBOCAN 2022 was 865,269 new cases, and mortality was 757,948 [1]. Most liver cancers are hepatocellular carcinoma (HCC) [2, 3]. The worldwide age-standardized annual mortality rates of liver cancer are 13.9 per 100,000 in men and 4.9 per 100,000 in women [4]. The most important risk factors for LC are preexisting liver cirrhosis and hepatitis B infection (due to both direct oncogenic effect and risk of cirrhosis) [2, 3, 5, 6]. Risk factors for liver cirrhosis (and therefore risk factors for LC) include hepatitis C infection, alcohol use, and nonalcoholic steatohepatitis [2, 3, 5, 6]. The incidence of LC is higher in men and generally follows the geographical distribution of hepatitis B virus and hepatitis C [2, 5, 6]. LC management is multidisciplinary and involves surgery (when possible), chemotherapy, targeted therapy, radiotherapy, and immunotherapy [2, 5, 6]. Despite optimal treatments, the 5-year survival is 22% in the United States of America [7].

Immunotherapy is a recent paradigm in treating cancers, including LC [8-10]. Cancer cells can escape the immune system through the PD-1/PD-L1 pathway [11, 12], and drugs targeting PD-1 or PD-L1 have been developed to restore the immunosurveillance of cancer cells and their destruction [8-10]. Still, the PD-1/PD-L1 usually plays roles in immune tolerance and preventing autoimmune reactions [11, 12], and inhibiting the PD-1/PD-L1 pathway can lead to immune-related adverse events (irAEs). The pathogenesis of irAEs is still poorly understood, but they involve inflammatory reactions of normal tissues that can be bothersome but also life-threatening [13-15].

Adequate nutrition is also essential in patients with LC to ensure optimal outcomes and nutritional support can be necessary in patients with inadequate nutrition due, for example, to

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adverse gastrointestinal events (AEs) from therapies [16, 17]. Still, the palliation of some symptoms of HCC (e.g., loss of appetite, weakness, fatigue, etc.) using androgens (since most LCs occur in males) can help alleviate the need for nutritional support [18]. The management of irAEs and nutrition involves healthcare providers. It can involve medical interventions (e.g., management of irAEs, enteral nutrition, and hospitalization). Still, they also involve patient self-management in taking proper preventive measures and knowing when to consult, for example, [19]. A knowledge, attitude, and practice (KAP) survey is a tool that provides quantitative and qualitative data about gaps, misconceptions, and misunderstandings that constitute barriers toward the optimal performance of a given task or set of tasks in a specific group of individuals [20, 21]. A systematic review showed that the eating habits of Chinese patients with cancer and chemotherapy were poor, but no data are available for immunotherapy specifically [22]. A study showed that Chinese patients with cancer had a basic understanding of irAEs [23], but the study was not specific to LC and did not evaluate attitudes and practices. Compared with other types of cancer, e.g., breast cancer, patients with LC have a poorer prognosis, and there is a male predominance. In addition, the risk factors for LC are different from other cancers, mainly encompassing chronic liver diseases, alcohol drinking, and hepatitis virus infection. Those differences could influence the KAP toward irAEs.

Therefore, this study aimed to investigate the KAP-lifestyle (KAP-L) of patients with LC and immunotherapy patients regarding nutritional support and irAEs. The results can provide crucial information to design educational interventions to improve patient self-management and outcomes.

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MATERIALS AND METHODS

Study design and participants

This cross-sectional study was conducted at Haikou People's Hospital from December 2022 to April 2023 and enrolled patients undergoing immunotherapy for LC. This study was approved by the Institutional Review Board of Haikou People's Hospital (2022-Ethical Review-231). All participants signed the informed consent form before completing the survey.

The inclusion criteria were 1) aged 18-90 years old, 2) pathologically confirmed locally advanced or unresectable liver cancer, and 3) undergoing immunotherapy (any line of treatment). The exclusion criteria were 1) surgical patients, 2) simultaneously suffering from other malignant tumors, 3) before or planned liver transplantation, 4) active autoimmune diseases, 5) ambiguous consciousness, unable to fill out by oneself or with assistance, or 6) withdrawal during the filling process.

Questionnaire and quality control

A self-designed questionnaire consisting of five dimensions was developed based on the relevant literature [13, 16, 17, 22-24]. After the questionnaire design, modifications were made by incorporating insights from 15 experts in nutrition in oncology and medical oncology, removing similar or redundant questions, and refining questions with unclear phrasing. Before the official distribution, a small-scale pilot test (70 participants) was conducted, yielding a Cronbach's α coefficient of 0.853 (0.879 for knowledge, 0.828 for attitudes, and 0.758 for practice), indicating strong internal consistency.

The final questionnaire was in Chinese and encompassed 1) participants' demographic information (including age, gender, residential area, education level and income level, et.al),

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2) knowledge dimension (10 items, with a score of 1 assigned for correct answers and 0 for incorrect or uncertain responses), 3) attitude dimension (10 items, scored using a 5-point Likert scale, ranging from "strongly positive" (5 points) to "strongly negative" (1 point)), 4) practice dimension (eight items, scored using a 5-point Likert scale, ranging from "always" (5 points) to "never" (1 point)), and 5) lifestyle dimension (11 items, also scored using a 5-point Likert scale, ranging from "always" (5 points) to "never" (1 point)). Higher scores correspond to better knowledge, more positive attitudes, and more proactive practices. Scores <60% were considered poor, scores 60%-79% were considered moderate, and scores ≥80% were considered adequate, based on the Bloom criteria [25].

An online questionnaire was developed using the WeChat-based Wenjuanxing platform. A QR code was generated for data collection via WeChat. The participants accessed and completed the questionnaire by scanning the QR code received via WeChat. In order to ensure the quality and completeness of the questionnaires, all items were made mandatory.

The research team members reviewed the integrity, internal consistency, and rationality of all collected questionnaires for quality control. A given IP address could be used to submit a questionnaire only once. Questionnaires that took <110 s to complete were excluded. Questionnaires completed using all the same options (e.g., the first option) were deemed invalid. Finally, questionnaires containing impossible values (e.g., impossible age, height, or weight) or logical errors were excluded. The Cronbach's α coefficient for all valid questionnaires was 0.840 (0.913 for knowledge, 0.800 for attitudes, and 0.718 for practice).

Statistical analysis

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The statistical analysis software was SPSS 26.0 (IBM, Armonk, NY, USA). Quantitative variables were described as means ± standard deviations (SD), while group comparisons were conducted using Student's t-test or analysis of variance (ANOVA). Categorical variables were presented as n (%). Pearson's correlation analysis explored the relationships between knowledge, attitude, and practice scores. The study used a structural equation modeling (SEM) analysis to validate various causality hypotheses empirically. These hypotheses encompassed 1) knowledge has a direct impact on attitudes, practices, and lifestyles, 2) attitudes have a direct influence on practices and lifestyles, 3) residential area and status have direct influences on attitudes, 4) gender has a direct influence on attitudes and lifestyles, and 5) assessing the direct association between the number of immunotherapy medication usage and lifestyles. All statistical tests were two-tailed, and P-values <0.05 were considered statistically significant.

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RESULTS

Characteristics of the participants

The study included 419 respondents. After removing the following cases: 1) 1 respondent with abnormal height and weight, 2) 9 respondents answered with logical errors, and 3) 7 respondents with a completion time of less than 110 seconds, a total of 402 valid questionnaires were included in the analysis **(Figure 1)**. The participants were 56.84±11.93 years old. Most participants were male (71.89%), had a BMI of 18.5-23.9 kg/m^2 (60.95%), were living in rural areas (55.97%), were not living alone (89.30%), were married (90.05%), had high school or technical secondary school education (34.08%), had an income of 2000-5000 RBM/months (48.76%), had health insurance (99.50%), had gastrointestinal symptom (50.75%), did not experience irAEs (89.80%), received one line of immunotherapy (54.23%), and were not familiar with the name of their immunotherapy (65.17%) (**Table S1**).

Knowledge

The mean knowledge score was 6.60±3.51 (/10, 66.00%)(**Table 1**). No significant differences were observed according to the characteristics of the participants. The knowledge item with the lowest score was K1 (50.75%; "Adverse reactions can occur during immunotherapy, but they are normal occurrences that do not require excessive attention."), while the item with the highest score was K9 (72.39%; "Prompt identification and timely reporting of symptoms of malnutrition and immune-related events to healthcare professionals are not only beneficial for immunotherapy and ameliorating immune-related adverse symptoms and nutritional status but also increase the likelihood of continuing immunotherapy.") (**Table S2**).

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Attitude

The mean attitude score was 41.26±5.06 (/50, 82.52%) (**Table 1**). Higher attitude scores were observed in urban dwellers (41.99±5.19 vs. 40.68±4.89, P=0.010), those not living alone (41.44±5.07 vs. 39.72±4.76, P=0.035), and those with higher income (>20,000 CNY/month: 43.50±3.46; <2000 CNY/month: 39.66±5.88; P=0.005) (**Table S1**). The attitude item with the lowest score was A1 (64.52%; "I consider nutritional support to be highly significant throughout the entire course of immunotherapy."), while the item with the highest score was A10 (93.28%; "I believe that maintaining a positive mindset and quality sleep are important during immunotherapy.") (**Table S2**).

Practice

The mean practice score was 30.74±4.20(/40, 76.85%) (**Table 1**). No significant differences were observed according to the characteristics of the participants. The practice item with the lowest score was P6 (39.53%; "If required, I am prepared to receive enteral feeding through nasogastric/nasoenteric tubes."), while the item with the highest score was P1 (86.07%; "I am capable of cooperating with medical personnel for comprehensive treatment monitoring and follow-up.") (**Table S2**).

Lifestyle

The mean lifestyle score was 42.37±6.04 (/55, 77.04%) (**Table 1**). Higher lifestyle scores were observed in females (43.43±5.36 vs. 41.95±6.24, P=0.027), widows (widows: 45.20±5.55; married: 42.49±5.99; unmarried: 39.09±6.45; P=0.031), and with more than one immunotherapy line (43.46±6.06 vs. 41.45±5.88, P=0.001) (**Table S1**). The lifestyle item with the lowest score was L11 (30.35%; "Citrus fruits (grapefruit, pomelo, honey pomelo, etc.).)"),

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while the item with the highest score was L2 (83.84%; "Alcohol consumption") (**Table S2**).

Correlations

The knowledge scores were correlated to the attitude scores (r=0.105, P=0.035). The attitude scores were correlated to the practice (r=0.460, P<0.001) and lifestyle (r=0.486, P<0.001) scores. The practice scores were correlated to the lifestyle scores (r=0.269, P<0.001) (**Table 2**).

Structural equation modeling

As shown in **Table 3** and **Figure 2**, attitude positively influenced practice (β=0.381, P<0.001) and lifestyle (β=1.928, P<0.001). The place of residence positively influenced attitude (β=1.242, P=0.013). The residential status positively influenced attitude (β=1.619, P=0.044). The number of immunotherapy lines positively influenced lifestyle (β=1.928, P<0.001). Gender positively influenced lifestyle (β=1.431, P=0.023). Table S1 shows that the SEM analysis had a good fit.

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DISCUSSION

Very few data are available in the literature concerning the KAP of patients with LC toward irAEs and lifestyle habits. The present study revealed moderate KAP toward lifestyle habits and irAEs. A systematic review showed that the eating habits of Chinese patients with cancer and chemotherapy were poor [22]; although no data were available for immunotherapy, it supported the present study. Another study showed that Chinese patients with cancer had a basic understanding of irAEs [23], but the study was not specific to LC and did not evaluate attitudes and practices. Intrinsic differences between patients with LC and those with other types of cancer could explain the differences.

Symptoms of advanced HCC affect quality of life, and the treatment of HCC can restore quality of life [26]. Thus, immunotherapy can potentially reverse the HCC-related symptoms and help improve quality of life. Nevertheless, the side effects of immunotherapy need to be factored in, as it can affect empowerment and self-management. Self-management is a critical component of cancer care. Indeed, the patients must remain aware of the signs and symptoms that should prompt consultation. At home, they are also responsible for maintaining lifestyle habits that could improve their prognosis or, at least, not worsen it [19]. A previous systematic review revealed poor KAP toward good eating habits among Chinese patients on chemotherapy for various types of cancers [22]. That previous study supports the present one, which showed poor lifestyle scores for several foods in patients with LC and immunotherapy. Increasing evidence indicates that a healthy diet can improve the outcomes of immunotherapy [27, 28]. Although the knowledge about which food can improve immunotherapy outcomes is lacking, it appears, for

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now, that a healthy diet, in general, improves the response to immunotherapy. Hence, good lifestyle habits should be promoted among patients on immunotherapy.

In this study, many participants were still regularly smoking, drinking alcohol, and had unhealthy dietary habits. Of importance, most participants did not take probiotics and were not eating citrus fruits. Probiotics are important in the management of gastrointestinal side effects of cancer treatments through maintaining a stable microbiota and preventing harmful bacteria from becoming predominant [29]. Citrus fruits are rich in vitamins and antioxidants and play roles in maintaining the integrity of immunological barriers and in supporting immune cells [30-32]. On the other hand, citrus fruits are rich in active ingredients, such as furacoumarin, naringin, and bergamot, that can inhibit the activity of metabolic enzymes (mainly UGT1A3 or UGT2B7) [33]. UGT1A3 is involved in the metabolic elimination of many aromatic hydrocarbons, amines, non-steroidal anti-inflammatory drugs, and statins [34]. UGT2B7 participates in drug glucuronidation reactions, including anticancer drugs, gemcitabine, etc. It can also bind many endogenous substances, such as bile acids, androgens, and estrogen [35]. When certain drugs metabolized by UGT1A3 or UGT2B7 enzymes are taken together with pomelo, it may affect the metabolism and excretion of the drugs, leading to increased adverse reactions. Therefore, in the future, intervention research on the impact of fruits such as grapefruit on medication can be strengthened. Branched-chain amino acids can also help improve the symptoms of LC and treatment complications [36]. Therefore, the healthy lifestyle of the study population was not ideal. Especially, smoking and alcohol consumption are independent risk factors for confirmed liver cancer [2, 3, 5, 6] because of their impact on inflammation, cancer progression, and health in general [37-39], and they affect liver function and immunotherapy efficacy [40]. Still, the high rates

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of smoking and drinking could reflect a poor knowledge of the risk factors for poor outcomes in LC but could also reflect patients wishing to maintain activities they associate with pleasure in the face of a disease with a poor prognosis. Women often have a higher healthcare literacy and higher health awareness than men [41-44]. In addition, family support plays an undeniable advantage in the management of cancer patients, helping them with daily tasks, cooking for them, caring for them, and remembering instructions and advice that the patients might forget due to the emotional charge associated with cancer-related events [45, 46]. The present study was not designed to assess that point. Nevertheless, efforts should be taken to teach patients with LC the proper lifestyle habits necessary to optimize prognosis.

Recent data also suggests that probiotics should be encouraged to prevent irAEs [47]. Indeed, regulation of the gut microbiome appears crucial in preventing irAEs [48]. The gut microbiota was also shown to modulate the response to immunotherapy, with distinct responses to immunotherapy according to the composition of the microbiome [49]. Gut dysbiosis can even lead to resistance to immunotherapy [49]. Hence, administering specific bacteria could be used to improve the response to immunotherapy and prevent irAEs [50].

