

Effect of Preoperative Nutritional and Exercise Intervention in Older Frail Patients Undergoing Hepatectomy for Hepatocellular Carcinoma

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Abstract

Background

Frailty is related with poor surgical outcomes in several types of cancer. This study aimed to investigate the importance of preoperative intervention with nutrition and exercise for older frail patients undergoing hepatectomy for hepatocellular carcinoma (HCC).

Methods

Older frail patients who underwent upfront hepatectomy for HCC at our institution between April 2007 and August 2024 were retrospectively reviewed. Clinicopathological factors were compared between the intervention and non-intervention groups.

Results

In 51 older patients with frailty, the postoperative hospital stay was significantly shorter in the intervention group than in the non-intervention group. The neutrophil-to-lymphocyte ratio was significantly decreased after the intervention compared with before the intervention ($p < 0.01$). When the postoperative hospital stay was analyzed according to the severity of frailty, the postoperative hospital stay was significantly shorter in the intervention group than in the non-intervention group (15 vs. 20 days, $p = 0.02$). The long-term outcome was not significantly different between intervention and non-intervention groups.

Conclusions

Preoperative intervention with nutrition and exercise may be associated with improved short-term outcomes in older frail patients with HCC who undergo hepatectomy.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a major malignancy worldwide and is associated with a substantial risk of cancer-related mortality (1). As the proportion of older individuals continues to increase, the number of older patients diagnosed with HCC is also expected to rise. Advances in surgical techniques and perioperative management have established hepatectomy as an important treatment option for patients with resectable HCC (2).

The progressive aging of the population has become an important consideration in the management of malignancies. In particular, chronological age alone may not adequately reflect the physiological reserve of older patients undergoing major surgery. Therefore, frailty has attracted increasing attention as a

multidimensional and heterogeneous condition characterized by reduced physiological reserve and increased vulnerability to stressors (3). We previously demonstrated that frailty was associated with unfavorable short- and long-term outcomes in patients with HCC who underwent hepatectomy (2). Therefore, strategies to improve surgical outcomes in frail patients are increasingly important, particularly in the context of an aging population.

Frailty is characterized by impaired physical function and is frequently accompanied by reduced muscle strength and an inadequate nutritional status. Previous studies have also suggested an association between frailty and systemic inflammation; elevated inflammatory markers are related to loss of muscle mass and strength, reduced physical activity, and impaired mobility in older individuals (4, 5). Additionally, insufficient nutrient intake and a poor nutritional status have been reported to be related to inflammation (6) and progression of frailty (7). These findings suggest that physical activity and the nutritional status represent potentially modifiable factors in frail patients. Accordingly, several studies have investigated the effects of exercise training, nutritional supplementation, or combined interventions on frailty and physical function (8). We also previously reported that a preoperative program combining exercise and nutritional support was associated with improved postoperative outcomes in patients who underwent gastrectomy for gastric cancer (9). However, whether a similar preoperative intervention can improve postoperative outcomes in frail patients with HCC undergoing hepatectomy remains unclear.

Therefore, this study aimed to evaluate the clinical utility of a preoperative exercise and nutritional intervention in frail patients with HCC undergoing hepatectomy.

PATIENTS AND METHODS

Patients

Fifty-one patients aged 65 years or older with frailty and HCC who underwent hepatectomy at Tokushima University Hospital between April 2007 and August 2024 were included in this retrospective study. The eligibility criteria were as follows: (a) age ≥ 65 years and the presence of frailty; (b) no previous treatment for HCC before hepatectomy and no extrahepatic metastases; and (c) pathological confirmation of HCC. The patients were classified into two groups according to whether they received preoperative intervention: the intervention group (n=21) and the non-intervention group (n=30).

The patients' demographics and baseline clinical characteristics, including sex, age, viral infection status, comorbidities, liver function parameters, and the indocyanine green retention rate at 15 min, were obtained from the medical records. Frailty was assessed using the Clinical Frailty Scale (CFS), which is a nine-point global assessment tool that evaluates multiple aspects of functional status, including mobility, energy, physical activity, and function (10). In this study, a CFS score ≥ 4 was considered indicative of frailty (2).

