Factors Predicting Over-Time Weight Increase After Liver Transplantation: A Retrospective Study

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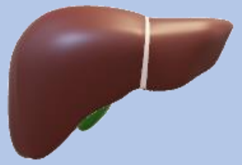
Graphical Abstract

Factors Predicting Over-Time Weight Increase After Liver Transplantation: A Retrospective Study

Background

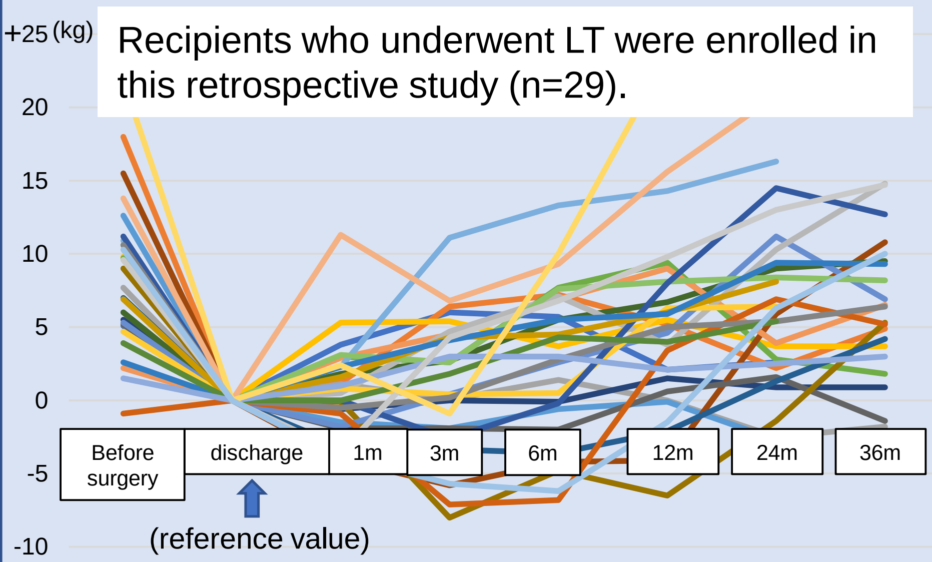
- Post- liver transplantation (LT) weight control is important for long-term outcomes.



- Recently, lifestyle-related diseases, such as obesity and nonalcoholic fatty liver disease (NAFLD), have gained attention as complications after LT.

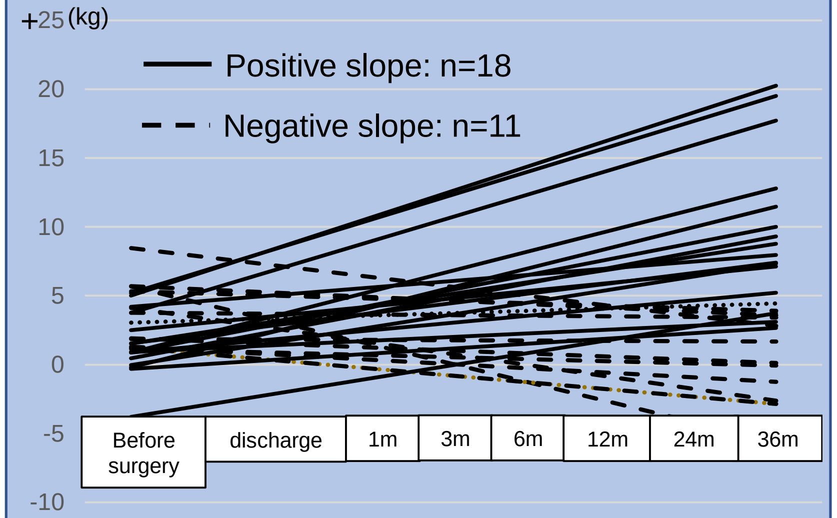
- The present study aimed to investigate the weight change over time after LT to identify risk factors for weight gain.

Over-time weight change



- Almost all transplant recipients had weight loss at discharge but experienced weight gain thereafter in the short term.
- non-obese recipients aged ≤50 years gained weight at earlier time points.

Trend of weight change in long term



- Body mass index (BMI) ≤23 had a positive trend in the slope of approximate postoperative weight line at longer periods.

Conclusion：Weight control in the early post-transplant period is important to improve long-term prognosis.

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Factors Predicting Over-Time Weight Increase After Liver Transplantation: A Retrospective Study

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Running Title: the risk factor of weight increase in liver transplantation

Abbreviations: ALBI; albumin-bilirubin, BMI; body mass index, ICU; intensive care unit, LT; liver transplantation, MELD; end-stage liver disease, NAFLD; nonalcoholic fatty liver disease, NASH; nonalcoholic steatohepatitis, ROC; receiver operating characteristic curve

Tables: 2

Figures: 3 (color – No)

Disclosures: The authors declare no conflicts of interest.