IrAEs can be simply bothersome but also life-threatening [13-15]. Still, irAEs appear to be related to the efficacy of immunotherapy [51, 52]. Therefore, patients have to maintain a good attitude and practice toward the management of irAEs, as well as know when to consult and how to deal with them. A study showed that Chinese patients with cancer had a basic understanding of irAEs [23] but that there were several gaps in knowledge, as observed in the present study. In particular, the patients should be educated on the nature of irAEs and their manifestations.

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People living in urban areas and not living alone often enjoy a higher socioeconomic status, and it is well-known that higher socioeconomic status is associated with better health literacy [53]. In the present study, the knowledge scores were only correlated to the attitude scores, while the attitude scores were correlated to the practice and lifestyle scores. Although knowledge did not influence attitude in the SEM, improving knowledge could translate into attitude, practice, and lifestyle improvements. Healthcare providers are a primary source of information for the patients, but previous studies revealed relatively poor KAP toward cancer nutritional support [24, 54] and irAEs [55] among healthcare providers. Patients with LC and immunotherapy should be encouraged to perform physical activity, which is akin to prehabilitation for liver resection to improve tolerance to treatment [56]. Future studies should examine the KAP toward irAEs and nutritional support among healthcare providers. Educational interventions should be designed for the patients and maybe also for the healthcare providers. Especially the nature and severity of the irAEs, the risk of malnutrition during immunotherapy, the role of the liver in human physiology, the importance of nutritional screening in LC, the role of nutritional support in LC, and the importance of promptly identifying and reacting to malnutrition and irAEs. Such education should be comprehensive and involve several healthcare providers working as a team for the management of patients with LC. It should be provided as soon as possible in the patient trajectory, with monitoring and reminders when necessary.

This study specifically examined the knowledge, attitude, practice (KAP), and lifestyle of patients with liver cancer (LC) undergoing immunotherapy, focusing on immune-related adverse events (irAEs) and nutritional support, which fills a significant gap in the literature. The study's comprehensive assessment of multiple aspects of patient care, including KAP and

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lifestyle, provides a holistic view of how patients manage their condition and treatment. With a relatively large sample size of 402 participants, the study enhances the statistical power and generalizability of the findings. We employed rigorous statistical methods, including regression analysis, to identify significant predictors of KAP and lifestyle, ensuring the reliability and validity of the results. The findings have practical implications for healthcare providers, policymakers, and researchers, as they can inform the development of targeted interventions to improve patient outcomes and quality of life. Additionally, the study's local context at Haikou People's Hospital provides valuable, context-specific insights that can guide tailored interventions and policies relevant to the specific population. Nevertheless, this study has limitations. It was a single-center study. Even though 402 patients with LC and immunotherapy represent a relatively large sample size, it is still too small to derive correlations and recommendations regarding the KAP-L in patients with LC. The questionnaire was designed by the investigators. It was reviewed by 15 experts in LC management, which could introduce bias from the healthcare perspective. In addition, some questions contained medical jargon that could introduce the Hawthorne effect. Future surveys should also be reviewed by nursing experts, laypeople, and a variety of professionals. The study was cross-sectional in design, preventing the analysis of causality. Still, a SEM analysis was performed to infer causality, but it must be remembered that the causality is purely statistical and remains to be confirmed. In addition, the data represent a single point in time. Still, the results could serve as a historical baseline to evaluate the effect of future interventions. Future studies should examine the impact of health education on the KAP-L of patients with LC and immunotherapy. The questionnaire was designed by local investigators based on local practice, policies, and

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reality, limiting generalizability. Finally, all KAP studies are at risk of the social desirability bias, in which some participants might be tempted to answer what they know they should do instead of what they are actually doing [57, 58]. The Hawthorn effect (a type of reactive human behavior in which people change their behavior when they feel observed) could also have introduced bias.

Expanding the scope of the survey and including hospitals in different regions and levels is recommended to validate the results of this study. Clinical intervention research should be performed on the knowledge, attitude, behavior, and lifestyle level of nutrition and irAEs in patients with LC and immunotherapy and evaluate the effectiveness of the intervention. The impact of good sleep and moderate exercise (as good lifestyles) in relation to nutrition and irAEs should also be examined.

In conclusion, patients with LC and immunotherapy had moderate KAP toward irAEs and nutritional support. They also displayed moderate lifestyle scores. Urban residents, people not living alone, females, and those having received two or more immunotherapy treatments positively influence attitude, while attitude positively influences practice and lifestyle.

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Declarations

Ethics approval and consent to participate

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved by the Institutional Review Board of Haikou People's Hospital (2022-Ethical Review-231). All participants signed the informed consent form before completing the survey.

The Patient and Public Involvement statement

Patients with LC were involved as participants. The patients with LC or the public were not involved in the study design or its completion.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this article and it's supplementary materials.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

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Wen Wen and Fangqing Gao carried out the studies, participated in collecting data, and drafted the manuscript. Yingshuang Chen and Liling Tong performed the statistical analysis and participated in its design. Wen Wen and Yingshuang Chen participated in the acquisition, analysis, or interpretation of data and drafted the manuscript. All authors read and approved the final manuscript. Fangqing Gao acted as guarantor.

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None.

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Table 1. KAP scores.

Dimension	N=402		
	Range, points	Mean score, mean ± SD	Proportion, %
Knowledge	0~10	6.60±3.51	66.00%
Attitude	10~50	41.26±5.06	82.52%
Practice	8~40	30.74±4.20	76.85%
Lifestyle	11~55	42.37±6.04	77.04%

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Table 2. Pearson correlation analysis.

	Knowledge	Attitude	Practice	Lifestyle
Knowledge	1			
Attitude	0.105 (P=**0.035**)	1		
Practice	0.018 (P=0.253)	0.460 (P<**0.001**)	1	
Lifestyle	-0.016 (P=0.755)	0.486 (P<**0.001**)	0.269 (P<**0.001**)	1

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Table 3. SEM, including lifestyle

			β	P
Attitude	<---	Gender	-0.457	0.407
Attitude	<---	Residential area	1.242	**0.013**
Attitude	<---	Knowledge	0.128	0.069
Attitude	<---	Residential status	1.619	**0.044**
Lifestyle	<---	Knowledge	-0.048	0.565
Practice	<---	Knowledge	0.011	0.841
Lifestyle	<---	Attitude	0.222	**<0.001**
Practice	<---	Attitude	0.381	**<0.001**
Lifestyle	<---	Number of immunotherapy	1.928	**<0.001**
Lifestyle	<---	Gender	1.431	**0.023**

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Figure legend

Figure 1. Questionnaire flowchart.

Figure 2. Structural equation modeling (SEM).

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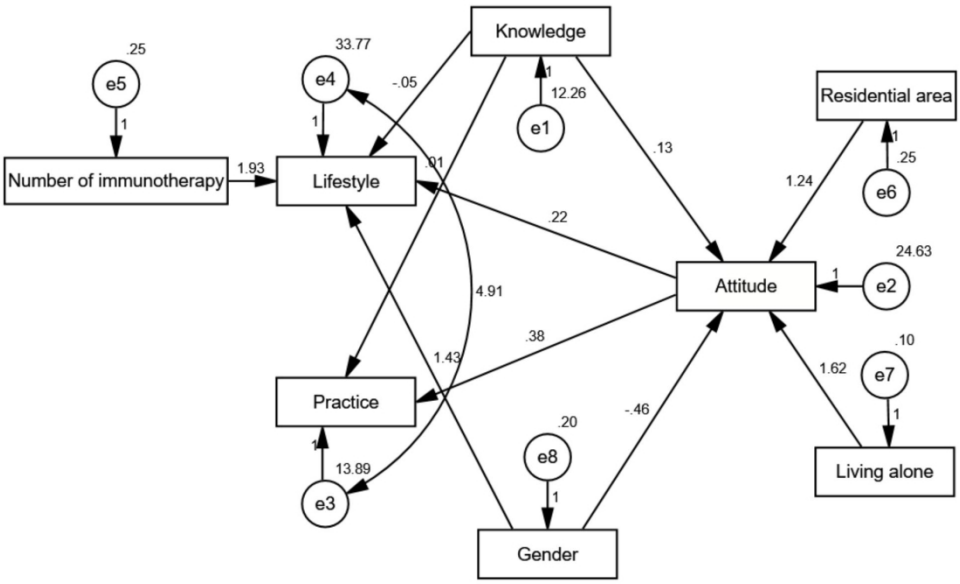

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Table S1 Characteristics of the participants.

Variables	n (%)	Knowledge score		Attitude score		Practice score		Lifestyle score	
		Mean ± SD	P	Mean ± SD	P	Mean ± SD	P	Mean ± SD	P
Gender			0.385		0.694		0.384		**0.027**
Male	289 (71.89)	6.69±3.39		41.32±4.63		30.86±3.92		41.95±6.24	
Female	113 (28.11)	6.35±3.79		41.10±6.05		30.45±4.75		43.43±5.36	
Age (years)	56.84±11.93								
Body mass index (kg/m^2)			0.550		0.687		0.406		0.570
<18.5	55 (13.68)	6.16±3.68		41.69±4.57		30.05±4.17		43.07±6.99	
18.5-23.9	245 (60.95)	6.61±3.44		41.09±5.13		30.90±4.37		42.36±5.78	
≥24	102 (25.37)	6.80±3.59		41.41±5.16		30.75±3.78		42.00±6.12	
Residential area			0.061		**0.010**		0.347		0.274
Rural	225 (55.97)	6.31±3.53		40.68±4.89		30.57±4.16		42.08±5.51	

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City	177 (44.03)	6.97±3.46		41.99±5.19		30.97±4.25		42.74±6.65	
Residential status			0.560		**0.035**		0.084		0.136
Living alone	43 (10.70)	6.30±3.56		39.72±4.76		29.70±4.61		41.07±6.00	
Living with others	359 (89.30)	6.63±3.50		41.44±5.07		30.87±4.11		42.52±6.03	
Marital Status			0.918		0.148		0.153		**0.031**
Unmarried	22 (5.47)	6.14±3.76		40.36±4.75		29.91±4.91		39.09±6.45	
Married	362 (90.05)	6.64±3.50		41.32±5.09		30.75±4.13		42.49±5.99	
Divorced	8 (1.99)	6.25±3.49		38.25±5.47		29.50±5.53		42.38±5.15	
Widowed	10 (2.49)	6.50±3.81		43.40±3.53		33.30±3.65		45.20±5.55	
Education			0.426		0.449		0.310		0.233
Junior high school and below	79 (19.65)	6.56±3.60		40.96±5.89		30.01±4.85		42.67±5.95	

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High school/technical secondary school	137 (34.08)	6.33±3.60	41.72±4.61	31.25±3.66	42.81±5.69	
College	112 (27.86)	6.92±3.36	40.72±5.05	30.71±3.80	42.12±6.04	
Bachelor's degree	68 (16.92)	6.82±3.46	41.35±5.03	30.56±4.28	41.99±6.39	
Postgraduate and above	6 (1.49)	4.67±3.27	43.33±3.33	31.67±2.25	37.33±9.61	
Average monthly income, RMB		0.500	**0.005**	0.276		0.094
<2000	86 (21.39)	6.13±3.70	39.66±5.88	30.05±4.86	42.19±5.97	
2000-5000	196 (48.76)	6.81±3.39	41.87±4.58	31.04±3.99	42.64±5.93	
5001-10,000	83 (20.65)	6.52±3.64	40.90±5.39	30.69±4.20	42.98±5.89	
10,001-20,000	23 (5.72)	6.30±3.50	41.87±3.86	30.22±3.69	39.26±6.88	
>20,000	14 (3.48)	7.50±3.16	43.50±3.46	32.07±3.25	41.21±6.55	
Types of health insurance						

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Urban Employee Basic Medical Insurance	134 (33.33)	6.94±3.37	41.70±4.90	30.93±4.11	42.82±5.96
New Rural Cooperative Medical Insurance	207 (51.49)	6.24±3.57	40.87±5.16	30.76±4.0	41.91±6.08
Urban Resident Basic Medical Insurance	53 (13.18)	7.11±3.46	42.06±4.72	30.75±3.2	43.66±5.73
Commercial Insurance	6 (1.49)	6.33±4.56	40.33±6.25	29.67±5.75	38.17±7.11
Self-payment	2 (0.50)	8.00±1.41	33.00±1.41	20.00±8.49	38.00±4.24
GI Symptoms					
Loss of appetite	113 (28.11)	6.09±3.45	41.15±4.33	30.44±4.65	40.89±6.72
Nausea and vomiting	54 (13.43)	6.80±3.20	40.89±4.90	29.81±5.12	39.52±7.87
Constipation	53 (13.18)	6.25±3.59	40.72±5.26	29.70±4.22	40.13±6.30
Diarrhea	34 (8.46)	7.41±2.84	40.88±3.67	30.00±4.71	41.15±6.63

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Oral ulcers	18 (4.48)	6.94±3.46	41.89±4.17	31.56±4.08	39.89±8.63	
Dry Mouth	45 (11.19)	6.11±3.49	41.07±4.86	30.24±4.47	41.91±6.78	
Altered taste perception	27 (6.72)	5.37±3.56	40.44±4.97	30.81±5.0	41.59±8.02	
Altered smell perception	8 (1.99)	4.75±3.45	41.13±3.72	29.13±6.2	41.00±8.64	
Swallowing Difficulties	13 (3.23)	6.38±3.64	40.08±6.49	29.31±5.2	41.38±7.09	
Feeling of fullness	48 (11.94)	5.65±3.44	41.65±4.35	31.40±4.35	43.33±6.57	
Pain	66 (16.42)	6.39±3.71	42.29±4.04	30.56±3.89	43.06±6.00	
None	198 (49.25)	6.80±3.52	40.98±5.45	30.88±4.07	43.28±5.18	
IrAEs		0.527	0.276	0.122	0.954	
Yes	41 (10.20)	6.27±3.78	42.07±4.42	29.78±4.18	42.32±6.60	
No	361 (89.80)	6.63±3.48	41.16±5.13	30.85±4.20	42.37±5.98	
Symptoms you experienced						

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Capillary Proliferation Syndrome	9 (2.24)	4.89±3.95	41.11±3.37	31.00±2.55	42.78±7.66
Other skin reactions (rash, papules, itching, vitiligo, etc.)	18 (4.48)	6.89±3.41	40.94±4.32	30.83±3.76	41.67±7.04
Gastrointestinal reactions (diarrhea, colitis, abdominal pain, nausea, vomiting, etc.)	16 (3.98)	6.75±3.24	41.75±4.30	30.00±4.76	40.25±6.22
Hepatic reactions	7 (1.74)	5.14±3.39	43.29±3.99	30.43±3.99	43.86±7.24
Endocrine reactions (hypothyroidism,	2 (0.50)	9.50±0.71	40.00±8.49	26.00±8.49	35.00±11.31

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hyperthyroidism, adrenal insufficiency, etc.)						
Pneumonia	1 (0.25)	9.00	40	29	30	
Cardiac reactions	0	0	0	0	0	
Renal toxicity (nephritis)	0	0	0	0	0	
Muscle or joint pain, muscle weakness	13 (3.23)	5.85±3.74	41.92±4.82	30.08±5.36	44.92±2.99	
Other	4 (1.00)	7.50±4.36	39.75±5.06	27.75±5.44	41.00±9.56	
Number of immunotherapy medication		0.736	0.529	0.620		**0.001**
1	218 (54.23)	6.65±3.50	41.11±5.04	30.84±3.71	41.45±5.88	
>1	184 (45.77)	6.53±3.52	41.43±5.09	30.63±4.73	43.46±6.06	

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Familiar with the specific names of the immunotherapy drugs		0.990	0.724	0.806	0.884	
Yes	140 (34.83)	6.60±3.62	41.38±5.03	30.81±4.38	42.43±6.71	
No	262 (65.17)	6.60±3.45	41.19±5.09	30.71±4.21	42.34±5.66	

RMB: renminbi, the official currency in China.