Tumor-related characteristics, including tumor markers, tumor number, maximum tumor diameter, vascular invasion, and tumor stage according to the Japanese Tumor-Node-Metastasis classification

established by the Liver Cancer Study Group of Japan, were also collected (11). The immuno-nutritional status was evaluated using the neutrophil-to-lymphocyte ratio (NLR) (12) and prognostic nutritional index (PNI) (13). Postoperative complications were graded according to the Clavien–Dindo classification (14). The median follow-up period was 1.7 years (range, 0.1–10.6 years). This study was approved by the Institutional Review Board of Tokushima University (approval No. 3366). This study was in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Nutrition and exercise intervention

Patients with frailty who received the preoperative intervention were instructed to achieve a daily energy intake of >30 kcal/kg of ideal body weight and a daily protein intake of >1.5 g/kg ideal body weight. The target energy and protein intakes were determined in consultation with a nutritional support specialist.

The preoperative exercise program consisted of walking, resistance training, and aerobic exercise (**Figure 1**). Initially, the patients performed the exercise program in the hospital ward. Patients who showed sufficient physical activity subsequently received training in the rehabilitation center. All exercise sessions were performed under the supervision of rehabilitation staff. The duration of the preoperative intervention ranged from 7 to 35 days, with a median duration of 14 days.

Statistical analysis

Continuous variables were compared between the two groups using the Mann–Whitney U test, whereas categorical variables were compared using the chi-square test. Overall survival curves were estimated using the Kaplan–Meier method, and differences between the groups were assessed using the log-rank test. A two-sided p value <0.05 was considered statistically significant. All statistical analyses were performed using JMP version 8.0.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patients' background

The baseline characteristics of the patients are shown in **Table 1**. Patients in the intervention group were significantly older than those in the non-intervention group ($p<0.01$). In contrast, no significant differences in sex, comorbidities, liver function parameters, or CFS were observed between the two groups. Similarly, tumor-related characteristics, including tumor markers, tumor number and size, and tumor stage, were not significantly different between the groups. No significant difference was observed in the type of surgical procedure performed between the two groups.

Short- and long-term outcomes

The short-term postoperative outcomes are shown in **Table 2**. The time to independent ambulation tended to be shorter in the intervention group than in the non-intervention group, although this was not

significant ($p=0.06$). In contrast, the postoperative hospital stay was significantly shorter in the intervention group than in the non-intervention group ($p=0.02$). The incidence of postoperative complications was not significantly different between the groups. When the postoperative hospital stay was analyzed according to the severity of frailty, patients with a CFS score of 4 had a significantly shorter hospital stay than those with a CFS score ≥ 5 ($p=0.02$; **Figure 2**). Regarding long-term outcomes, cancer-specific survival was not significantly different between the intervention and non-intervention groups (**Figure 3**).

Immuno-nutritional status

Changes in immuno-nutritional parameters before and after the preoperative intervention are shown in **Figure 4**. The NLR was decreased after the intervention in 16 of the 21 patients compared with before the intervention, resulting in a significant reduction in the NLR in the intervention group. In contrast, neither the PNI nor serum albumin levels showed a significant change following the intervention.

Representative cases

1. Case with improvement

A 76-year-old woman with a CFS score of 4 underwent 8 days of preoperative intervention followed by partial hepatectomy of segment 8. She showed good adherence to the exercise program, and several parameters improved after the intervention. Her handgrip strength increased from 19 to 21 kg, while her NLR decreased from 2.8 to 1.4 and her PNI increased from 42 to 46. She was able to participate in rehabilitation training by postoperative day 6 and was discharged on postoperative day 12.

2. Case without improvement

A 78-year-old man with a CFS score of 6 underwent 20 days of preoperative intervention followed by partial hepatectomy of segments 4 and 8. His exercise program was limited to activities of daily living because of left hemiparesis resulting from a previous stroke. Additionally, his daily energy intake was approximately 1,500 kcal, which is below the target intake of 1,800 kcal/day. His NLR increased from 2.2 to 3.5, and his PNI decreased from 39 to 35 after the intervention. Postoperatively, he required enteral nutrition, and independent ambulation was achieved on postoperative day 8. He was unable to return home and was transferred to another hospital on postoperative day 23.