Highlights:

- Post-transplant weight control is an important factor affecting long-term outcomes.
- Younger patients and those with BMI <25 were at risk of post-transplant weight gain.
- Education on post-transplant weight control is necessary for good outcomes.
- This can important to improve long-term prognosis after LT.

ABSTRACT

Background: Post-transplantation weight control is important for long-term outcomes; however, few reports have examined postoperative weight change. This study aimed to identify perioperative factors that contribute to post-transplantation weight change.

Patients and Methods: Twenty-nine patients who underwent liver transplantation between 2015 and 2019 with an overall survival of >3 years were analyzed.

Main Findings: The median age, model for end-stage liver disease score, and preoperative body mass index (BMI) of the recipients were 57, 25, and 23.7, respectively. Although all but one recipient lost weight, the percentage of recipients who gained weight increased to 55% (1 month), 72% (6 months), and 83% (12 months). Among perioperative factors, recipient age ≤50 years and BMI ≤25 were identified as risk factors for weight gain within 12 months ($P < 0.05$), and patients with age ≤50 years or BMI ≤25 recipients gained weight more rapidly ($P < 0.05$). The recovery time of serum albumin level ≥4.0 mg/dL was not statistically different between the two groups. The weight change during the first 3 years after discharge was represented by an approximately straight line, with 18 and 11 recipients showing a positive and negative slope, respectively. BMI ≤23 was identified as a risk factor for a positive slope of weight gain ($P < 0.05$).

Conclusions: Although postoperative weight gain implies recovery after transplantation, a recipient with a lower preoperative BMI should strictly manage body weight as they may be at

higher risk of rapid weight increase.

Keywords: preoperative, body mass index, weight change, post-transplant, risk factor, obesity

INTRODUCTION

Liver transplantation (LT) is the only definitive treatment for patients with end-stage liver disease. According to an annual report published by the Japanese Society for Liver Transplantation, the 1-year recipient survival rates for brain-dead and living donor liver transplantation performed through 2010 were 80.5% and 83.4%, respectively [1]. In 2017, the survival rates increased to 88.5% and 85.0%, respectively, suggesting improved surgical techniques and perioperative management after transplantation. After the establishment of LT as a treatment option for end-stage liver disease worldwide, the number of long-term survivors has continued to increase annually. Longer follow-up periods inevitably require longer exposure to immunosuppression, which leads to the development of cardiovascular disease [2-4], *de novo* malignancy [5], infections, and renal dysfunction [6, 7]. Recently, lifestyle-related diseases, such as obesity and nonalcoholic fatty liver disease (NAFLD), have gained attention as complications after LT [8, 9]. The occurrence rate of obesity is reportedly approximately 20% in recipients after LT, which is comparable to the 20–28% occurrence rate in the general population [10]. Moreover, obesity, a hallmark of metabolic syndrome, results in increased postoperative complications and mortality [11]. Another study reported that an increased body mass index (BMI) of >10% after LT was a risk factor for NAFLD [12]. Although some studies have reported the risk factors for obesity after LT [9, 10], the relationship between weight change over time and the overall weight change after LT has not yet been clarified. The present study aimed to investigate the weight change over time after LT to identify risk factors for weight gain.

MATERIALS AND METHODS

Patient Selection

Recipients who underwent LT at Kobe University Hospital, Kobe, Hyogo, Japan between January 2015 and July 2019 and survived more than 3 years after LT were enrolled in this retrospective cohort study. The exclusion criteria for the present study were: i) overall survival (OS) <3 years and ii) development of a malignant tumor after LT. The indications for LT in our institution were: (1) liver cirrhosis with hepatocellular carcinoma within the Milan criteria (≤3 cm, ≤3 nodules; or ≤5 cm, ≤1 nodule); (2) hepatitis B and C viral cirrhosis; (3) alcoholic steatohepatitis; (4) nonalcoholic steatohepatitis; (5) primary sclerosing cholangitis; (6) primary biliary cirrhosis; (7) autoimmune hepatitis; (8) acute liver failure; and (9) end-stage liver disease that could not be treated by other methods. The recipients were followed up until July 2022. Demographic, clinical, and pathological data were recorded and analyzed retrospectively.

This study complied with the standards of the Declaration of Helsinki and was approved by the Institutional Ethics Board of Kobe University Hospital in January 2023 (Approval number: B220166). Informed consent was obtained from all participants using an opt-out form. The requirement for individual consent was waived owing to the retrospective study design.