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Table S2. Knowledge, attitudes, and practices

Statement	Accuracy, n (%)
K1. Adverse reactions can occur during immunotherapy, but they are normal occurrences that do not require excessive attention.	204 (50.75)
K2. Skin toxicities (rashes, dermatitis, capillary proliferation), endocrine toxicities (hypothyroidism, hyperthyroidism, adrenal insufficiency), hepatic toxicities, cardiac toxicities, gastrointestinal toxicities (abdominal pain, diarrhea), pneumonia, renal toxicity (immune nephritis leading to proteinuria), etc., might emerge during the immunotherapy process.	247 (61.44)
K3. The liver is engaged in digestion, synthesis, and metabolic processes of various nutrients; impaired liver function significantly elevates the incidence of malnutrition in liver cancer patients.	245 (60.95)
K4. Tumor progression and immunotherapy can exacerbate malnutrition due to deteriorating liver function, which, in turn, affects the prognosis of liver cancer patients, leading to a vicious cycle.	231 (57.46)

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K5. Liver cancer patients undergoing treatment should undergo nutritional screening and assessment, followed by personalized nutritional interventions based on their nutritional status.	281 (69.90)
K6. Nutritional risk screening and assessment include disease status, dietary surveys, weight changes, anthropometric measurements, laboratory examinations, etc.	290 (72.14)
K7. Nutritional support encompasses dietary guidance, oral supplements, enteral nutrition, and parenteral nutrition.	283 (70.40)
K8. Appropriate and effective nutritional interventions can optimize the intake structure and quantity of nutrients, improve nutritional status and liver function, enhance tolerance to surgery or other treatments, enhance immune conditions, reduce complications during treatment, elevate quality of life, and extend survival time.	290 (72.14)
K9. Prompt identification and timely reporting of symptoms of malnutrition and immune-related events to healthcare professionals are not only beneficial for immunotherapy and ameliorating immune-related adverse symptoms and nutritional status but also increase the likelihood of continuing immunotherapy.	291 (72.39)

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K10. Liver cancer patients receiving immunotherapy should be managed comprehensively throughout the cycle, from screening and assessment to diagnosis, supportive treatment, monitoring, and follow-up, focusing on nutritional and adverse event management. 290 (72.14)

Attitude	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
A1. I consider nutritional support highly significant throughout the entire course of immunotherapy.	230 (27.21)	150 (37.31)	16 (3.98)	2 (0.50)	4 (1.00)
A2. I believe that targeted nutritional interventions can enhance the efficacy of immunotherapy.	196 (48.76)	175 (43.53)	25 (6.22)	2 (0.50)	4 (1.00)
A3. I deem continuous monitoring of adverse immune events to be essential.	208 (51.74)	160 (39.80)	32 (7.96)	0	2 (0.50)
A4. I would be concerned about adverse reactions following immunotherapy.	169 (42.04)	183 (45.52)	36 (8.96)	6 (1.49)	8 (1.99)

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A5. I find it necessary to monitor nutrition-related indicators comprehensively.	188 (46.77)	172 (42.79)	30 (7.46)	6 (1.49)	6 (1.49)
A6. I think consuming high-quality proteins, abundant dietary fiber, and appropriate carbohydrates is crucial.	216 (53.73)	158 (39.30)	23 (5.72)	3 (0.75)	2 (0.50)
A7. I wish to acquire further knowledge about nutritional support through professional channels.	200 (49.75)	163 (40.55)	32 (7.96)	2 (0.50)	5 (1.24)
A8. I desire to gain more insights through professional channels regarding self-management, emergency responses, and precautions for managing adverse events during immunotherapy.	193 (48.01)	175 (43.53)	27 (6.72)	4 (1.00)	3 (0.75)
A9. I am confident in maintaining a relatively favorable nutritional status.	179 (44.53)	165 (41.04)	45 (11.19)	7 (1.74)	6 (1.49)

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A10. I believe that maintaining a positive mindset and quality sleep are important during immunotherapy.	214 (53.23)	161 (40.05)	19 (4.73)	3 (0.75)	5 (1.24)

Practice	**Always**	**Frequently**	**Sometimes**	**Occasionally**	**Never**
P1. I can cooperate with medical personnel for comprehensive treatment monitoring and follow-up.	216 (53.73)	130 (32.34)	43 (10.70)	6 (1.49)	7 (1.74)
P2. I will regularly monitor nutrition-related indicators such as body weight, body mass index, grip strength, albumin, and prognostic nutritional index.	177 (44.03)	140 (34.83)	55 (13.68)	22 (5.47)	8 (1.99)
P3. If a physician recommends it, I will take medication to enhance appetite, digestion, and absorption.	192 (47.76)	132 (32.84)	53 (13.18)	18 (4.48)	7 (1.74)
P4. I will proactively seek relevant knowledge about immunotherapy nutrition and adverse reactions through	172 (42.79)	126 (31.34)	64 (15.92)	27 (6.72)	13 (3.23)

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professional channels such as healthcare providers, health promotion columns, books, and television.					
P5. I will undergo oral nutritional supplementation, including branched-chain amino acids, omega-3 fatty acids, and vitamin D if necessary.	162 (40.30)	118 (29.35)	60 (14.93)	31 (7.71)	31 (7.71)
P6. If required, I am prepared to receive enteral feeding through nasogastric/nasoenteric tubes.	133 (33.08)	38 (6.45)	46 (11.44)	36 (8.96)	149 (37.06)
P7. If necessary, I am open to receiving parenteral nutrition support (intravenous administration).	123 (30.60)	43 (10.70)	52 (12.94)	56 (13.93)	128 (31.84)
P8. I will maintain moderate physical exercise to improve my overall physical condition.	176 (43.78)	122 (30.35)	55 (13.68)	34 (8.46)	15 (3.73)
Lifestyle	**Never**	**Occasionally**	**Sometimes**	**Frequently**	**Always**

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In your daily lifestyle habits, what is your eating frequency for the following types:					
L1. Smoking	272 (67.66)	38 (9.45)	27 (63.72)	35 (8.71)	30 (7.46)
L2. Alcohol consumption	285 (70.90)	52 (12.94)	27 (6.72)	21 (5.22)	17 (4.23)
L3. Cooking methods involving frying, smoking, baking, pickling, etc.	223 (55.47)	100 (24.88)	47 (11.69)	19 (4.73)	13 (3.23)
L4. High-fat, high-salt, spicy foods (such as chili peppers, onions, ginger, raw garlic, and pepper)	212 (52.74)	100 (24.88)	50 (12.44)	27 (6.72)	13 (3.23)
L5. High-quality protein sources (legumes, eggs, meat, fish, shellfish, dairy products, etc.)	22 (5.47)	21 (5.22)	37 (9.20)	224 (55.72)	98 (24.38)
L6. Light and easily digestible foods (egg custard, millet porridge, lotus root powder, Chinese yam)	15 (3.73)	42 (10.45)	61 (15.17)	213 (52.99)	71 (17.66)

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L7. Foods rich in vitamins (fresh vegetables and fruits, such as spinach, cabbage, kiwi, tomatoes, etc.)	8 (1.99)	34 (8.46)	42 (10.45)	217 (53.98)	101 (25.12)
L8. Stimulants like coffee, chocolate, and strong tea	247 (61.44)	70 (17.41)	30 (7.46)	38 (9.45)	17 (4.23)
L9. Probiotics	202 (50.25)	90 (22.39)	51 (12.69)	37 (9.20)	22 (5.47)
L10. Sugary beverages	215 (53.48)	114 (28.36)	45 (11.19)	20 (4.98)	8 (1.99)
L11. Citrus fruits (grapefruit, pomelo, honey pomelo, etc.)	93 (23.13)	112 (27.86)	75 (18.66)	92 (22.89)	30 (7.46)

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Table S3. SEM model fit

Indicators	Reference	Results
CMIN/DF	1-3 Excellent, 3-5 Good	3.10
RMSEA	<0.08 Good	0.039
IFI	>0.8 Good	0.939
TLI	>0.8 Good	0.893
CFI	>0.8 Good	0.935

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Knowledge, attitude, and practice of nutritional support and immune-related adverse events among patients undergoing immunotherapy for liver cancer: a cross-sectional study

Running title: KAP of irAEs and nutrition and lifestyle

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ABSTRACT

Objectives: No study specifically examined the knowledge, attitude, and practice (KAP) toward immune-related adverse events (irAEs) and nutritional support in patients with liver cancer (LC), nor have they explored their lifestyle. This study aimed to address that issue.

Design: This cross-sectional study

Setting: This cross-sectional study was conducted at Haikou People's Hospital from December 2022 to April 2023.

Participants: Patients undergoing immunotherapy for LC.

Primary and secondary outcome measures: The mean knowledge, attitude, practice, and lifestyle scores using an investigator-designed questionnaire completed during immunotherapy.

Results: The study included 402 participants. The mean knowledge, attitude, practice, and lifestyle scores were 6.60±3.51 (/10, 66.00%), 41.26±5.06 (/50, 82.52%), 30.74±4.20 (/40, 76.85%), and 42.37±6.04 (/55, 77.04%). Attitude positively influenced practice (β=0.381, P<0.001) and lifestyle (β=1.928, P<0.001). The place of residence positively influenced attitude (β=1.242, P=0.013). The residential status positively influenced attitude (β=1.619, P=0.044). The number of immunotherapy lines positively influenced lifestyle (β=1.928, P<0.001). Gender positively influenced lifestyle (β=1.431, P=0.023).

Conclusion: Patients with LC and immunotherapy had moderate KAP toward irAEs and nutritional support. They also displayed moderate lifestyle scores. Urban residents, people not living alone, females, and those having received two or more immunotherapy treatments positively influence attitude, while attitude positively influences practice and lifestyle.

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Keywords: knowledge, attitude, practice; liver cancer; nutritional support; immune-related adverse events (ir AEs); lifestyle; cross-sectional study

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Strengths and limitations of this study

1. While a cross-sectional design is useful for capturing data at a single time point, it limits the ability to establish causality or infer temporal relationships between variables.

2. Conducting the study at a single hospital may introduce selection bias and limit the generalizability of the findings to other settings or populations.

3. The reliance on self-reported measures for assessing knowledge, attitude, practice, and lifestyle introduces the potential for response bias and social desirability bias, impacting the accuracy of the results.

4. Although the study identifies certain factors influencing attitudes and lifestyle, there may be other unmeasured confounding variables that could affect the outcomes.

5. While the study assesses KAP toward irAEs, nutritional support, and lifestyle factors, it may not capture all relevant aspects influencing patient care and outcomes during immunotherapy for LC.

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INTRODUCTION

The estimated worldwide incidence of liver cancer in GLOBOCAN 2022 was 865,269 new cases, and mortality was 757,948 [1]. Most liver cancers are hepatocellular carcinoma (HCC) [2 3]. The worldwide age-standardized annual mortality rates of liver cancer are 13.9 per 100,000 in men and 4.9 per 100,000 in women [4]. The most important risk factors for LC are preexisting liver cirrhosis and hepatitis B infection (due to both direct oncogenic effect and risk of cirrhosis) [2 3 5 6]. Risk factors for liver cirrhosis (and therefore risk factors for LC) include hepatitis C infection, alcohol use, and nonalcoholic steatohepatitis [2 3 5 6]. The incidence of LC is higher in men and generally follows the geographical distribution of hepatitis B virus and hepatitis C [2 5 6]. LC management is multidisciplinary and involves surgery (when possible), chemotherapy, targeted therapy, radiotherapy, and immunotherapy [2 5 6]. Despite optimal treatments, the 5-year survival is 22% in the United States of America [7] and 12.1% in China [8], with lower survival in rural China (11.2%) compared with urban areas (14.0%) [9].

Immunotherapy is a recent paradigm in treating cancers, including LC [10-12]. Cancer cells can escape the immune system through the PD-1/PD-L1 pathway [13 14], and drugs targeting PD-1 or PD-L1 have been developed to restore the immunosurveillance of cancer cells and their destruction [10-12]. Still, the PD-1/PD-L1 usually plays roles in immune tolerance and preventing autoimmune reactions [13 14], and inhibiting the PD-1/PD-L1 pathway can lead to immune-related adverse events (irAEs). The pathogenesis of irAEs is still poorly understood, but they involve inflammatory reactions of normal tissues that can be bothersome but also life-threatening [15-17]. Adequate nutrition is also essential in patients with LC to ensure optimal outcomes, and nutritional support can be necessary in patients with inadequate nutrition due, for example, to

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adverse gastrointestinal events (AEs) from therapies [18 19]. Still, the palliation of some symptoms of HCC (e.g., loss of appetite, weakness, fatigue, etc.) using androgens (since most LCs occur in males) can help alleviate the need for nutritional support [20]. The management of irAEs and nutrition involves healthcare providers. It can involve medical interventions (e.g., management of irAEs, enteral nutrition, and hospitalization). Still, they also involve patient self-management in taking proper preventive measures and knowing when to consult, for example, [21]. A knowledge, attitude, and practice (KAP) survey is a tool that provides quantitative and qualitative data about gaps, misconceptions, and misunderstandings that constitute barriers toward the optimal performance of a given task or set of tasks in a specific group of individuals [22 23]. A systematic review showed that the eating habits of Chinese patients with cancer and chemotherapy were poor, but no data are available for immunotherapy specifically [24]. A study showed that Chinese patients with cancer had a basic understanding of irAEs [25], but the study was not specific to LC and did not evaluate attitudes and practices. Compared with other types of cancer, e.g., breast cancer, patients with LC have a poorer prognosis, and there is a male predominance. In addition, the risk factors for LC are different from other cancers, mainly encompassing chronic liver diseases, alcohol drinking, and hepatitis virus infection. Those differences could influence the KAP toward irAEs.

Therefore, this study aimed to investigate the KAP-lifestyle (KAP-L) of patients with LC and immunotherapy patients regarding nutritional support and irAEs. The results can provide crucial information to design educational interventions to improve patient self-management and outcomes.

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MATERIALS AND METHODS

Study design and participants

This cross-sectional study was conducted at Haikou People's Hospital from December 2022 to April 2023 and enrolled patients undergoing immunotherapy for LC. This study was approved by the Institutional Review Board of Haikou People's Hospital (2022-Ethical Review-231). All participants signed the informed consent form before completing the survey.