DISCUSSION

In this study, we retrospectively investigated the effects of preoperative nutrition and exercise intervention in frail patients with HCC who underwent hepatectomy. Although cancer-specific survival was not significantly different between the two groups, preoperative intervention was associated with improved postoperative short-term outcomes and a reduction in the NLR.

Recently, the adverse effect of frailty has received increasing attention in surgery. Frailty is an aggregate expression of susceptibility to adverse health outcomes because of age-related and disease-related deficits that accumulate across multiple domains (10). Longitudinal studies in geriatric populations have shown that frailty is associated with functional decline, hospitalization, and death (15, 16). We previously reported that patients with frailty who had radical surgery for cancer had a poor prognosis (2, 17, 18). In HCC, frail patients showed worse short- and long-term outcomes (2). The worse short-term outcomes may be attributable to the patients' increased vulnerability to physiological stress, which may lead to postoperative complications and a prolonged hospital stay (19). Improving outcomes after surgery of frail patients is an urgent issue because of the increasingly aging society.

Some studies have examined the effect of prehabilitation. Aerobic exercise has been reported to improve cardiopulmonary and functional capacity in older or surgical populations (20). Furthermore, short-term resistance exercise prehabilitation has been shown to mitigate disuse-induced muscle anabolic resistance, thereby reducing muscle atrophy (21). A recent randomized, controlled trial (22) on prehabilitation for patients undergoing liver surgery showed that a prehabilitation program did not affect postoperative clinical outcomes, but it showed an improvement in functional capacity. In this trial, the duration of exercise was only 1 week, and this program did not include nutritional intervention. Frail patients show not only muscle atrophy but also a low nutritional status. Therefore, combined intervention of exercise and nutrition appears to be necessary for frail patients. In fact, a meta-analysis showed that protein supplementation (including amino acid and enriched protein supplements) plus exercise training resulted in greater effects on outcomes, such as lean body mass, hand grip and leg strength, than with exercise training alone (23).

We have previously reported the usefulness of nutrition and exercise intervention in frail patients with gastric cancer who underwent gastrectomy (9). This intervention shortened the postoperative hospital stay and improved the NLR, similar to the current study. Regarding the NLR, there is a broad consensus that chronic low-grade inflammation may play an important role in the advancement of frailty (24), and the NLR reflects an inflammatory response and surgical stress (25). In older inpatients with comorbidities, the NLR showed a positive correlation with the frailty index (26). Some reports have indicated that intervention improves the NLR. A supervised exercise program decreased the NLR in patients with cancer undergoing anti-cancer therapy (27), and enteral nutrition support also decreased the NLR and endotoxin levels in patients undergoing gastrectomy (28). Furthermore, patients with gastrointestinal cancer and a high NLR showed a longer hospital stay and worse postoperative outcomes. These findings suggest that a high NLR reflects the systemic inflammatory status and is associated with delayed postoperative recovery and a prolonged hospital stay. In our study, the NLR improved after intervention, whereas the PNI and albumin levels did not significantly change. One possible explanation for this difference in results is that inflammatory markers, such as the NLR, may respond more rapidly to short-term preoperative intervention than conventional nutritional parameters, such as albumin or the PNI. Although an improvement in the NLR might be related to a short postoperative hospital stay, further studies are warranted to clarify whether the reduction in the NLR contributes to improved postoperative recovery.

In this study, frail patients with a CFS score ≥ 5 showed a significantly longer hospital stay than those with a score of 4, and the effect of preoperative intervention might be limited. Some studies have shown a longer duration of prehabilitation in gastrointestinal cancer (22, 29). Regarding hepatectomy, 2 weeks of intervention appears to be appropriate for frail patients with a CFS score of 4, and a longer intervention period may be necessary for patients with CFS score ≥ 5 .

This study has several limitations. First, the patients in our study were enrolled in only one center, and the number of cases was small. Second, temporal confounding cannot be excluded because the intervention group consisted of patients treated after the implementation of the preoperative intervention program, whereas the non-intervention group consisted of patients treated before its implementation. Changes in perioperative management and surgical practice over time may have affected postoperative outcomes. Further study in a larger, prospectively collected population is warranted to confirm these results.

In conclusion, preoperative intervention with exercise and nutrition may improve the short-term outcome in older frail patients who undergo hepatectomy for HCC.

