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The effect of oral nutritional supplementation combined with probiotics on the liver function and intestinal microflora in lung cancer chemotherapy patients through the gut-liver axis

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The role of gut microbiota in cancer treatment research is receiving increasing attention. This study aims to evaluate the oral nutritional supplementation combined with probiotics on the liver function and intestinal microflora of lung cancer chemotherapy patients. An evaluation was conducted involving 113 patients with lung cancer, who were given routine hospitalization diet and oral nutrition supplement (ONS). The intervention group received probiotic supplementation, while the control group received placebo. It lasted for 21 days. The primary endpoint was the changes in liver function and intestinal microflora. Secondary endpoints included nutrition and immune status, and blood lipids. Compared with the control group, there were differences in the serum levels of ALT, AST, endotoxin and the amount of gut microbiota in the intervention group ($P < 0.05$). However, no significant changes were found in nutrition, immune, and the blood lipids status. ONS combined with probiotics could improve the liver function and gut microbiota status of lung cancer chemotherapy patients. We speculate that this may be due to the role of supplementing probiotics in regulating the gut-liver axis.

Keywords Oral nutritional supplementation, Probiotics, Lung cancer, Gut-liver axis

Chemotherapy is a two-edged sword. On the one hand, it can inhibit the growth of tumors and the development of cancer; On the other hand, it causes cytotoxicity and side effects, which is closely linked to chemotherapy-induced gut microbial imbalances[1,2]. The imbalanced intestinal flora is not only linked to cancer developing and progressing, but also affects its therapeutic effects. Therefore, it is crucial to find new strategies to reduce the side effects of chemotherapy and to rebuild the microbiota in the gut.

Our previous research found that oral nutrition supplementation (ONS) can improve the nutritional and immune status of lung cancer patients[3], but there is limited research on the regulation of the gut-liver axis by oral nutrition combined with probiotics. Many studies have reported the probiotics could decrease the incidence of chemotherapy-induced gastrointestinal complications[4,5]. However, there is limited research on the effects of probiotics on liver function in chemotherapy patients. Therefore, in order to fill the gap, our study aims to observe the effect of oral nutritional supplementation combined with probiotics on the liver function and intestinal microflora of lung cancer chemotherapy patients through the gut-liver axis.

Methods and participants

This study was designed as a double-blinded randomized controlled trial. Neither the patients nor the study nurses/doctors knew the types of probiotics during the intervention. All patients, staff and outcome assessors remained blind until the final analysis. 113 patients with lung adenocarcinoma were selected from January 2023

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to December 2023 from Yuhuangding Hospital and they were randomized to the intervention group ($n=56$) and the control group ($n=57$) by one of the investigators, who was not involved in the trial, using computer-generated random numbers. One chemotherapy cycle was 21 days. The patients received pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 on day 1. The other clinical treatments and time points for the two groups of patients were the same. All were given routine hospitalization diet and ONS. The intervention group received probiotic supplementation, while the control group received placebo. It lasted for 21 days. The flow of the patient selection is shown in Fig. 1.

Ethics approval statements

The Ethics Committee of the Yuhuangding Hospital approved our interviews (approval: 2022 – 237) on December 1, 2022. Respondents gave written consent for review and signature before starting interviews.

The inclusion criteria (1) Lung cancer patients aged 60–70 who have been pathologically confirmed and require chemotherapy; (2) Not accompanied by severe liver and kidney dysfunction or metabolic diseases; (3) Tumor without metastasis.

The exclusion criteria (1) Used antibiotics within two weeks; (2) Patients with inflammatory bowel disease and other intestinal diseases; (3) Other factors that may affect the research results.

Probiotic and placebo

The probiotic beverage and placebo (both 100 ml/ bottle) were used as the test beverages. The probiotic beverage contained 10 billion or more *Lactobacillus casei* strain Shirota bacterial cells. The placebo was prepared with the same ingredients, except that it did not contain *Lactobacillus casei* and other probiotics. All patients were.