The inclusion criteria were 1) aged 18-90 years old, 2) pathologically confirmed locally advanced or unresectable liver cancer, and 3) undergoing immunotherapy (any line of treatment). The exclusion criteria were 1) surgical patients, 2) simultaneously suffering from other malignant tumors, 3) before or planned liver transplantation, 4) active autoimmune diseases, 5) ambiguous consciousness, unable to fill out by oneself or with assistance, or 6) withdrawal during the filling process.

Questionnaire and quality control

A self-designed questionnaire consisting of five dimensions was developed based on the relevant literature [15 18 19 24-26]. After the questionnaire design, modifications were made by incorporating insights from 15 experts in nutrition in oncology and medical oncology, removing similar or redundant questions, and refining questions with unclear phrasing. Before the official distribution, a small-scale pilot test (70 participants) was conducted, yielding a Cronbach's α coefficient of 0.853 (0.879 for knowledge, 0.828 for attitudes, and 0.758 for practice), indicating strong internal consistency.

The final questionnaire was in Chinese and encompassed 1) participants' demographic information (including age, gender, residential area, education level and income level, et.al),

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2) knowledge dimension (10 items, with a score of 1 assigned for correct answers and 0 for incorrect or uncertain responses), 3) attitude dimension (10 items, scored using a 5-point Likert scale, ranging from "strongly positive" (5 points) to "strongly negative" (1 point)), 4) practice dimension (eight items, scored using a 5-point Likert scale, ranging from "always" (5 points) to "never" (1 point)), and 5) lifestyle dimension (11 items, also scored using a 5-point Likert scale, ranging from "always" (5 points) to "never" (1 point)). Higher scores correspond to better knowledge, more positive attitudes, and more proactive practices. Scores <60% were considered poor, scores 60%-79% were considered moderate, and scores ≥80% were considered adequate, based on Bloom's criteria [27].

An online questionnaire was developed using the WeChat-based Wenjuanxing platform. A QR code was generated for data collection via WeChat. The participants accessed and completed the questionnaire by scanning the QR code received via WeChat. In order to ensure the quality and completeness of the questionnaires, all items were made mandatory. Incomplete questionnaires were excluded during the quality control process. Therefore, all items were responded to, which would not affect the results.

The research team members reviewed the integrity, internal consistency, and rationality of all collected questionnaires for quality control. A given IP address could be used to submit a questionnaire only once. Questionnaires that took <110 s to complete were excluded. Questionnaires completed using all the same options (e.g., the first option) were deemed invalid. Finally, questionnaires containing impossible values (e.g., impossible age, height, or weight) or logical errors were excluded. The Cronbach's α coefficient for all valid questionnaires was 0.840 (0.913 for knowledge, 0.800 for attitudes, and 0.718 for practice).

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Statistical analysis

The statistical analysis software was SPSS 26.0 (IBM, Armonk, NY, USA). Quantitative variables were described as means ± standard deviations (SD), while group comparisons were conducted using Student's t-test or analysis of variance (ANOVA). Categorical variables were presented as n (%). Pearson's correlation analysis explored the relationships between knowledge, attitude, and practice scores. The study used a structural equation modeling (SEM) analysis to validate various causality hypotheses empirically. These hypotheses encompassed 1) knowledge has a direct impact on attitudes, practices, and lifestyles, 2) attitudes have a direct influence on practices and lifestyles, 3) residential area and status have direct influences on attitudes, 4) gender has a direct influence on attitudes and lifestyles, and 5) assessing the direct association between the number of immunotherapy medication usage and lifestyles. All statistical tests were two-tailed, and P-values <0.05 were considered statistically significant.

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RESULTS

Characteristics of the participants

The study included 419 respondents. After removing the following cases: 1) 1 respondent with abnormal height and weight, 2) 9 respondents answered with logical errors, and 3) 7 respondents with a completion time of less than 110 seconds, a total of 402 valid questionnaires were included in the analysis **(Figure 1)**. The participants were 56.84±11.93 years old. Most participants were male (71.89%), had a BMI of 18.5-23.9 kg/m^2 (60.95%), were living in rural areas (55.97%), were not living alone (89.30%), were married (90.05%), had high school or technical secondary school education (34.08%), had an income of 2000-5000 RBM/months (48.76%), had health insurance (99.50%), had gastrointestinal symptom (50.75%), did not experience irAEs (89.80%), received one line of immunotherapy (54.23%), and were not familiar with the name of their immunotherapy (65.17%) (**Table S1**).

Knowledge

The mean knowledge score was 6.60±3.51 (/10, 66.00%)(**Table 1**). No significant differences were observed according to the characteristics of the participants. The knowledge item with the lowest score was K1 (50.75%; "Adverse reactions can occur during immunotherapy, but they are normal occurrences that do not require excessive attention."), while the item with the highest score was K9 (72.39%; "Prompt identification and timely reporting of symptoms of malnutrition and immune-related events to healthcare professionals are not only beneficial for immunotherapy and ameliorating immune-related adverse symptoms and nutritional status but also increase the likelihood of continuing immunotherapy.") (**Table S2**).

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Attitude

The mean attitude score was 41.26±5.06 (/50, 82.52%) (**Table 1**). Higher attitude scores were observed in urban dwellers (41.99±5.19 vs. 40.68±4.89, P=0.010), those not living alone (41.44±5.07 vs. 39.72±4.76, P=0.035), and those with higher income (>20,000 CNY/month: 43.50±3.46; <2000 CNY/month: 39.66±5.88; P=0.005) (**Table S1**). The attitude item with the lowest score was A1 (64.52%; "I consider nutritional support to be highly significant throughout the entire course of immunotherapy."), while the item with the highest score was A10 (93.28%; "I believe that maintaining a positive mindset and quality sleep are important during immunotherapy.") (**Table S2**).

Practice

The mean practice score was 30.74±4.20(/40, 76.85%) (**Table 1**). No significant differences were observed according to the characteristics of the participants. The practice item with the lowest score was P6 (39.53%; "If required, I am prepared to receive enteral feeding through nasogastric/nasoenteric tubes."), while the item with the highest score was P1 (86.07%; "I am capable of cooperating with medical personnel for comprehensive treatment monitoring and follow-up.") (**Table S2**).

Lifestyle

The mean lifestyle score was 42.37±6.04 (/55, 77.04%) (**Table 1**). Higher lifestyle scores were observed in females (43.43±5.36 vs. 41.95±6.24, P=0.027), widows (widows: 45.20±5.55; married: 42.49±5.99; unmarried: 39.09±6.45; P=0.031), and with more than one immunotherapy line (43.46±6.06 vs. 41.45±5.88, P=0.001) (**Table S1**). The lifestyle item with the lowest score was L11 (30.35%; "Citrus fruits (grapefruit, pomelo, honey pomelo, etc.).)"),

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while the item with the highest score was L2 (83.84%; "Alcohol consumption") (**Table S2**).

Correlations

The knowledge scores were correlated to the attitude scores (r=0.105, P=0.035). The attitude scores were correlated to the practice (r=0.460, P<0.001) and lifestyle (r=0.486, P<0.001) scores. The practice scores were correlated to the lifestyle scores (r=0.269, P<0.001) (**Table 2**).

Structural equation modeling

As shown in **Table 3** and **Figure 2**, attitude positively influenced practice (β=0.381, P<0.001) and lifestyle (β=1.928, P<0.001). The place of residence positively influenced attitude (β=1.242, P=0.013). The residential status positively influenced attitude (β=1.619, P=0.044). The number of immunotherapy lines positively influenced lifestyle (β=1.928, P<0.001). Gender positively influenced lifestyle (β=1.431, P=0.023). Table S1 shows that the SEM analysis had a good fit.

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DISCUSSION

Very few data are available in the literature concerning the KAP of patients with LC toward irAEs and lifestyle habits. The present study revealed moderate KAP toward lifestyle habits and irAEs. A systematic review showed that the eating habits of Chinese patients with cancer and chemotherapy were poor [24]; although no data were available for immunotherapy, it supported the present study. Another study showed that Chinese patients with cancer had a basic understanding of irAEs [25], but the study was not specific to LC and did not evaluate attitudes and practices. Intrinsic differences between patients with LC and those with other types of cancer could explain the differences.

Symptoms of advanced HCC affect quality of life, and the treatment of HCC can restore quality of life [28]. Thus, immunotherapy can potentially reverse the HCC-related symptoms and help improve quality of life. Nevertheless, the side effects of immunotherapy need to be factored in, as it can affect empowerment and self-management. Self-management is a critical component of cancer care. Indeed, the patients must remain aware of the signs and symptoms that should prompt consultation. At home, they are also responsible for maintaining lifestyle habits that could improve their prognosis or, at least, not worsen it [21]. A previous systematic review revealed poor KAP toward good eating habits among Chinese patients on chemotherapy for various types of cancers [24]. That previous study supports the present one, which showed poor lifestyle scores for several foods in patients with LC and immunotherapy. Increasing evidence indicates that a healthy diet can improve the outcomes of immunotherapy [29 30]. Although the knowledge about which food can improve immunotherapy outcomes is lacking, it appears, for

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now, that a healthy diet, in general, improves the response to immunotherapy. Hence, good lifestyle habits should be promoted among patients on immunotherapy.

In this study, many participants with LC were still regularly smoking, drinking alcohol, and had unhealthy dietary habits, all of which are associated with LC development and progression [31-34]. Of importance, most participants did not take probiotics and were not eating citrus fruits. Probiotics are important in the management of gastrointestinal side effects of cancer treatments through maintaining a stable microbiota and preventing harmful bacteria from becoming predominant [35]. Citrus fruits are rich in vitamins and antioxidants and play roles in maintaining the integrity of immunological barriers and in supporting immune cells [36-38]. On the other hand, citrus fruits are rich in active ingredients, such as furacoumarin, naringin, and bergamot, that can inhibit the activity of metabolic enzymes (mainly UGT1A3 or UGT2B7) [39]. UGT1A3 is involved in the metabolic elimination of many aromatic hydrocarbons, amines, non-steroidal anti-inflammatory drugs, and statins [40]. UGT2B7 participates in drug glucuronidation reactions, including anticancer drugs, gemcitabine, etc. It can also bind many endogenous substances, such as bile acids, androgens, and estrogen [41]. When certain drugs metabolized by UGT1A3 or UGT2B7 enzymes are taken together with pomelo, it may affect the metabolism and excretion of the drugs, leading to increased adverse reactions. Therefore, in the future, intervention research on the impact of fruits such as grapefruit on medication can be strengthened. Branched-chain amino acids can also help improve the symptoms of LC and treatment complications [42]. Therefore, the lifestyle of the study population was not ideal in terms of LC prognosis [31-34]. Especially, smoking and alcohol consumption are independent risk factors for confirmed liver cancer [2 3 5 6] because of their impact on inflammation, cancer

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progression, and health in general [43-45], and they affect liver function and immunotherapy efficacy [46]. Still, the high rates of smoking and drinking could reflect a poor knowledge of the risk factors for poor outcomes in LC but could also reflect patients wishing to maintain activities they associate with pleasure in the face of a disease with a poor prognosis. Women often have a higher healthcare literacy and higher health awareness than men [47-50]. In addition, family support plays an undeniable advantage in the management of cancer patients, helping them with daily tasks, cooking for them, caring for them, and remembering instructions and advice that the patients might forget due to the emotional charge associated with cancer-related events [51 52]. The present study was not designed to assess that point. Nevertheless, efforts should be taken to teach patients with LC the proper lifestyle habits necessary to optimize prognosis.

Recent data also suggests that probiotics should be encouraged to prevent irAEs [53]. Indeed, regulation of the gut microbiome appears crucial in preventing irAEs [54]. The gut microbiota was also shown to modulate the response to immunotherapy, with distinct responses to immunotherapy according to the composition of the microbiome [55]. Gut dysbiosis can even lead to resistance to immunotherapy [55]. Hence, administering specific bacteria could be used to improve the response to immunotherapy and prevent irAEs [56].

IrAEs can be simply bothersome but also life-threatening [15-17]. Still, irAEs appear to be related to the efficacy of immunotherapy [57 58]. Therefore, patients have to maintain a good attitude and practice toward the management of irAEs, as well as know when to consult and how to deal with them. A study showed that Chinese patients with cancer had a basic understanding of irAEs [25] but that there were several gaps in knowledge, as observed in the present study. In particular, the patients should be educated on the nature of irAEs and their manifestations.

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People living in urban areas and not living alone often enjoy a higher socioeconomic status, and it is well-known that higher socioeconomic status is associated with better health literacy [59]. In the present study, the knowledge scores were only correlated to the attitude scores, while the attitude scores were correlated to the practice and lifestyle scores. Although knowledge did not influence attitude in the SEM, improving knowledge could translate into attitude, practice, and lifestyle improvements. Healthcare providers are a primary source of information for the patients, but previous studies revealed relatively poor KAP toward cancer nutritional support [26 60] and irAEs [61] among healthcare providers. Patients with LC and immunotherapy should be encouraged to perform physical activity, which is akin to prehabilitation for liver resection to improve tolerance to treatment [62]. It should help reduce the side effects or increase the patient's tolerance to them, hence improving patient outcomes. Still, the most optimal regimens remain to be determined. Future studies should examine the KAP toward irAEs and nutritional support among healthcare providers. Educational interventions should be designed for the patients and maybe also for the healthcare providers. Especially the nature and severity of the irAEs, the risk of malnutrition during immunotherapy, the role of the liver in human physiology, the importance of nutritional screening in LC, the role of nutritional support in LC, and the importance of promptly identifying and reacting to malnutrition and irAEs. Such education should be comprehensive and involve several healthcare providers working as a team for the management of patients with LC. It should be provided as soon as possible in the patient trajectory, with monitoring and reminders when necessary.

This study specifically examined the knowledge, attitude, practice (KAP), and lifestyle of patients with liver cancer (LC) undergoing immunotherapy, focusing on immune-related

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adverse events (irAEs) and nutritional support, which fills a significant gap in the literature. The study's comprehensive assessment of multiple aspects of patient care, including KAP and lifestyle, provides a holistic view of how patients manage their condition and treatment. With a relatively large sample size of 402 participants, the study enhances the statistical power and generalizability of the findings. We employed rigorous statistical methods, including regression analysis, to identify significant predictors of KAP and lifestyle, ensuring the reliability and validity of the results. The findings have practical implications for healthcare providers, policymakers, and researchers, as they can inform the development of targeted interventions to improve patient outcomes and quality of life. Additionally, the study's local context at Haikou People's Hospital provides valuable, context-specific insights that can guide tailored interventions and policies relevant to the specific population. Nevertheless, this study has limitations. It was a single-center study. Even though 402 patients with LC and immunotherapy represent a relatively large sample size, it is still too small to derive correlations and recommendations regarding the KAP-L in patients with LC. The questionnaire was designed by the investigators. It was reviewed by 15 experts in LC management, which could introduce bias from the healthcare perspective. In addition, some questions contained medical jargon that could introduce the Hawthorne effect. Future surveys should also be reviewed by nursing experts, laypeople, and a variety of professionals. The study was cross-sectional in design, preventing the analysis of causality. Still, a SEM analysis was performed to infer causality, but it must be remembered that the causality is purely statistical and remains to be confirmed. In addition, the data represent a single point in time. Still, the results could serve as a historical baseline to evaluate the effect of future interventions. Future studies should

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examine the impact of health education on the KAP-L of patients with LC and immunotherapy. The questionnaire was designed by local investigators based on local practice, policies, and reality, limiting generalizability. Finally, all KAP studies are at risk of the social desirability bias, in which some participants might be tempted to answer what they know they should do instead of what they are actually doing [63 64]. The Hawthorn effect (a type of reactive human behavior in which people change their behavior when they feel observed) could also have introduced bias.