Abbreviations

HCC, hepatocellular carcinoma; ICGR15, indocyanine green retention rate at 15 min; CFS, Clinical Frailty Scale; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; BMI: body mass index, B: type B hepatitis, C: type C hepatitis, NBNC: non-B and non-C hepatitis, AFP: α -fetoprotein, PIVKA-II; protein induced by vitamin K absence or antagonist-II; CD, Clavien–Dindo

Declarations

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Conflict of interest

All authors have no conflict of interest related to this study.

Ethics statement

This study was approved by the ethics committee of Tokushima University Hospital in Tokushima, Japan (no. 3366), and all methods were carried out in accordance with relevant guidelines and regulations.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Patient consent for publication: The requirement for informed consent was waived with approval by the ethics committee of Tokushima University Hospital, and an information disclosure statement was uploaded onto the homepage of our hospital website for opt-out.

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Tables

Table 1 Patient characteristics in two groups

Variable	Intervention (n=21)	Without intervention (n=30)	P-value
Age (years)	81 (66-93)	76 (65-84)	<0.01
Sex (M / F)	15 / 6	18 / 12	0.40
BMI (kg/m ²)	23.1 (22.3-25.7)	23.9 (20.1-26.4)	0.89
Etiology (B / C / NBNC)	1 / 6 / 14	3 / 13 / 14	0.35
Cerebrovascular disease	5 (23.8%)	3 (10.0%)	0.19
Cardiovascular disease	4 (19.1%)	4 (13.3%)	0.58
Hemoglobin (g/dL)	12.3 (11.3-13.0)	12.7 (11.8-13.5)	0.58
Platelet (*10 ⁴ /μL)	17.2 (13.3-28.1)	19.6 (13.9-24.5)	1.00
Albumin (g / dL)	3.9 (3.5-4.3)	3.7 (3.3-4.1)	0.28
ICGR15 (%)	11.7 (8.4-16.0)	13.2 (7.0-20.0)	0.86
Child-Pugh score (5 / ≥6)	14 / 7	19 / 11	0.81
CFS (4 / ≥5)	14 / 7	21 / 9	0.80
AFP (ng/mL)	9 (4-365)	18 (6-82)	56
PIVKA-II (AU/mL)	386 (84-3835)	367 (29-2114)	0.32
Tumor number (single / multiple)	18 / 3	25 / 5	0.90
Tumor diameter (cm)	5.2 (3.5-7.0)	4.2 (3.0-6.4)	0.19
Portal vein invasion (- / +)	16 / 5	26 / 4	0.34
Tumor differentiation (well / mod / por)	1 / 17 / 3	2 / 21 / 7	0.67
Stage (I, II / III, IV)	15 / 6	21 / 9	0.91
Procedure (minor / major)	16 / 5	16 / 14	0.35

BMI: body mass index, B: type B hepatitis, C: type C hepatitis, NBNC: non-B and non-C hepatitis, ICG15R: indocyanine green retention rate, CFS: clinical frailty scale. AFP: α-fetoprotein, PIVKA-II; protein induced by vitamin K absence or antagonist-II

Values are presented as median (IQR).

Table 2 Factors of postoperative short-term outcomes in two groups

Variable	Intervention (n=21)	Without intervention (n=30)	P-value
Delirium	4 (19.1%)	5 (16.7%)	0.83
Postoperative complications			
Total	6 (28.6%)	9 (30.0%)	0.91
CD $\geq$ III	2 (9.5%)	4 (13.3%)	0.67
Pneumoniae	0 (0%)	2 (6.7%)	0.14
Bile leakage	1 (4.8%)	1 (3.3%)	0.80
Refractory ascites	0 (0%)	3 (10.0%)	0.07
Time to independent walk (days)	2 (2-3)	3 (2-5)	0.06
Postoperative hospital stay (days)	15 (13-20)	20 (16-24)	0.02

CD: Clavien-Dindo

Values are presented as median (IQR).

Figures

Figure 1



Figure 1

Preoperative rehabilitation in our department.