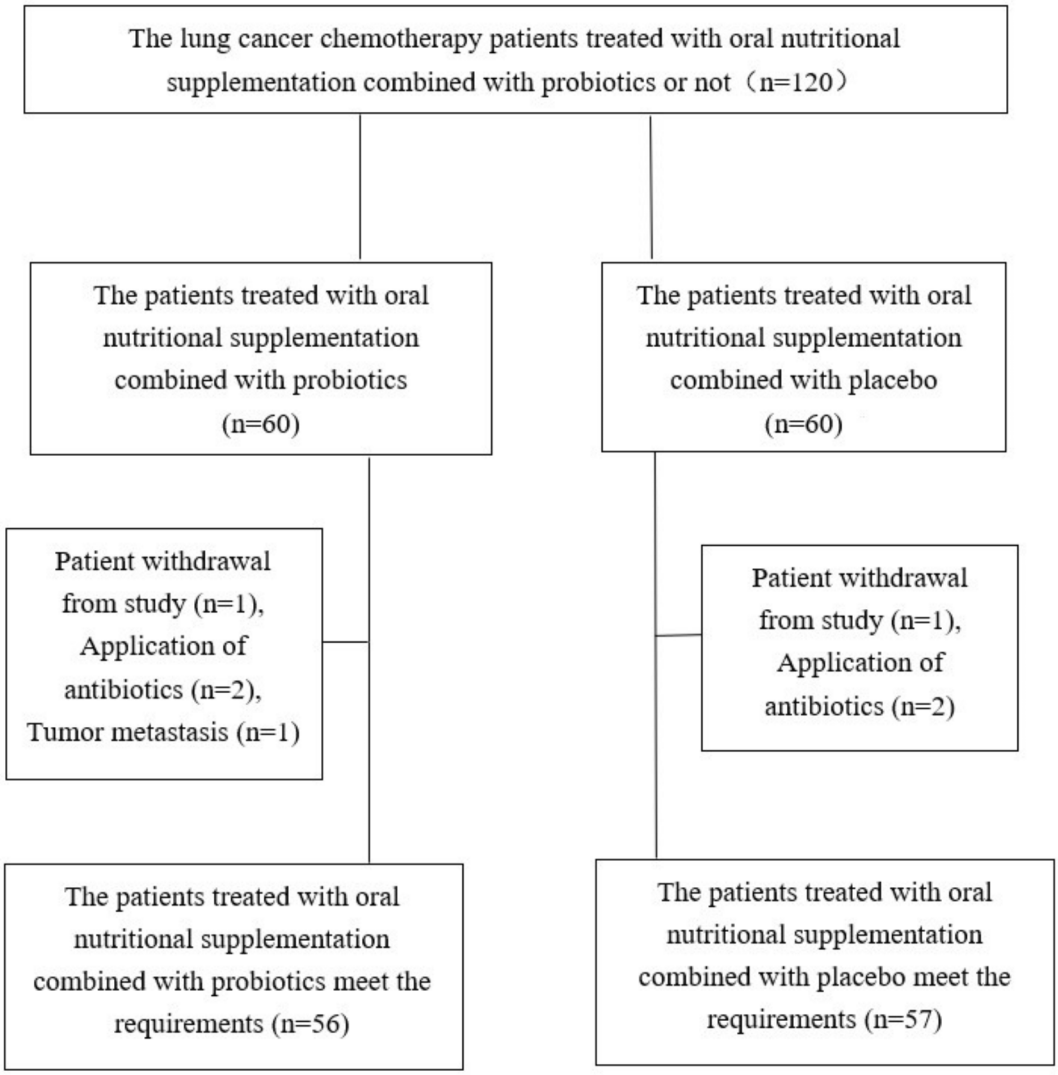

Fig. 1. The flow of the patient selection.

given 1 bottle/day.

Diet and ONS

The recommended diet calorie intake was set at 25 kcal/kg and protein at 1.0 g/kg[6]. The ONS used in this study was the "TEAIQIRUI" (Synutra International Inc) and it contains 250 kcal energy, 34.0 g carbohydrate, 10.1 g protein and 7.8 g fat per pack. All patients took two ONS packs daily. All patients were required to maintain the same dietary plan and daily physical activity during the intervention. They were asked to avoid using any probiotic supplements other than those provided by the researchers. All patients were reminded by phone or video. All patients were given one week dose of intervention at the beginning and returned to the hospital one week later to receive the next week's dose. By counting the empty bottles brought back by patients every week and calculating their dietary diary, the patient's compliance with the dietary plan and supplements was indirectly evaluated.