Expanding the scope of the survey and including hospitals in different regions and levels is recommended to validate the results of this study. Clinical intervention research should be performed on the knowledge, attitude, behavior, and lifestyle level of nutrition and irAEs in patients with LC and immunotherapy and evaluate the effectiveness of the intervention. The impact of good sleep and moderate exercise (as good lifestyles) in relation to nutrition and irAEs should also be examined.

In conclusion, patients with LC and immunotherapy had moderate KAP toward irAEs and nutritional support. They also displayed moderate lifestyle scores. Urban residents, people not living alone, females, and those having received two or more immunotherapy treatments positively influence attitude, while attitude positively influences practice and lifestyle.

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Declarations

Ethics approval and consent to participate

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved by the Institutional Review Board of Haikou People's Hospital (2022-Ethical Review-231). All participants signed the informed consent form before completing the survey.

The Patient and Public Involvement statement

Patients with LC were involved as participants. The patients with LC or the public were not involved in the study design or its completion.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this article and it's supplementary materials.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

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Wen Wen and Fangqing Gao carried out the studies, participated in collecting data, and drafted the manuscript. Yingshuang Chen and Liling Tong performed the statistical analysis and participated in its design. Wen Wen and Yingshuang Chen participated in the acquisition, analysis, or interpretation of data and drafted the manuscript. All authors read and approved the final manuscript. Fangqing Gao acted as guarantor.

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Table 1. KAP scores.

Dimension	N=402		
	Range, points	Mean score, mean ± SD	Proportion, %
Knowledge	0~10	6.60±3.51	66.00%
Attitude	10~50	41.26±5.06	82.52%
Practice	8~40	30.74±4.20	76.85%
Lifestyle	11~55	42.37±6.04	77.04%

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Table 2. Pearson correlation analysis.

	Knowledge	Attitude	Practice	Lifestyle
Knowledge	1			
Attitude	0.105 (P=**0.035**)	1		
Practice	0.018 (P=0.253)	0.460 (P<**0.001**)	1	
Lifestyle	-0.016 (P=0.755)	0.486 (P<**0.001**)	0.269 (P<**0.001**)	1

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Table 3. SEM, including lifestyle

			β	P
Attitude	<---	Gender	-0.457	0.407
Attitude	<---	Residential area	1.242	**0.013**
Attitude	<---	Knowledge	0.128	0.069
Attitude	<---	Residential status	1.619	**0.044**
Lifestyle	<---	Knowledge	-0.048	0.565
Practice	<---	Knowledge	0.011	0.841
Lifestyle	<---	Attitude	0.222	**<0.001**
Practice	<---	Attitude	0.381	**<0.001**
Lifestyle	<---	Number of immunotherapy	1.928	**<0.001**
Lifestyle	<---	Gender	1.431	**0.023**

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Figure legend

Figure 1. Questionnaire flowchart.

Figure 2. Structural equation modeling (SEM).

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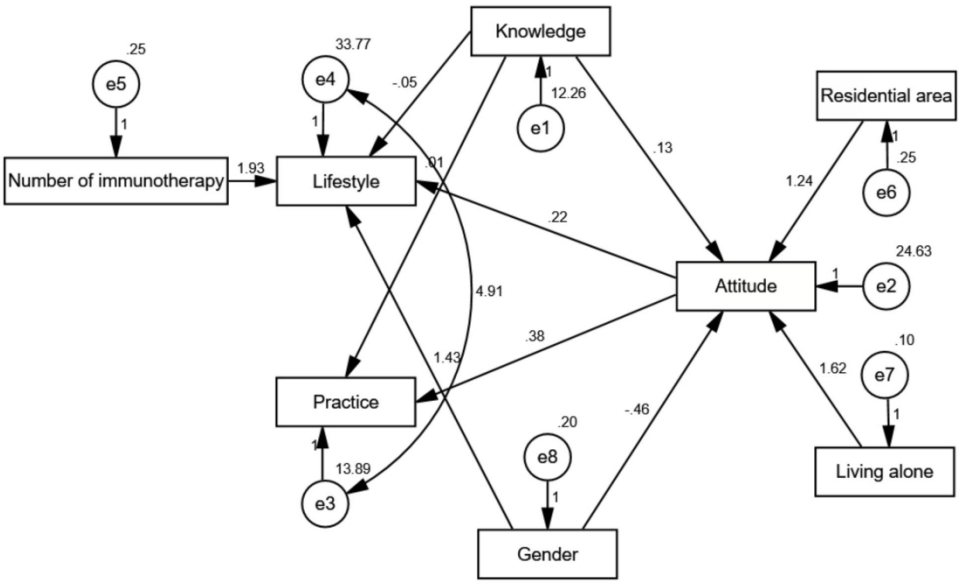

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Table S1 Characteristics of the participants.

Variables	n (%)	Knowledge score		Attitude score		Practice score		Lifestyle score	
		Mean ± SD	P	Mean ± SD	P	Mean ± SD	P	Mean ± SD	P
Gender			0.385		0.694		0.384		**0.027**
Male	289 (71.89)	6.69±3.39		41.32±4.63		30.86±3.92		41.95±6.24	
Female	113 (28.11)	6.35±3.79		41.10±6.05		30.45±4.75		43.43±5.36	
Age (years)	56.84±11.93								
Body mass index (kg/m^2)			0.550		0.687		0.406		0.570
<18.5	55 (13.68)	6.16±3.68		41.69±4.57		30.05±4.17		43.07±6.99	
18.5-23.9	245 (60.95)	6.61±3.44		41.09±5.13		30.90±4.37		42.36±5.78	
≥24	102 (25.37)	6.80±3.59		41.41±5.16		30.75±3.78		42.00±6.12	
Residential area			0.061		**0.010**		0.347		0.274
Rural	225 (55.97)	6.31±3.53		40.68±4.89		30.57±4.16		42.08±5.51	

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City	177 (44.03)	6.97±3.46		41.99±5.19		30.97±4.25	42.74±6.65	
Residential status			0.560		**0.035**		0.084	0.136
Living alone	43 (10.70)	6.30±3.56		39.72±4.76		29.70±4.62	41.07±6.00	
Living with others	359 (89.30)	6.63±3.50		41.44±5.07		30.87±4.21	42.52±6.03	
Marital Status			0.918		0.148		0.153	**0.031**
Unmarried	22 (5.47)	6.14±3.76		40.36±4.75		29.91±4.91	39.09±6.45	
Married	362 (90.05)	6.64±3.50		41.32±5.09		30.75±4.13	42.49±5.99	
Divorced	8 (1.99)	6.25±3.49		38.25±5.47		29.50±5.53	42.38±5.15	
Widowed	10 (2.49)	6.50±3.81		43.40±3.53		33.30±3.65	45.20±5.55	
Education			0.426		0.449		0.310	0.233
Junior high school and below	79 (19.65)	6.56±3.60		40.96±5.89		30.01±4.85	42.67±5.95	

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High school/technical secondary school	137 (34.08)	6.33±3.60	41.72±4.61	31.25±3.66	42.81±5.69	
College	112 (27.86)	6.92±3.36	40.72±5.05	30.71±3.80	42.12±6.04	
Bachelor's degree	68 (16.92)	6.82±3.46	41.35±5.03	30.56±4.28	41.99±6.39	
Postgraduate and above	6 (1.49)	4.67±3.27	43.33±3.33	31.67±2.25	37.33±9.61	
Average monthly income, RMB		0.500	**0.005**	0.276		0.094
<2000	86 (21.39)	6.13±3.70	39.66±5.88	30.05±4.86	42.19±5.97	
2000-5000	196 (48.76)	6.81±3.39	41.87±4.58	31.04±3.99	42.64±5.93	
5001-10,000	83 (20.65)	6.52±3.64	40.90±5.39	30.69±4.20	42.98±5.89	
10,001-20,000	23 (5.72)	6.30±3.50	41.87±3.86	30.22±3.69	39.26±6.88	
>20,000	14 (3.48)	7.50±3.16	43.50±3.46	32.07±3.25	41.21±6.55	
Types of health insurance						

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Urban Employee Basic Medical Insurance	134 (33.33)	6.94±3.37	41.70±4.90	30.93±4.11	42.82±5.96
New Rural Cooperative Medical Insurance	207 (51.49)	6.24±3.57	40.87±5.16	30.76±4.0	41.91±6.08
Urban Resident Basic Medical Insurance	53 (13.18)	7.11±3.46	42.06±4.72	30.75±3.2	43.66±5.73
Commercial Insurance	6 (1.49)	6.33±4.56	40.33±6.25	29.67±5.75	38.17±7.11
Self-payment	2 (0.50)	8.00±1.41	33.00±1.41	20.00±8.49	38.00±4.24
GI Symptoms					
Loss of appetite	113 (28.11)	6.09±3.45	41.15±4.33	30.44±4.65	40.89±6.72
Nausea and vomiting	54 (13.43)	6.80±3.20	40.89±4.90	29.81±5.12	39.52±7.87
Constipation	53 (13.18)	6.25±3.59	40.72±5.26	29.70±4.22	40.13±6.30
Diarrhea	34 (8.46)	7.41±2.84	40.88±3.67	30.00±4.71	41.15±6.63

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Oral ulcers	18 (4.48)	6.94±3.46	41.89±4.17	31.56±4.08	39.89±8.63	
Dry Mouth	45 (11.19)	6.11±3.49	41.07±4.86	30.24±4.47	41.91±6.78	
Altered taste perception	27 (6.72)	5.37±3.56	40.44±4.97	30.81±5.0	41.59±8.02	
Altered smell perception	8 (1.99)	4.75±3.45	41.13±3.72	29.13±6.2	41.00±8.64	
Swallowing Difficulties	13 (3.23)	6.38±3.64	40.08±6.49	29.31±5.2	41.38±7.09	
Feeling of fullness	48 (11.94)	5.65±3.44	41.65±4.35	31.40±4.35	43.33±6.57	
Pain	66 (16.42)	6.39±3.71	42.29±4.04	30.56±3.89	43.06±6.00	
None	198 (49.25)	6.80±3.52	40.98±5.45	30.88±4.07	43.28±5.18	
IrAEs		0.527	0.276	0.122	0.954	
Yes	41 (10.20)	6.27±3.78	42.07±4.42	29.78±4.18	42.32±6.60	
No	361 (89.80)	6.63±3.48	41.16±5.13	30.85±4.20	42.37±5.98	
Symptoms you experienced						

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Capillary Proliferation Syndrome	9 (2.24)	4.89±3.95	41.11±3.37	31.00±2.55	42.78±7.66
Other skin reactions (rash, papules, itching, vitiligo, etc.)	18 (4.48)	6.89±3.41	40.94±4.32	30.83±3.76	41.67±7.04
Gastrointestinal reactions (diarrhea, colitis, abdominal pain, nausea, vomiting, etc.)	16 (3.98)	6.75±3.24	41.75±4.30	30.00±4.76	40.25±6.22
Hepatic reactions	7 (1.74)	5.14±3.39	43.29±3.99	30.43±3.99	43.86±7.24
Endocrine reactions (hypothyroidism,	2 (0.50)	9.50±0.71	40.00±8.49	26.00±8.49	35.00±11.31

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hyperthyroidism, adrenal insufficiency, etc.)						
Pneumonia	1 (0.25)	9.00	40	29	30	
Cardiac reactions	0	0	0	0	0	
Renal toxicity (nephritis)	0	0	0	0	0	
Muscle or joint pain, muscle weakness	13 (3.23)	5.85±3.74	41.92±4.82	30.08±5.36	44.92±2.99	
Other	4 (1.00)	7.50±4.36	39.75±5.06	27.75±5.44	41.00±9.56	
Number of immunotherapy medication		0.736	0.529	0.620		**0.001**
1	218 (54.23)	6.65±3.50	41.11±5.04	30.84±3.71	41.45±5.88	
>1	184 (45.77)	6.53±3.52	41.43±5.09	30.63±4.73	43.46±6.06	

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Familiar with the specific names of the immunotherapy drugs		0.990	0.724	0.806	0.884
Yes	140 (34.83)	6.60±3.62	41.38±5.03	30.81±4.38	42.43±6.71
No	262 (65.17)	6.60±3.45	41.19±5.09	30.71±4.21	42.34±5.66

RMB: renminbi, the official currency in China.