Assessment and Study Design

Data on weight were collected, and weight changes over time after LT were calculated at each of the time points (before LT, at discharge, and 3, 6, 9, 12, 24, and 36 months after discharge). Preoperative mean age, sex, end-stage liver disease (MELD) score, albumin-bilirubin (ALBI) score, presence of nonalcoholic steatohepatitis (NASH), BMI, serum albumin level, total cholesterol level, intraoperative ascites volume, and length of intensive care unit (ICU) stay were examined to identify the risk factors for early weight gain after LT. Because weight gain indicates recovery from pre-transplant undernutrition, we performed an additional analysis to examine its association with the timing of reaching a serum albumin level ≥4.0 mg/dL, which represents favorable nutritional status.

An approximately straight line was extrapolated to determine the trend of weight change after discharge, and the recipients were divided into two groups based on the negative or positive slope. To identify the factors for a positive slope trend in weight change, the recipients' backgrounds were divided into two groups. The cutoff values for preoperative mean age, sex, MELD score, ALBI score, presence of NASH, BMI, serum albumin level, total cholesterol level, intraoperative ascites volume, and postoperative length of ICU stay were set based on the receiver operating characteristic (ROC) curve (area under the curve: 0.53, 0.65, 0.60, 0.64, 0.60, 0.55, 0.58, and 0.51, respectively).

Statistical Analyses

All statistical analyses were two-tailed, and the threshold for significance was set at $P < 0.05$. Descriptive data are presented as medians, ranges, numbers, and percentages. Continuous variables are presented as medians and ranges. Qualitative variables are shown as numbers and percentages for the whole group. Categorical variables were compared using the chi-square test, while the continuous variables were compared using the Student's t-test or the Mann–Whitney U test. The cutoff value for each variable was determined using ROC curve analysis. All statistical analyses were performed using JMP16® software (SAS Institute, Cary, North Carolina, USA).

RESULTS

Patient characteristics

A total of 29 recipients were enrolled in this study, and their characteristics and clinical features are described in Table 1. The median patient age was 52 years, and 79.3% of the patients were females. The median BMI was 23.7, and five patients (17.2%) were preoperatively diagnosed with NASH.

Progression of Weight Change after Discharge

Figure 1 shows the pattern of weight change over time from body weight at discharge for all recipients. At the time of discharge, all but one recipient showed weight loss from the day before LT. Initial weight gain was observed in 16 recipients (55%) at 1 month, 20 recipients (69%) at 3 months, 21 recipients (72%) at 6 months, and 24 recipients (83%) at 12 months after discharge. Additional analysis was performed to examine the association between the timing of initial weight gain and recipient background factors. Among the recipients with initial weight gain at 1 month after discharge, age ≤50 years, male sex, and BMI ≤25 were identified as factors in the uni- and multi-variate analyses ($P < 0.05$). Among the recipients with initial weight gain at 3 and 6 months after discharge, BMI ≤25 was identified as a factor in the uni- and multi-variate analyses ($P < 0.05$). Among the recipients with initial weight gain at 12 months after discharge, recipient age ≤50 years was identified as a factor in the uni- ($P = 0.009$) and multi-variate analyses ($P = 0.048$). These results show that recipient age ≤50 and BMI ≤25 were risk factors for early weight gain. Accordingly, the percentage of recipients with initial weight gain was further analyzed between the two groups divided by recipient age ≤50 years and BMI ≤25. Figure 2A shows the percentage of recipients with initial weight gain at each time point divided by age ≤50 years. At 1 month after discharge, 11 (85%) recipients aged ≤50 years and only 5 (31%) recipients aged >50 years showed initial weight gain (*P* = 0.003). The percentage difference between the two groups decreased in a time-dependent manner: 12 (92%) vs. 8 (50%) at 3 months (*P* = 0.010), 12 (92%) vs. 9 (56%) at 6 months 9 (*P* = 0.023), 13 (100%) vs. 11 (69%) at 12 months (*P* = 0.009), and did not show a statistically significant difference thereafter. Figure 2B shows the percentage of patients with initial weight gain at each time point divided by a BMI ≤25. At 1 month after discharge, 13 (68%) recipients with BMI ≤25 and only 3 (30%) with BMI >25 exhibited initial weight gain (*P* = 0.046). The percentage difference between the two groups decreased in a time-dependent manner: 16 (84%) vs. 4 (40%) at 3 months (*P* = 0.015), 17 (89%) vs. 4 (40%) at 6 months (*P* = 0.005), and 18 (94%) vs. 6 (60%) at 12 months (*P* = 0.021) with no statistical difference thereafter. These data indicate that recipient age ≤50 years and BMI ≤ 25 were identified as risk factors for early weight gain, as these recipients gained weight more rapidly than those aged >50 or >25 years.