Data collection

The fresh feces and fasting blood samples were collected in the morning before and after intervention. Body mass index (BMI) was calculated and used in the analysis. The laboratory data included alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), total protein (TP), prealbumin (PA), albumin (ALB), Hemoglobin (Hb), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), Endotoxin, IgG, IgA, and IgM.

Real-time fluorescence quantitation polymerase chain reaction (PCR) was used to quantify bacterial genomic DNA content, involving *Escherichia coil*, *Enterococcus*, *Bacteroides fragilis*, *Bifidobacterium*, and *Lactobacillus.*

Statistical analyses

We conducted all statistical analyses in SPSS 22.0. The group differences were tested by one-way ANOVA or chi-squared test. We carried out the generalized linear models (GLM) to assess the effects of the supplementation on all the outcomes between the two groups. The GLM with adjustment for age, BMI, liver function, lipid metabolism and immune status was used to test for differences between groups. $P < 0.05$ was considered to be statistically significant.

Results

Baseline information

Table 1 shows the baseline information of all enrolled patients. There were no significant differences between the two groups ($P > 0.05$).

Comparison of liver function and blood lipids

As shown in Table 2, the serum levels of ALT and AST in the intervention group were significantly decreased than those in the control group after intervention ($P < 0.05$). However, there was no significant difference in serum levels of GGT, TG, TC, HDLC, and LDLC between the two groups of patients after intervention ($P > 0.05$).

Comparison of nutritional status and immune function

After intervention, the TP, ALB, PA, and Hb were reassessed to monitor nutrition stability. The IgA, IgG, and IgM were assessed to monitor immune function changes. As shown in Table 3, compared with the control group, there was no significant difference between the nutrition and immune status indicators after intervention ($P > 0.05$). The endotoxin in the intervention group were significantly decreased than those in the control group after intervention ($P < 0.05$).

Comparison of gut microbiota status

As shown in Table 4, the amount of *Lactobacillus acidophilus*, *Bifidobacterium longum*, and *Bacteroides fragilis* in the intervention group were significantly increased than that in the control group ($P < 0.05$), while the amount of *Escherichia coli* and *Enterococcus facalis* were significantly decreased after intervention ($P < 0.05$).

Discussion

Chemotherapy can damage the gastrointestinal mucosa, destroy the immune system, and cause changes in gut microbiota[7]. In this study, we demonstrated that ONS combined with probiotics could improve the liver function and gut microbiota status of lung cancer chemotherapy patients. We speculate that this may be due to the role of supplementing probiotics in regulating the gut-liver axis.

Proper nutritional therapy is crucial for cancer patients, as malnutrition not only weakens the immune system but also affects their survival and recovery[8,9]. The additional use of ONS is advised when the normal food is not effective in reaching nutritional goals[10]. Previous studies have shown that ONS can improve the nutritional and immune status of cancer patients[11,12]. In this research, the TP, ALB, PA, and Hb were reassessed to monitor nutrition stability. Although these indicators may not reflect nutritional status well due to the influence of other factors, their level is still the critical parameters of the assessment of nutritional status in clinical practice[13]. The patients in this study were required to have the same diet and ONS and there is no difference in energy and nutrient intake, which may be the reason why we did not observe significant changes in nutritional and immune status.

The previous studies have shown that modulation of the gut microbiota can improve the function of the liver and reduce inflammation[14–16]. This is consistent with our research findings. In this study, we found significant differences in liver function between the intervention group and the control group, indicating that probiotic