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Table S2. Knowledge, attitudes, and practices

Statement	Accuracy, n (%)
K1. Adverse reactions can occur during immunotherapy, but they are normal occurrences that do not require excessive attention.	204 (50.75)
K2. Skin toxicities (rashes, dermatitis, capillary proliferation), endocrine toxicities (hypothyroidism, hyperthyroidism, adrenal insufficiency), hepatic toxicities, cardiac toxicities, gastrointestinal toxicities (abdominal pain, diarrhea), pneumonia, renal toxicity (immune nephritis leading to proteinuria), etc., might emerge during the immunotherapy process.	247 (61.44)
K3. The liver is engaged in digestion, synthesis, and metabolic processes of various nutrients; impaired liver function significantly elevates the incidence of malnutrition in liver cancer patients.	245 (60.95)
K4. Tumor progression and immunotherapy can exacerbate malnutrition due to deteriorating liver function, which, in turn, affects the prognosis of liver cancer patients, leading to a vicious cycle.	231 (57.46)

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K5. Liver cancer patients undergoing treatment should undergo nutritional screening and assessment, followed by personalized nutritional interventions based on their nutritional status.	281 (69.90)
K6. Nutritional risk screening and assessment include disease status, dietary surveys, weight changes, anthropometric measurements, laboratory examinations, etc.	290 (72.14)
K7. Nutritional support encompasses dietary guidance, oral supplements, enteral nutrition, and parenteral nutrition.	283 (70.40)
K8. Appropriate and effective nutritional interventions can optimize the intake structure and quantity of nutrients, improve nutritional status and liver function, enhance tolerance to surgery or other treatments, enhance immune conditions, reduce complications during treatment, elevate quality of life, and extend survival time.	290 (72.14)
K9. Prompt identification and timely reporting of symptoms of malnutrition and immune-related events to healthcare professionals are not only beneficial for immunotherapy and ameliorating immune-related adverse symptoms and nutritional status but also increase the likelihood of continuing immunotherapy.	291 (72.39)

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K10. Liver cancer patients receiving immunotherapy should be managed comprehensively throughout the cycle, from screening and assessment to diagnosis, supportive treatment, monitoring, and follow-up, focusing on nutritional and adverse event management. 290 (72.14)

Attitude	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
A1. I consider nutritional support highly significant throughout the entire course of immunotherapy.	230 (27.21)	150 (37.31)	16 (3.98)	2 (0.50)	4 (1.00)
A2. I believe that targeted nutritional interventions can enhance the efficacy of immunotherapy.	196 (48.76)	175 (43.53)	25 (6.22)	2 (0.50)	4 (1.00)
A3. I deem continuous monitoring of adverse immune events to be essential.	208 (51.74)	160 (39.80)	32 (7.96)	0	2 (0.50)
A4. I would be concerned about adverse reactions following immunotherapy.	169 (42.04)	183 (45.52)	36 (8.96)	6 (1.49)	8 (1.99)

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A5. I find it necessary to monitor nutrition-related indicators comprehensively.	188 (46.77)	172 (42.79)	30 (7.46)	6 (1.49)	6 (1.49)
A6. I think consuming high-quality proteins, abundant dietary fiber, and appropriate carbohydrates is crucial.	216 (53.73)	158 (39.30)	23 (5.72)	3 (0.75)	2 (0.50)
A7. I wish to acquire further knowledge about nutritional support through professional channels.	200 (49.75)	163 (40.55)	32 (7.96)	2 (0.50)	5 (1.24)
A8. I desire to gain more insights through professional channels regarding self-management, emergency responses, and precautions for managing adverse events during immunotherapy.	193 (48.01)	175 (43.53)	27 (6.72)	4 (1.00)	3 (0.75)
A9. I am confident in maintaining a relatively favorable nutritional status.	179 (44.53)	165 (41.04)	45 (11.19)	7 (1.74)	6 (1.49)

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A10. I believe that maintaining a positive mindset and quality sleep are important during immunotherapy.	214 (53.23)	161 (40.05)	19 (4.73)	3 (0.75)	5 (1.24)

Practice	**Always**	**Frequently**	**Sometimes**	**Occasionally**	**Never**
P1. I can cooperate with medical personnel for comprehensive treatment monitoring and follow-up.	216 (53.73)	130 (32.34)	43 (10.70)	6 (1.49)	7 (1.74)
P2. I will regularly monitor nutrition-related indicators such as body weight, body mass index, grip strength, albumin, and prognostic nutritional index.	177 (44.03)	140 (34.83)	55 (13.68)	22 (5.47)	8 (1.99)
P3. If a physician recommends it, I will take medication to enhance appetite, digestion, and absorption.	192 (47.76)	132 (32.84)	53 (13.18)	18 (4.48)	7 (1.74)
P4. I will proactively seek relevant knowledge about immunotherapy nutrition and adverse reactions through	172 (42.79)	126 (31.34)	64 (15.92)	27 (6.72)	13 (3.23)

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professional channels such as healthcare providers, health promotion columns, books, and television.					
P5. I will undergo oral nutritional supplementation, including branched-chain amino acids, omega-3 fatty acids, and vitamin D if necessary.	162 (40.30)	118 (29.35)	60 (14.93)	31 (7.71)	31 (7.71)
P6. If required, I am prepared to receive enteral feeding through nasogastric/nasoenteric tubes.	133 (33.08)	38 (6.45)	46 (11.44)	36 (8.96)	149 (37.06)
P7. If necessary, I am open to receiving parenteral nutrition support (intravenous administration).	123 (30.60)	43 (10.70)	52 (12.94)	56 (13.93)	128 (31.84)
P8. I will maintain moderate physical exercise to improve my overall physical condition.	176 (43.78)	122 (30.35)	55 (13.68)	34 (8.46)	15 (3.73)
Lifestyle	**Never**	**Occasionally**	**Sometimes**	**Frequently**	**Always**

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In your daily lifestyle habits, what is your eating frequency for the following types:					
L1. Smoking	272 (67.66)	38 (9.45)	27 (63.72)	35 (8.71)	30 (7.46)
L2. Alcohol consumption	285 (70.90)	52 (12.94)	27 (6.72)	21 (5.22)	17 (4.23)
L3. Cooking methods involving frying, smoking, baking, pickling, etc.	223 (55.47)	100 (24.88)	47 (11.69)	19 (4.73)	13 (3.23)
L4. High-fat, high-salt, spicy foods (such as chili peppers, onions, ginger, raw garlic, and pepper)	212 (52.74)	100 (24.88)	50 (12.44)	27 (6.72)	13 (3.23)
L5. High-quality protein sources (legumes, eggs, meat, fish, shellfish, dairy products, etc.)	22 (5.47)	21 (5.22)	37 (9.20)	224 (55.72)	98 (24.38)
L6. Light and easily digestible foods (egg custard, millet porridge, lotus root powder, Chinese yam)	15 (3.73)	42 (10.45)	61 (15.17)	213 (52.99)	71 (17.66)

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L7. Foods rich in vitamins (fresh vegetables and fruits, such as spinach, cabbage, kiwi, tomatoes, etc.)	8 (1.99)	34 (8.46)	42 (10.45)	217 (53.98)	101 (25.12)
L8. Stimulants like coffee, chocolate, and strong tea	247 (61.44)	70 (17.41)	30 (7.46)	38 (9.45)	17 (4.23)
L9. Probiotics	202 (50.25)	90 (22.39)	51 (12.69)	37 (9.20)	22 (5.47)
L10. Sugary beverages	215 (53.48)	114 (28.36)	45 (11.19)	20 (4.98)	8 (1.99)
L11. Citrus fruits (grapefruit, pomelo, honey pomelo, etc.)	93 (23.13)	112 (27.86)	75 (18.66)	92 (22.89)	30 (7.46)

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Table S3. SEM model fit

Indicators	Reference	Results
CMIN/DF	1-3 Excellent, 3-5 Good	3.10
RMSEA	<0.08 Good	0.039
IFI	>0.8 Good	0.939
TLI	>0.8 Good	0.893
CFI	>0.8 Good	0.935

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Knowledge, attitudes, and practices relating to nutritional support and immune-related adverse events among patients undergoing immunotherapy for liver cancer: cross-sectional study

Running title: KAP of irAEs and nutrition and lifestyle

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ABSTRACT

Objectives: To examine the knowledge, attitude, and practice (KAP) regarding immune-related adverse events (irAEs) and nutritional support amongst patients with liver cancer (LC).

Design: Cross-sectional study.

Setting: Recruitment was carried out at Haikou People's Hospital, Haikou, China, from December 2022 to April 2023.

Participants: Patients undergoing immunotherapy for LC.

Primary and secondary outcome measures: Mean knowledge, attitudes, practices, and lifestyle scores were assessed using an investigator-designed questionnaire completed by patients during immunotherapy.

Results: The study included 402 participants. The mean knowledge, attitudes, practices, and lifestyle scores were 6.60±3.51 (/10, 66.00%), 41.26±5.06 (/50, 82.52%), 30.74±4.20 (/40, 76.85%), and 42.37±6.04 (/55, 77.04%). Attitude scores were associated with practice scores (β=0.381, P<0.001) and lifestyle (β=1.928, P<0.001). Urban residence was associated with higher attitude scores (β=1.242, P=0.013). Living with someone was associated with a higher attitude score (β=1.619, P=0.044). More than one immunotherapy line was associated with a higher lifestyle score (β=1.928, P<0.001). Finally, the female gender was associated with a lifestyle score (β=1.431, P=0.023).

Conclusion: Patients with LC and undergoing immunotherapy had moderate KAP toward irAEs and nutritional support. They also displayed moderate lifestyle scores. Urban residents, people not living alone, females, and those having received two or more immunotherapy

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treatments were positively associated with attitude, while attitude was positively associated with practice and lifestyle.

Keywords: knowledge, attitude, practice; liver cancer; nutritional support; immune-related adverse events (ir AEs); lifestyle; cross-sectional study

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Strengths and limitations of this study

1. While a cross-sectional design is useful for capturing data at a single time point, it limits the ability to establish causality or infer temporal relationships between variables.

2. Conducting the study at a single hospital may introduce selection bias and limit the generalizability of the findings to other settings or populations.

3. The reliance on self-reported measures for assessing knowledge, attitude, practice, and lifestyle introduces the potential for response bias and social desirability bias, impacting the accuracy of the results.

4. Although the study identifies certain factors that were associated with attitudes and lifestyle, there may be other unmeasured confounding variables that could affect the outcomes.

5. While the study assessed KAP toward irAEs, nutritional support, and lifestyle factors, it may not capture all relevant aspects involved in patient care and outcomes during immunotherapy for LC.

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INTRODUCTION

The estimated worldwide incidence of liver cancer in GLOBOCAN 2022 was 865,269 new cases, and mortality was 757,948 [1]. Most liver cancers are hepatocellular carcinoma (HCC) [2 3]. The worldwide age-standardized annual mortality rates of liver cancer are 13.9 per 100,000 in men and 4.9 per 100,000 in women [4]. The most important risk factors for LC are preexisting liver cirrhosis and hepatitis B infection (due to both direct oncogenic effect and risk of cirrhosis) [2 3 5 6]. Risk factors for liver cirrhosis (and therefore risk factors for LC) include hepatitis C infection, alcohol use, and nonalcoholic steatohepatitis [2 3 5 6]. The incidence of LC is higher in men and generally follows the geographical distribution of hepatitis B virus and hepatitis C [2 5 6]. LC management is multidisciplinary and involves surgery (when possible), chemotherapy, targeted therapy, radiotherapy, and immunotherapy [2 5 6]. Despite optimal treatments, the 5-year survival is 22% in the United States of America [7] and 12.1% in China [8], with lower survival in rural China (11.2%) compared with urban areas (14.0%) [9].

Immunotherapy is a recent paradigm in treating cancers, including LC [10-12]. Cancer cells can escape the immune system through the PD-1/PD-L1 pathway [13 14], and drugs targeting PD-1 or PD-L1 have been developed to restore the immunosurveillance of cancer cells and their destruction [10-12]. Still, the PD-1/PD-L1 usually plays roles in immune tolerance and preventing autoimmune reactions [13 14], and inhibiting the PD-1/PD-L1 pathway can lead to immune-related adverse events (irAEs). The pathogenesis of irAEs is still poorly understood, but they involve inflammatory reactions of normal tissues that can be bothersome but also life-threatening [15-17]. Adequate nutrition is also essential in patients with LC to ensure optimal outcomes, and nutritional support can be necessary in patients with inadequate nutrition due, for example, to

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adverse gastrointestinal events (AEs) from therapies [18 19]. Still, the palliation of some symptoms of HCC (e.g., loss of appetite, weakness, fatigue, etc.) using androgens (since most LCs occur in males) can help alleviate the need for nutritional support [20]. The management of irAEs and nutrition involves healthcare providers. It can involve medical interventions (e.g., management of irAEs, enteral nutrition, and hospitalization). However, patient self-management is also important to ensure that preventive measures are taken (such as not smoking, not drinking, and eating properly) and so that patients know when to consult [21].

A systematic review showed that the eating habits of Chinese patients with cancer and chemotherapy were poor, but no data are available for immunotherapy specifically [22]. Another study suggested that Chinese patients with cancer had a basic understanding of irAEs [23], but this study was not specific to LC and did not evaluate attitudes and practices. A knowledge, attitude, and practice (KAP) survey is a tool that provides quantitative and qualitative data about gaps, misconceptions, and misunderstandings that constitute barriers toward the optimal performance of a given task or set of tasks in a specific group of individuals [24 25]. Compared with other types of cancer, e.g., breast cancer, patients with LC have a poorer prognosis, and men are more at risk. In addition, the risk factors for LC are different from other cancers, mainly encompassing chronic liver diseases, alcohol drinking, and hepatitis virus infection. Those differences could influence patients' KAP toward irAEs.

Therefore, this study aimed to investigate the KAP-lifestyle (KAP-L) of patients with LC and immunotherapy patients regarding nutritional support and irAEs. The results can provide crucial information to design educational interventions to improve patient self-management and outcomes.

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MATERIALS AND METHODS

Study design and participants

This cross-sectional study was conducted at Haikou People's Hospital from December 2022 to April 2023 and enrolled patients undergoing immunotherapy for LC. This study was approved by the Institutional Review Board of Haikou People's Hospital (2022-Ethical Review-231). All participants signed the informed consent form before completing the survey.

The inclusion criteria were 1) aged 18-90 years old, 2) pathologically confirmed locally advanced or unresectable liver cancer, and 3) undergoing immunotherapy (any line of treatment). The exclusion criteria were 1) surgical patients, 2) simultaneously suffering from other malignant tumors, 3) before or planned liver transplantation, 4) active autoimmune diseases, 5) ambiguous consciousness, unable to fill out by oneself or with assistance, or 6) withdrawal during the filling process.

Questionnaire and quality control

A self-designed questionnaire consisting of five dimensions was developed based on the relevant literature [15 18 19 22 23 26]. After the questionnaire design, modifications were made by incorporating insights from 15 experts in nutrition in oncology and medical oncology, removing similar or redundant questions, and refining questions with unclear phrasing. Before the official distribution, a small-scale pilot test (70 participants) was conducted, yielding a Cronbach's α coefficient of 0.853 (0.879 for knowledge, 0.828 for attitudes, and 0.758 for practice), indicating strong internal consistency.

The final questionnaire was in Chinese and encompassed 1) participants' demographic information (including age, gender, residential area, education level and income level, et.al),

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2) knowledge dimension (10 items, with a score of 1 assigned for correct answers and 0 for incorrect or uncertain responses), 3) attitude dimension (10 items, scored using a 5-point Likert scale, ranging from "strongly positive" (5 points) to "strongly negative" (1 point)), 4) practice dimension (eight items, scored using a 5-point Likert scale, ranging from "always" (5 points) to "never" (1 point)), and 5) lifestyle dimension (11 items, also scored using a 5-point Likert scale, ranging from "always" (5 points) to "never" (1 point)). Higher scores correspond to better knowledge, more positive attitudes, and more proactive practices. Scores <60% were considered poor, scores 60%-79% were considered moderate, and scores ≥80% were considered adequate, based on Bloom's criteria [27].

An online questionnaire was developed using the WeChat-based Wenjuanxing platform. A QR code was generated for data collection via WeChat. The participants accessed and completed the questionnaire by scanning the QR code received via WeChat. In order to ensure the quality and completeness of the questionnaires, all items were made mandatory. Incomplete questionnaires were excluded during the quality control process. Therefore, all items were responded to, which would not affect the results.

The research team members reviewed the integrity, internal consistency, and rationality of all collected questionnaires for quality control. A given IP address could be used to submit a questionnaire only once. Questionnaires that took <110 s to complete were excluded. Questionnaires completed using all the same options (e.g., the first option) were deemed invalid. Finally, questionnaires containing impossible values (e.g., impossible age, height, or weight) or logical errors were excluded. The Cronbach's α coefficient for all valid questionnaires was 0.840 (0.913 for knowledge, 0.800 for attitudes, and 0.718 for practice).