Figure 2

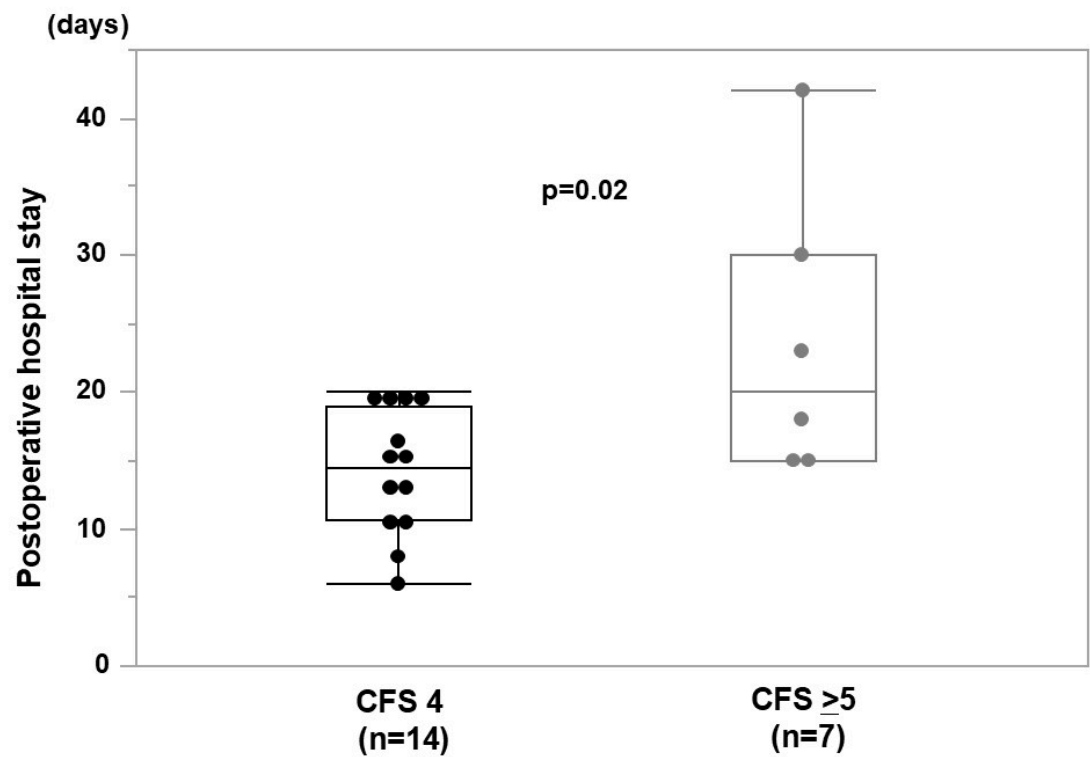


Figure 2

Postoperative hospital stay of frail patients with intervention. Patients with CFS 4 had a significantly shorter postoperative hospital stay than those with CFS ≥ 5 .