	The intervention group ($n=56$)	The control group ($n=57$)	P
Age	62.05 ± 5.13	63.38 ± 6.02	0.213
BMI (kg/m^2)	17.56 ± 2.25	18.22 ± 2.07	0.408
TP (g/L)	60.13 ± 5.27	62.42 ± 6.08	0.429
ALB(g/L)	32.42 ± 3.36	33.65 ± 3.78	0.335
PA (mg/L)	103.79 ± 13.62	112.49 ± 14.83	0.392
Hb (g/L)	101.74 ± 5.56	99.82 ± 4.93	0.336
ALT, U/L	25.38 ± 5.42	27.05 ± 6.07	0.461
AST, U/L	21.25 ± 5.67	20.38 ± 6.12	0.257
GGT, U/L	50.50 ± 9.07	48.25 ± 8.29	0.472
TG, mmol/L	1.51 ± 0.61	1.47 ± 0.28	0.372
TC, mmol/L	4.74 ± 1.08	4.83 ± 0.77	0.413
LDLC, mmol/L	2.91 ± 0.43	3.05 ± 0.32	0.569
HDLC, mmol/L	1.00 ± 0.21	1.02 ± 0.19	0.486
Endotoxin, EU/ml	0.16 ± 0.02	0.17 ± 0.01	0.318
IgA (g/L)	2.83 ± 0.32	2.57 ± 0.28	0.416
IgG (g/L)	11.28 ± 0.89	10.67 ± 1.01	0.272
IgM (g/L)	1.62 ± 0.26	1.55 ± 0.18	0.204
Escherichia coli, copies/g	7.14 ± 0.52	7.26 ± 0.64	0.583
Enterococcus facalis, copies/g	6.82 ± 1.06	7.01 ± 0.94	0.275
Bacteroides fragilis, copies/g	7.43 ± 1.22	8.45 ± 1.27	0.622
Bifidobacterium longum, copies/g	8.04 ± 0.82	7.96 ± 0.77	0.376
Lactobacillus acidophilus, copies/g	6.82 ± 1.02	7.24 ± 1.13	0.426
Stage III	29(51.79)	28(49.12)	0.327
Stage IV	27(48.21)	29(50.88)	

Table 1. Baseline data of patients with lung cancer. Values are presented as mean ± SD or percentages. *BMI* Body Mass Index, *Hb* hemoglobin, *TP* total protein, *ALB* albumin, *PA* prealbumin, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* gamma-glutamyltransferase, *TG* triglyceride, *TC* total cholesterol, *HDLC* high density lipoprotein cholesterol, *LDLC* low density lipoprotein cholesterol.

	The intervention group ($n=56$)	The control group ($n=57$)	Between-group comparisons	
			P^1	P^2
ALT, U/L	12.01 ± 4.37	26.98 ± 5.13*	0.000	0.013
AST, U/L	11.47 ± 4.22	20.19 ± 4.82*	0.000	0.026
GGT, U/L	42.16 ± 8.24	47.93 ± 6.26	0.000	0.257
TG, mmol/L	1.48 ± 0.53	1.42 ± 0.39	0.000	0.388
TC, mmol/L	4.26 ± 0.83	4.57 ± 0.69	0.000	0.546
LDLC, mmol/L	2.25 ± 0.34	2.89 ± 0.27	0.000	0.338
HDLC, mmol/L	1.21 ± 0.35	1.07 ± 0.21	0.000	0.613

Table 2. Effect of oral nutritional supplementation combined with probiotics on liver function and lipid metabolism. Values are presented as mean ± SD. *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* gamma-glutamyltransferase, *TG* triglyceride, *TC* total cholesterol, *HDLC* high density lipoprotein cholesterol, *LDLC* low density lipoprotein cholesterol; *$P<0.05$ versus the intervention group. P^1 value was calculated by a crude general linear model to test the difference in treatment effects between the groups. P^2 value was calculated by a full general linear model with adjustments for age, BMI, the liver function, lipid metabolism and immune status to test the difference in treatment effects between the groups.

supplementation has an improvement effect on liver function in cancer patients. One of the key elements contributing to the regulation of host health is now considered to be the gut microbiota and the gut microbiota abnormalities have been linked to many diseases[17]. There is increasing evidence that the gut microbiota and its metabolites directly influence the integrity of the intestinal mucosa, while the increased permeability and endotoxemia result from intestinal dysbiosis, resulting in aberrant activation of inflammation[18–20]. In this study, we found the amount of *Lactobacillus acidophilus*, *Bifidobacterium longum*, and *Bacteroides fragilis* in the intervention group were significantly increased than that in the control group, while the amount of *Escherichia*