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Statistical analysis

The statistical analysis software was SPSS 26.0 (IBM, Armonk, NY, USA). Quantitative variables were described as means ± standard deviations (SD), while group comparisons were conducted using Student's t-test or analysis of variance (ANOVA). Categorical variables were presented as n (%). Pearson's correlation analysis explored the relationships between knowledge, attitude, and practice scores. The study used a structural equation modeling (SEM) analysis to validate various causality hypotheses empirically. These hypotheses encompassed 1) knowledge has direct associations with attitudes, practices, and lifestyles, 2) attitudes have direct associations with practices and lifestyles, 3) residential area and status have direct associations with attitudes, 4) gender has direct associations with attitudes and lifestyles, and 5) the number of immunotherapy medication usage has a direct association with lifestyles. All statistical tests were two-tailed, and P-values <0.05 were considered statistically significant.

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RESULTS

Characteristics of the participants

The study included 419 respondents. After removing the following cases: 1) one respondent with impossible height and weight, 2) nine respondents answered with contradictory answers, and 3) seven respondents with a completion time of less than 110 seconds, a total of 402 valid questionnaires were included in the analysis **(Figure 1)**. The participants were 56.84±11.93 years old. Most participants were male (71.89%), had a BMI of 18.5-23.9 kg/m^2 (60.95%), were living in rural areas (55.97%), were not living alone (89.30%), were married (90.05%), had high school or technical secondary school education (34.08%), had an income of 2000-5000 RBM/months (48.76%), had health insurance (99.50%), had gastrointestinal symptom (50.75%), did not experience irAEs (89.80%), received one line of immunotherapy (54.23%), and were not familiar with the name of their immunotherapy (65.17%) (**Table S1**).

Knowledge

The mean knowledge score was 6.60±3.51 (/10, 66.00%) (**Table 1**). No significant differences were observed according to the characteristics of the participants. The knowledge item with the lowest score was K1 (50.75%; "Adverse reactions can occur during immunotherapy, but they are normal occurrences that do not require excessive attention."), while the item with the highest score was K9 (72.39%; "Prompt identification and timely reporting of symptoms of malnutrition and immune-related events to healthcare professionals are not only beneficial for immunotherapy and ameliorating immune-related adverse symptoms and nutritional status but also increase the likelihood of continuing immunotherapy.") (**Table**

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S2).

Attitude

The mean attitude score was 41.26±5.06 (/50, 82.52%) (**Table 1**). Higher attitude scores were observed in urban dwellers (41.99±5.19 vs. 40.68±4.89, P=0.010), those not living alone (41.44±5.07 vs. 39.72±4.76, P=0.035), and those with higher income (>20,000 CNY/month: 43.50±3.46; <2000 CNY/month: 39.66±5.88; P=0.005) (**Table S1**). The attitude item with the lowest score was A1 (64.52%; "I consider nutritional support to be highly significant throughout the entire course of immunotherapy."), while the item with the highest score was A10 (93.28%; "I believe that maintaining a positive mindset and quality sleep are important during immunotherapy.") (**Table S2**).

Practice

The mean practice score was 30.74±4.20(/40, 76.85%) (**Table 1**). No significant differences were observed according to the characteristics of the participants. The practice item with the lowest score was P6 (39.53%; "If required, I am prepared to receive enteral feeding through nasogastric/nasoenteric tubes."), while the item with the highest score was P1 (86.07%; "I am capable of cooperating with medical personnel for comprehensive treatment monitoring and follow-up.") (**Table S2**).

Lifestyle

The mean lifestyle score was 42.37±6.04 (/55, 77.04%) (**Table 1**). Higher lifestyle scores were observed in females (43.43±5.36 vs. 41.95±6.24, P=0.027), widows (widows: 45.20±5.55; married: 42.49±5.99; unmarried: 39.09±6.45; P=0.031), and with more than one immunotherapy line (43.46±6.06 vs. 41.45±5.88, P=0.001) (**Table S1**). The lifestyle item with

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the lowest score was L11 (30.35%; “Citrus fruits (grapefruit, pomelo, honey pomelo, etc.).)”), while the item with the highest score was L2 (83.84%; “Alcohol consumption”) (**Table S2**).

Correlations

The knowledge scores were correlated to the attitude scores (r=0.105, P=0.035). The attitude scores were correlated to the practice (r=0.460, P<0.001) and lifestyle (r=0.486, P<0.001) scores. The practice scores were correlated to the lifestyle scores (r=0.269, P<0.001) (**Table 2**).

Structural equation modeling

As shown in **Table 3** and **Figure 2**, higher attitude scores were associated with higher practice scores (β=0.381, P<0.001) and lifestyle (β=1.928, P<0.001). Urban residence was associated with higher attitude scores (β=1.242, P=0.013). Living with someone was associated with higher attitude scores (β=1.619, P=0.044). More than one line of immunotherapy lines was associated with higher lifestyle scores (β=1.928, P<0.001). The female gender was associated with higher lifestyle scores (β=1.431, P=0.023). **Table S3** shows that the SEM analysis had a good fit.

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DISCUSSION

Very few data are available in the literature concerning the KAP of patients with LC toward irAEs and lifestyle habits. The present study revealed moderate KAP toward lifestyle habits and irAEs. A previous systematic review has shown that the eating habits of Chinese patients with cancer and chemotherapy were poor [22]. Although no data were available within this systematic review for immunotherapy, its findings are generally in alignment with our present study. Another study has shown that Chinese patients with cancer had a basic understanding of irAEs [23], but the study was not specific to LC and did not evaluate attitudes and practices. Intrinsic differences between patients with LC and those with other types of cancer could explain the differences in findings.

Symptoms of advanced HCC affect quality of life, and the treatment of HCC can restore quality of life [28]. Thus, immunotherapy can potentially reverse the HCC-related symptoms and help improve quality of life. Nevertheless, the side effects of immunotherapy need to be factored in, as it can affect empowerment and self-management. Self-management is a critical component of cancer care. Indeed, the patients must remain aware of the signs and symptoms that should prompt consultation. At home, they are also responsible for maintaining lifestyle habits that could improve their prognosis or, at least, not worsen it [21]. A previous systematic review revealed poor KAP toward good eating habits among Chinese patients on chemotherapy for various types of cancers [22]. That previous study supports the present one, which also showed poor lifestyle scores for several foods in patients with LC and immunotherapy. Increasing evidence indicates that a healthy diet can improve the outcomes of immunotherapy [29 30].

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In this study, many participants with LC were still regularly smoking, drinking alcohol, and had unhealthy dietary habits, all of which are associated with LC development and progression [31-34]. Especially, smoking and alcohol consumption are independent risk factors for confirmed liver cancer [2 3 5 6] because of their impact on inflammation, cancer progression, and health in general [35-37], and they affect liver function and immunotherapy efficacy [38]. Still, the high rates of smoking and drinking could reflect a poor knowledge of the risk factors for poor outcomes in LC but could also reflect patients wishing to maintain activities they associate with pleasure in the face of a disease with poor prognosis. The majority of the participants were not eating citrus fruits. Citrus fruits are rich in vitamins and antioxidants and play roles in maintaining the integrity of immunological barriers and in supporting immune cells [39-41]. On the other hand, citrus fruits are rich in active ingredients, such as furacoumarin, naringin, and bergamot, that can inhibit the activity of metabolic enzymes (mainly UGT1A3 or UGT2B7) [42]. Therefore, in the future, intervention research on the impact of fruits such as grapefruit on medication can be strengthened. Therefore, the lifestyle of the study population was not ideal in terms of LC prognosis [31-34].

The participants mostly reported not taking probiotics. Recent data also suggests that probiotics should be encouraged to prevent irAEs [43]. Indeed, regulation of the gut microbiome appears crucial in preventing irAEs [44]. The gut microbiota was also shown to modulate the response to immunotherapy, with distinct responses to immunotherapy according to the composition of the microbiome [45]. Gut dysbiosis can even lead to resistance to immunotherapy [45]. Hence, administering specific bacteria could be used to improve the response to immunotherapy and prevent irAEs [46].

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People living in urban areas and not living alone often enjoy a higher socioeconomic status, and it is well-known that higher socioeconomic status is associated with better health literacy [47]. In this study, living in urban areas was associated with higher attitude scores than participants from rural areas.

Women often have a higher healthcare literacy and higher health awareness than men [48-51], supporting the association observed in the present study between gender and lifestyle. In addition, family support plays an undeniable advantage in the management of cancer patients, helping them with daily tasks, cooking for them, caring for them, and remembering instructions and advice that the patients might forget due to the emotional charge associated with cancer-related events [52 53]. The present study was not designed to assess that point. Nevertheless, efforts should be taken to teach patients with LC the proper lifestyle habits necessary to optimize prognosis. Expanding the scope of the survey and including hospitals in different regions and levels is recommended to validate the results of this study. Clinical intervention research should be performed on the knowledge, attitude, behavior, and lifestyle level of nutrition and irAEs in patients with LC and immunotherapy and evaluate the effectiveness of the intervention. The impact of good sleep and moderate exercise (as good lifestyles) in relation to nutrition and irAEs should also be examined.

In the present study, the knowledge scores were only correlated to the attitude scores, while the attitude scores were correlated to the practice and lifestyle scores. Although knowledge was not associated with attitude in the SEM, improving knowledge could translate into attitude, practice, and lifestyle improvements. Healthcare providers are a primary source of information for the patients, but previous studies revealed relatively poor KAP toward cancer nutritional

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support [26 54] and irAEs [55] among healthcare providers. Patients with LC and immunotherapy should be encouraged to perform physical activity, which is akin to prehabilitation for liver resection to improve tolerance to treatment [56]. It should help reduce the side effects or increase the patient's tolerance to them, hence improving patient outcomes.

This study has limitations. It was a single-center study. Even though 402 patients with LC and immunotherapy represent a relatively large sample size, it is still too small to derive correlations and recommendations regarding the KAP-L in patients with LC. The questionnaire was designed by the investigators. It was reviewed by 15 experts in LC management, which could introduce bias from the healthcare perspective. In addition, some questions contained medical jargon that could introduce the Hawthorne effect (a type of reactive human behavior in which people change their behavior when they feel observed). The question length could be a potential source of bias on the importance ratings. Participants can consider a long and complicated sentence as important and a short sentence as being less important, causing bias. Future surveys should also be reviewed by nursing experts, laypeople, and a variety of professionals. The study was cross-sectional in design, preventing us from drawing conclusions around causality. Still, a SEM analysis was performed to examine the structured associations between variables, but it must be remembered that the associations are purely statistical and remain to be confirmed. In addition, the data represent a single point in time. Still, the results could serve as a historical baseline to evaluate the effect of future interventions. The questionnaire was designed by local investigators based on local practice, policies, and reality, limiting generalizability. Finally, all KAP studies are at risk of social desirability bias, in which

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some participants might be tempted to answer what they know they should do instead of what they are actually doing [57 58].

In conclusion, patients with LC and immunotherapy had moderate KAP toward irAEs and nutritional support. They also displayed moderate lifestyle scores. Urban residents, people not living alone, females, and having received two or more immunotherapy treatments were positively associated with attitude, while attitude was positively associated with practice and lifestyle.

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Declarations

Ethics approval and consent to participate

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved by the Institutional Review Board of Haikou People's Hospital (2022-Ethical Review-231). All participants signed the informed consent form before completing the survey.

The Patient and Public Involvement statement

Patients with LC were involved as participants. The patients with LC or the public were not involved in the study design or its completion.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this article and it's supplementary materials.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

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Wen Wen and Fangqing Gao carried out the studies, participated in collecting data, and drafted the manuscript. Yingshuang Chen and Liling Tong performed the statistical analysis and participated in its design. Wen Wen and Yingshuang Chen participated in the acquisition, analysis, or interpretation of data and drafted the manuscript. All authors read and approved the final manuscript. Fangqing Gao acted as guarantor.

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Table 1. KAP scores.

Dimension	N=402		
	Range, points	Mean score, mean ± SD	Proportion, %
Knowledge	0~10	6.60±3.51	66.00%
Attitude	10~50	41.26±5.06	82.52%
Practice	8~40	30.74±4.20	76.85%
Lifestyle	11~55	42.37±6.04	77.04%

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Table 2. Pearson correlation analysis.

	Knowledge	Attitude	Practice	Lifestyle
Knowledge	1			
Attitude	0.105 (P=**0.035**)	1		
Practice	0.018 (P=0.253)	0.460 (P<**0.001**)	1	
Lifestyle	-0.016 (P=0.755)	0.486 (P<**0.001**)	0.269 (P<**0.001**)	1

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Table 3. SEM, including lifestyle

			β	P
Attitude	<---	Gender	-0.457	0.407
Attitude	<---	Residential area	1.242	**0.013**
Attitude	<---	Knowledge	0.128	0.069
Attitude	<---	Residential status	1.619	**0.044**
Lifestyle	<---	Knowledge	-0.048	0.565
Practice	<---	Knowledge	0.011	0.841
Lifestyle	<---	Attitude	0.222	**<0.001**
Practice	<---	Attitude	0.381	**<0.001**
Lifestyle	<---	Number of immunotherapy	1.928	**<0.001**
Lifestyle	<---	Gender	1.431	**0.023**

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Figure legend

Figure 1. Questionnaire flowchart.

Figure 2. Structural equation modeling (SEM).

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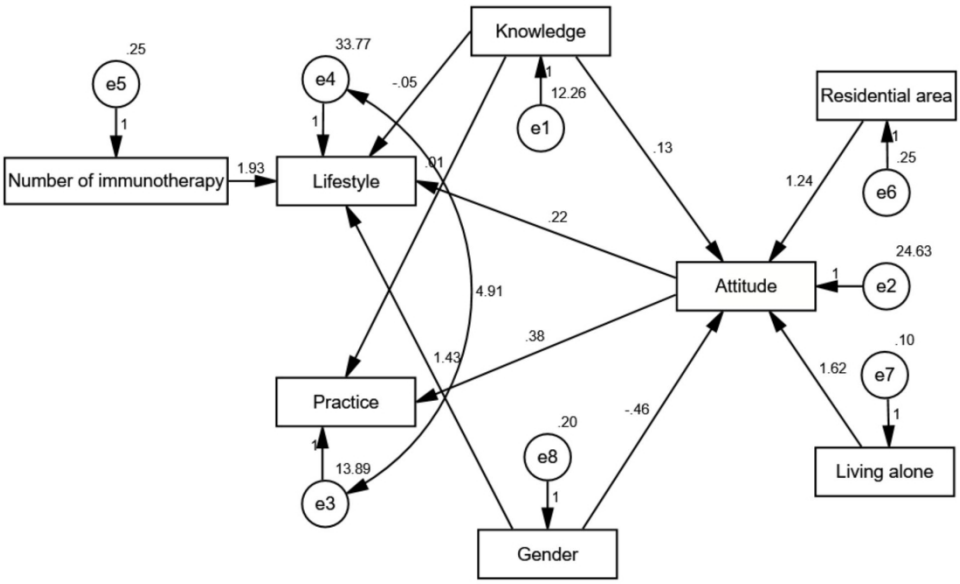

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Table S1 Characteristics of the participants.