Figure 3

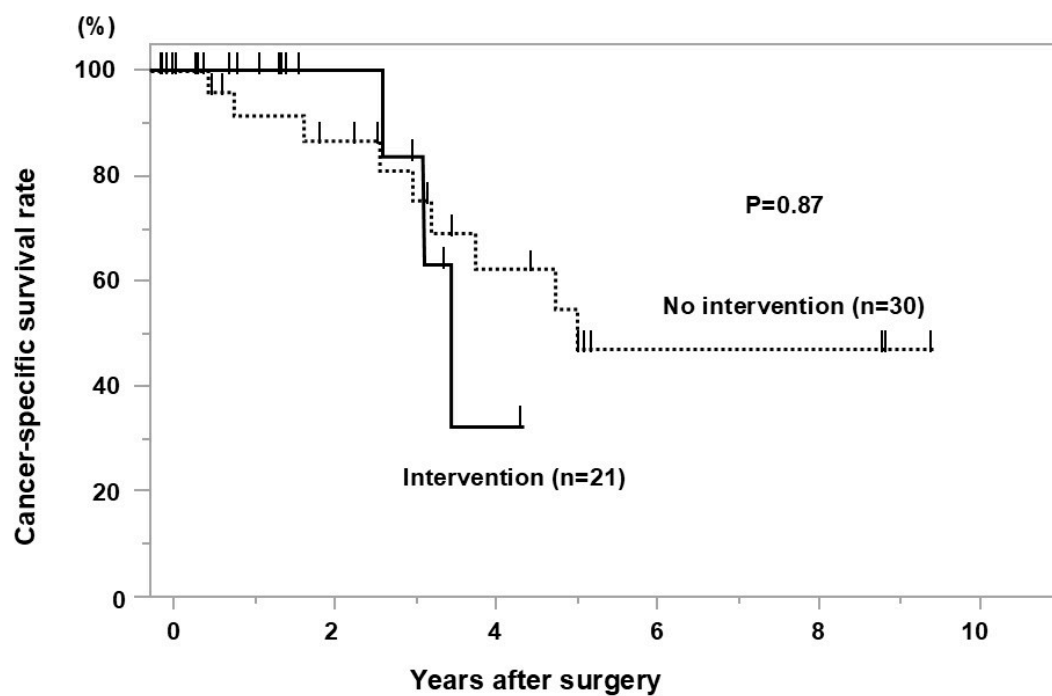


Figure 3

Cancer-specific survival rate of frail patients. There was no significant difference between two groups.

Figure 4

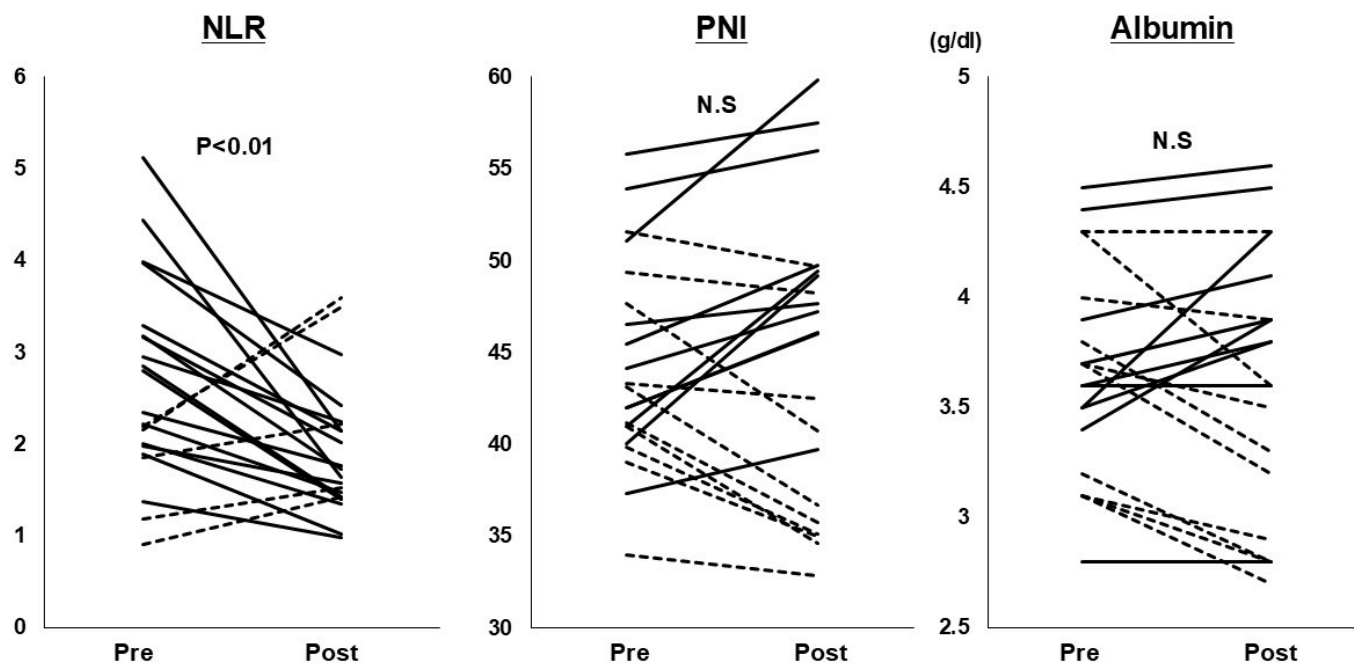


Figure 4

Changes of NLR, PNI and albumin levels between pre- and post-intervention. The NLR decreased after the intervention in 16 of the 21 patients, resulting in a significant reduction in NLR in the intervention group ($p < 0.01$). In contrast, neither PNI nor serum albumin levels showed a significant change following the intervention.