	The intervention group ($n=56$)	The control group ($n=57$)	Between-group comparisons	
			P^1	P^2
TP (g/L)	61.25 ± 4.83	63.14 ± 5.29	0.000	0.358
ALB(g/L)	33.19 ± 3.26	33.47 ± 3.64	0.000	0.416
PA (mg/L)	128.54 ± 12.17	121.32 ± 13.16	0.000	0.143
Hb (g/L)	104.55 ± 4.87	100.76 ± 4.25	0.000	0.287
Endotoxin, EU/ml	0.03 ± 0.11	0.21 ± 0.12*	0.000	0.037
IgA (g/L)	2.94 ± 0.33	2.62 ± 0.27	0.000	0.355
IgG (g/L)	13.56 ± 0.73	11.12 ± 1.25	0.000	0.483
IgM (g/L)	1.71 ± 0.24	1.61 ± 0.23	0.000	0.376

Table 3. Comparison of the nutrition, immune, and endotoxin status between two groups after intervention. Values are presented as mean ± SD. *Hb* hemoglobin, *TP* total protein, *ALB* albumin, *PA* prealbumin; $^*P<0.05$ versus the intervention group. P^1 value was calculated by a crude general linear model to test the difference in treatment effects between the groups. P^2 value was calculated by a full general linear model with adjustments for age, BMI, the liver function, lipid metabolism and immune status to test the difference in treatment effects between the groups.

	The intervention group ($n=56$)	The control group ($n=57$)	*P*
Escherichia coli, copies/g	5.26 ± 0.49	9.47 ± 0.58	0.034
Enterococcus facalis, copies/g	5.04 ± 1.13	8.26 ± 1.05	0.032
Bacteroides fragilis, copies/g	8.17 ± 1.15	6.38 ± 1.27	0.047
Bifidobacterium longum, copies/g	9.76 ± 0.64	5.13 ± 0.71	0.018
Lactobacillus acidophilus, copies/g	7.96 ± 1.13	4.82 ± 1.04	0.026

Table 4. Comparison of the amount of gut microbiota. Values are presented as mean ± SD.

coli and *Enterococcus facalis* were significantly decreased after intervention. Meanwhile, the endotoxin in the intervention group were significantly decreased than those in the control group after intervention. Previous studies have indicated that after receiving chemotherapy, cancer patients experience a decrease in probiotics and an increase in pathogenic bacteria[21,22], which is consistent with our research findings. Our research findings indicate that chemotherapy can lead to dysbiosis of the gut microbiota, while supplementing with *Lactobacillus casei* can increase beneficial bacteria while reducing harmful microbial species. The protective effect of *Lactobacillus acidophilus* on the integrity of the intestinal barrier is thought to be due to its small non-protein molecules[23]. However, we assumed that the supplementation of probiotics had played a positive role by regulating the gut-liver axis. On the one hand, it reduced intestinal mucosal damage to lower endotoxin levels; On the other hand, it protected liver function by increasing beneficial bacterial communities. Our previous research has confirmed that supplementation of Lactobacillus casei could improve liver function and regulate intestinal flora disorders in patients with alcoholic liver injury[24]. Previous studies have shown that supplementation with probiotics can effectively reduce gastrointestinal complications caused by chemotherapy and restore bacterial diversity at the phylum and genus levels[25]. The supplementation of probiotics significantly reduced the incidence of chemotherapy related cognitive impairment and altered the composition of gut microbiota[26] and may help regulate the immune system of chemotherapy patients[27]. Our results showed no significant difference in immunity, which may be due to the same nutritional support between the two groups, or due to the short intervention time or different intervention doses.

The limitation of this study was the short intervention period. In addition, the design of the study and the analysis of the data did not take into account the influence of the heterogeneity of the gut microbiome caused by individual differences on the experimental results. Third, to further explore the underlying mechanisms of action of probiotics, more well-designed and large-scale studies are urgently needed. Fourth, the standardized clinical use of probiotics, including probiotic species, optimal dose and duration of use, should be more clearly defined in the future.

Conclusions

In summary, ONS combined with probiotics could improve the liver function and gut microbiota status of lung cancer chemotherapy patients. We speculate that this may be due to the role of supplementing probiotics in regulating the gut-liver axis. According to our research findings, the combination therapy of ONS and probiotics may be a promising adjuvant therapy for cancer chemotherapy patients.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Author contributions

X L, Y W, and W G equally contributed to the conception and design of the research; K T contributed to the design of the research; J K contributed to the acquisition and analysis of the data; F S contributed to the interpretation of the data; X L and Y W drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

The study was approved by the Ethics Committee of the Yuhuangding Hospital (No. 2022 – 237). All procedures involving human participants have been conducted according to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Additional information

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