Variables	n (%)	Knowledge score		Attitude score		Practice score		Lifestyle score	
		Mean ± SD	P	Mean ± SD	P	Mean ± SD	P	Mean ± SD	P
Gender			0.385		0.694		0.384		**0.027**
Male	289 (71.89)	6.69±3.39		41.32±4.63		30.86±3.92		41.95±6.24	
Female	113 (28.11)	6.35±3.79		41.10±6.05		30.45±4.75		43.43±5.36	
Age (years)	56.84±11.93								
Body mass index (kg/m^2)			0.550		0.687		0.406		0.570
<18.5	55 (13.68)	6.16±3.68		41.69±4.57		30.05±4.17		43.07±6.99	
18.5-23.9	245 (60.95)	6.61±3.44		41.09±5.13		30.90±4.37		42.36±5.78	
≥24	102 (25.37)	6.80±3.59		41.41±5.16		30.75±3.78		42.00±6.12	
Residential area			0.061		**0.010**		0.347		0.274
Rural	225 (55.97)	6.31±3.53		40.68±4.89		30.57±4.16		42.08±5.51	

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City	177 (44.03)	6.97±3.46		41.99±5.19		30.97±4.25		42.74±6.65	
Residential status			0.560		**0.035**		0.084		0.136
Living alone	43 (10.70)	6.30±3.56		39.72±4.76		29.70±4.61		41.07±6.00	
Living with others	359 (89.30)	6.63±3.50		41.44±5.07		30.87±4.11		42.52±6.03	
Marital Status			0.918		0.148		0.153		**0.031**
Unmarried	22 (5.47)	6.14±3.76		40.36±4.75		29.91±4.91		39.09±6.45	
Married	362 (90.05)	6.64±3.50		41.32±5.09		30.75±4.13		42.49±5.99	
Divorced	8 (1.99)	6.25±3.49		38.25±5.47		29.50±5.53		42.38±5.15	
Widowed	10 (2.49)	6.50±3.81		43.40±3.53		33.30±3.65		45.20±5.55	
Education			0.426		0.449		0.310		0.233
Junior high school and below	79 (19.65)	6.56±3.60		40.96±5.89		30.01±4.85		42.67±5.95	

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High school/technical secondary school	137 (34.08)	6.33±3.60	41.72±4.61	31.25±3.66	42.81±5.69	
College	112 (27.86)	6.92±3.36	40.72±5.05	30.71±3.80	42.12±6.04	
Bachelor's degree	68 (16.92)	6.82±3.46	41.35±5.03	30.56±4.28	41.99±6.39	
Postgraduate and above	6 (1.49)	4.67±3.27	43.33±3.33	31.67±2.25	37.33±9.61	
Average monthly income, RMB		0.500	**0.005**	0.276		0.094
<2000	86 (21.39)	6.13±3.70	39.66±5.88	30.05±4.86	42.19±5.97	
2000-5000	196 (48.76)	6.81±3.39	41.87±4.58	31.04±3.99	42.64±5.93	
5001-10,000	83 (20.65)	6.52±3.64	40.90±5.39	30.69±4.20	42.98±5.89	
10,001-20,000	23 (5.72)	6.30±3.50	41.87±3.86	30.22±3.69	39.26±6.88	
>20,000	14 (3.48)	7.50±3.16	43.50±3.46	32.07±3.25	41.21±6.55	
Types of health insurance						

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Urban Employee Basic Medical Insurance	134 (33.33)	6.94±3.37	41.70±4.90	30.93±4.11	42.82±5.96
New Rural Cooperative Medical Insurance	207 (51.49)	6.24±3.57	40.87±5.16	30.76±4.0	41.91±6.08
Urban Resident Basic Medical Insurance	53 (13.18)	7.11±3.46	42.06±4.72	30.75±3.2	43.66±5.73
Commercial Insurance	6 (1.49)	6.33±4.56	40.33±6.25	29.67±5.75	38.17±7.11
Self-payment	2 (0.50)	8.00±1.41	33.00±1.41	20.00±8.49	38.00±4.24
GI Symptoms					
Loss of appetite	113 (28.11)	6.09±3.45	41.15±4.33	30.44±4.65	40.89±6.72
Nausea and vomiting	54 (13.43)	6.80±3.20	40.89±4.90	29.81±5.12	39.52±7.87
Constipation	53 (13.18)	6.25±3.59	40.72±5.26	29.70±4.22	40.13±6.30
Diarrhea	34 (8.46)	7.41±2.84	40.88±3.67	30.00±4.71	41.15±6.63

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Oral ulcers	18 (4.48)	6.94±3.46	41.89±4.17	31.56±4.08	39.89±8.63	
Dry Mouth	45 (11.19)	6.11±3.49	41.07±4.86	30.24±4.47	41.91±6.78	
Altered taste perception	27 (6.72)	5.37±3.56	40.44±4.97	30.81±5.0	41.59±8.02	
Altered smell perception	8 (1.99)	4.75±3.45	41.13±3.72	29.13±6.2	41.00±8.64	
Swallowing Difficulties	13 (3.23)	6.38±3.64	40.08±6.49	29.31±5.2	41.38±7.09	
Feeling of fullness	48 (11.94)	5.65±3.44	41.65±4.35	31.40±4.35	43.33±6.57	
Pain	66 (16.42)	6.39±3.71	42.29±4.04	30.56±3.89	43.06±6.00	
None	198 (49.25)	6.80±3.52	40.98±5.45	30.88±4.07	43.28±5.18	
IrAEs		0.527	0.276	0.122	0.954	
Yes	41 (10.20)	6.27±3.78	42.07±4.42	29.78±4.18	42.32±6.60	
No	361 (89.80)	6.63±3.48	41.16±5.13	30.85±4.20	42.37±5.98	
Symptoms you experienced						

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Capillary Proliferation Syndrome	9 (2.24)	4.89±3.95	41.11±3.37	31.00±2.55	42.78±7.66
Other skin reactions (rash, papules, itching, vitiligo, etc.)	18 (4.48)	6.89±3.41	40.94±4.32	30.83±3.76	41.67±7.04
Gastrointestinal reactions (diarrhea, colitis, abdominal pain, nausea, vomiting, etc.)	16 (3.98)	6.75±3.24	41.75±4.30	30.00±4.76	40.25±6.22
Hepatic reactions	7 (1.74)	5.14±3.39	43.29±3.99	30.43±3.99	43.86±7.24
Endocrine reactions (hypothyroidism,	2 (0.50)	9.50±0.71	40.00±8.49	26.00±8.49	35.00±11.31

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hyperthyroidism, adrenal insufficiency, etc.)						
Pneumonia	1 (0.25)	9.00	40	29	30	
Cardiac reactions	0	0	0	0	0	
Renal toxicity (nephritis)	0	0	0	0	0	
Muscle or joint pain, muscle weakness	13 (3.23)	5.85±3.74	41.92±4.82	30.08±5.36	44.92±2.99	
Other	4 (1.00)	7.50±4.36	39.75±5.06	27.75±5.44	41.00±9.56	
Number of immunotherapy medication		0.736	0.529	0.620		**0.001**
1	218 (54.23)	6.65±3.50	41.11±5.04	30.84±3.71	41.45±5.88	
>1	184 (45.77)	6.53±3.52	41.43±5.09	30.63±4.73	43.46±6.06	

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Familiar with the specific names of the immunotherapy drugs		0.990	0.724	0.806	0.884	
Yes	140 (34.83)	6.60±3.62	41.38±5.03	30.81±4.38	42.43±6.71	
No	262 (65.17)	6.60±3.45	41.19±5.09	30.71±4.21	42.34±5.66	

RMB: renminbi, the official currency in China.

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Table S2. Knowledge, attitudes, and practices

Statement	Accuracy, n (%)
K1. Adverse reactions can occur during immunotherapy, but they are normal occurrences that do not require excessive attention.	204 (50.75)
K2. Skin toxicities (rashes, dermatitis, capillary proliferation), endocrine toxicities (hypothyroidism, hyperthyroidism, adrenal insufficiency), hepatic toxicities, cardiac toxicities, gastrointestinal toxicities (abdominal pain, diarrhea), pneumonia, renal toxicity (immune nephritis leading to proteinuria), etc., might emerge during the immunotherapy process.	247 (61.44)
K3. The liver is engaged in digestion, synthesis, and metabolic processes of various nutrients; impaired liver function significantly elevates the incidence of malnutrition in liver cancer patients.	245 (60.95)
K4. Tumor progression and immunotherapy can exacerbate malnutrition due to deteriorating liver function, which, in turn, affects the prognosis of liver cancer patients, leading to a vicious cycle.	231 (57.46)

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K5. Liver cancer patients undergoing treatment should undergo nutritional screening and assessment, followed by personalized nutritional interventions based on their nutritional status.	281 (69.90)
K6. Nutritional risk screening and assessment include disease status, dietary surveys, weight changes, anthropometric measurements, laboratory examinations, etc.	290 (72.14)
K7. Nutritional support encompasses dietary guidance, oral supplements, enteral nutrition, and parenteral nutrition.	283 (70.40)
K8. Appropriate and effective nutritional interventions can optimize the intake structure and quantity of nutrients, improve nutritional status and liver function, enhance tolerance to surgery or other treatments, enhance immune conditions, reduce complications during treatment, elevate quality of life, and extend survival time.	290 (72.14)
K9. Prompt identification and timely reporting of symptoms of malnutrition and immune-related events to healthcare professionals are not only beneficial for immunotherapy and ameliorating immune-related adverse symptoms and nutritional status but also increase the likelihood of continuing immunotherapy.	291 (72.39)

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K10. Liver cancer patients receiving immunotherapy should be managed comprehensively throughout the cycle, from screening and assessment to diagnosis, supportive treatment, monitoring, and follow-up, focusing on nutritional and adverse event management. 290 (72.14)

Attitude	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
A1. I consider nutritional support highly significant throughout the entire course of immunotherapy.	230 (27.21)	150 (37.31)	16 (3.98)	2 (0.50)	4 (1.00)
A2. I believe that targeted nutritional interventions can enhance the efficacy of immunotherapy.	196 (48.76)	175 (43.53)	25 (6.22)	2 (0.50)	4 (1.00)
A3. I deem continuous monitoring of adverse immune events to be essential.	208 (51.74)	160 (39.80)	32 (7.96)	0	2 (0.50)
A4. I would be concerned about adverse reactions following immunotherapy.	169 (42.04)	183 (45.52)	36 (8.96)	6 (1.49)	8 (1.99)

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A5. I find it necessary to monitor nutrition-related indicators comprehensively.	188 (46.77)	172 (42.79)	30 (7.46)	6 (1.49)	6 (1.49)
A6. I think consuming high-quality proteins, abundant dietary fiber, and appropriate carbohydrates is crucial.	216 (53.73)	158 (39.30)	23 (5.72)	3 (0.75)	2 (0.50)
A7. I wish to acquire further knowledge about nutritional support through professional channels.	200 (49.75)	163 (40.55)	32 (7.96)	2 (0.50)	5 (1.24)
A8. I desire to gain more insights through professional channels regarding self-management, emergency responses, and precautions for managing adverse events during immunotherapy.	193 (48.01)	175 (43.53)	27 (6.72)	4 (1.00)	3 (0.75)
A9. I am confident in maintaining a relatively favorable nutritional status.	179 (44.53)	165 (41.04)	45 (11.19)	7 (1.74)	6 (1.49)

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A10. I believe that maintaining a positive mindset and quality sleep are important during immunotherapy.	214 (53.23)	161 (40.05)	19 (4.73)	3 (0.75)	5 (1.24)

Practice	**Always**	**Frequently**	**Sometimes**	**Occasionally**	**Never**
P1. I can cooperate with medical personnel for comprehensive treatment monitoring and follow-up.	216 (53.73)	130 (32.34)	43 (10.70)	6 (1.49)	7 (1.74)
P2. I will regularly monitor nutrition-related indicators such as body weight, body mass index, grip strength, albumin, and prognostic nutritional index.	177 (44.03)	140 (34.83)	55 (13.68)	22 (5.47)	8 (1.99)
P3. If a physician recommends it, I will take medication to enhance appetite, digestion, and absorption.	192 (47.76)	132 (32.84)	53 (13.18)	18 (4.48)	7 (1.74)
P4. I will proactively seek relevant knowledge about immunotherapy nutrition and adverse reactions through	172 (42.79)	126 (31.34)	64 (15.92)	27 (6.72)	13 (3.23)

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professional channels such as healthcare providers, health promotion columns, books, and television.					
P5. I will undergo oral nutritional supplementation, including branched-chain amino acids, omega-3 fatty acids, and vitamin D if necessary.	162 (40.30)	118 (29.35)	60 (14.93)	31 (7.71)	31 (7.71)
P6. If required, I am prepared to receive enteral feeding through nasogastric/nasoenteric tubes.	133 (33.08)	38 (6.45)	46 (11.44)	36 (8.96)	149 (37.06)
P7. If necessary, I am open to receiving parenteral nutrition support (intravenous administration).	123 (30.60)	43 (10.70)	52 (12.94)	56 (13.93)	128 (31.84)
P8. I will maintain moderate physical exercise to improve my overall physical condition.	176 (43.78)	122 (30.35)	55 (13.68)	34 (8.46)	15 (3.73)
Lifestyle	**Never**	**Occasionally**	**Sometimes**	**Frequently**	**Always**

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In your daily lifestyle habits, what is your eating frequency for the following types:					
L1. Smoking	272 (67.66)	38 (9.45)	27 (63.72)	35 (8.71)	30 (7.46)
L2. Alcohol consumption	285 (70.90)	52 (12.94)	27 (6.72)	21 (5.22)	17 (4.23)
L3. Cooking methods involving frying, smoking, baking, pickling, etc.	223 (55.47)	100 (24.88)	47 (11.69)	19 (4.73)	13 (3.23)
L4. High-fat, high-salt, spicy foods (such as chili peppers, onions, ginger, raw garlic, and pepper)	212 (52.74)	100 (24.88)	50 (12.44)	27 (6.72)	13 (3.23)
L5. High-quality protein sources (legumes, eggs, meat, fish, shellfish, dairy products, etc.)	22 (5.47)	21 (5.22)	37 (9.20)	224 (55.72)	98 (24.38)
L6. Light and easily digestible foods (egg custard, millet porridge, lotus root powder, Chinese yam)	15 (3.73)	42 (10.45)	61 (15.17)	213 (52.99)	71 (17.66)

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L7. Foods rich in vitamins (fresh vegetables and fruits, such as spinach, cabbage, kiwi, tomatoes, etc.)	8 (1.99)	34 (8.46)	42 (10.45)	217 (53.98)	101 (25.12)
L8. Stimulants like coffee, chocolate, and strong tea	247 (61.44)	70 (17.41)	30 (7.46)	38 (9.45)	17 (4.23)
L9. Probiotics	202 (50.25)	90 (22.39)	51 (12.69)	37 (9.20)	22 (5.47)
L10. Sugary beverages	215 (53.48)	114 (28.36)	45 (11.19)	20 (4.98)	8 (1.99)
L11. Citrus fruits (grapefruit, pomelo, honey pomelo, etc.)	93 (23.13)	112 (27.86)	75 (18.66)	92 (22.89)	30 (7.46)

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Table S3. SEM model fit

Indicators	Reference	Results
CMIN/DF	1-3 Excellent, 3-5 Good	3.10
RMSEA	<0.08 Good	0.039
IFI	>0.8 Good	0.939
TLI	>0.8 Good	0.893
CFI	>0.8 Good	0.935

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