As weight gain also exhibits a favorable postoperative recovery process, we performed an additional analysis focusing on the initial timing of reaching a serum albumin level ≥4.0 mg/dL. Figure 3 shows the percentage of recipients with a serum albumin level ≥4.0 mg/dL at each of the time points divided by recipient age ≤50 years (Figure 3A) and BMI >25 (Figure 3B). Throughout the study period, the percentages did not show a statistically significant difference between the two groups. These data showed that recipient age ≤50 years and BMI

≤25 are risk factors for early weight gain but are not indicative of improved postoperative nutrition status.

Trend of Weight Change Relative to Recipient Perioperative Factors

As previously mentioned, this study's data showed that recipient age ≤50 years and BMI ≤25 are risk factors for early weight gain after discharge. To further analyze the trend of total weight change, an approximated straight line of weight change was extrapolated. Figure 4 shows an approximated straight line for all the recipients. Based on the slope, recipients were divided into two groups: 11 recipients showed a negative slope and 18 recipients showed a positive slope. Among the recipient factors, BMI ≤23 was identified as a risk factor associated with positive linear postoperative weight gain in both univariate ($P = 0.020$) and multivariate ($P = 0.042$) analyses (Table 2). These data showed that a low preoperative BMI affects postoperative weight change as a whole, suggesting that recipients with lower BMI gain weight rapidly after LT, not due to improved postoperative nutrition status, as weight gain continues throughout the long-term period up to 3 years after LT.

DISCUSSION

The present study demonstrated that 82% of post-LT recipients gained weight within 1 year after discharge, despite losing weight at the time of discharge relative to their preoperative weight. Recipient age ≤ 50 years and BMI ≤ 25 were identified as risk factors for weight gain, as they gained weight more rapidly than those aged >50 and >25 years. In the long-term period, recipients with BMI ≤23 showed a positive slope in the approximated straight line of weight change.

Our study had two novel findings. The first finding is that younger recipient age was associated with early weight gain after LT. This result is consistent with previous studies reported by Miyaaki, et al [13]. In general, after LT, transplanted livers show improved function, such as lipid-protein metabolism, and subsequently, the recipient starts to overeat during the postoperative period. We speculate that this type of overeating is more pronounced among younger recipients, as they usually consume a high-fat diet before liver cirrhosis occurs. Another previous study reported that the prevalence of NAFLD was higher among younger patients in recent years because of the increased intake of fructose, especially sugar-sweetened beverages, which also supports our speculation [14].

The second finding was that non-obese recipients linearly gained weight in the long-term period after LT. Although some studies examined BMI trends over time [10, 15-17], no reports have concluded that lower BMI is a risk factor for postoperative weight gain. This discrepancy may be partly explained by the fact that these previous manuscripts' datasets included patients who underwent LT a long time ago. With the increased number of cases, a patient education system on weight control after transplantation was established, resulting in a change in the trend of post-LT weight gain due to changes in patient perception. Obesity at 1 year after LT has been previously reported as an increased risk factor for mortality in decades [17]. Body weight control is essential for preventing obesity. Results of the approximate straight lines showed that even non-obese recipients linearly gained weight in the long-term period after LT. This further stresses the importance of patient education starting from the early post-transplant period. Interestingly, recipient age did not show a statistically significant difference in the recovery process of nutritional status, as measured by serum albumin. Miyaaki *et al*. previously reported that older recipient age could limit the improvement in nutritional status after LT [13]. Our data showed that the negative effects of recipient age on nutritional status could be improved by perioperative medical nutrition therapy, making transplantation therapy viable even for older recipients [10].

The limitations of this study include its retrospective nature, single-center design, and small sample size. Despite these limitations, considering that this is the first study evaluating the risk factors of weight increase after LT and their relationship with over-time weight change, our findings are clinically significant as they provide evidence for the first time that recipient education for postoperative weight control is essential for improved recipient outcomes and survival. Future prospective, multicenter clinical studies, with the assessment of sarcopenia, are necessary to validate our findings.

CONCLUSION

In conclusion, the present study showed that almost all transplant recipients had weight loss at discharge but experienced weight gain thereafter in the short term. Of note, non-obese recipients aged ≤50 years gained weight at earlier time points compared to older recipients who were obese. Moreover, because recipients with BMI ≤23 had a positive trend in the slope of the approximate postoperative weight line at longer periods, proper recipient education for weight control in the early post-transplant period is important to improve long-term prognosis after LT, even among younger recipients who are not obese.

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Figure legends

Figure 1. Over-time progression pattern of weight change for all the recipients. Weight data were collected and over-time weight changes after LT were calculated at each of the time points (before LT, at discharge, 3, 6, 9, 12, 24, and 36 months after discharge).

Figure 2. The percentage of recipients with weight gain at each of the time points.

(A) Recipients were categorized into two groups those with age ≤50 years and >50 years. **(B)** Recipients were categorized into two groups those with BMI ≤25 and >25.

Figure 3. The percentage of recipients with serum albumin level ≥4.0 mg/dL at each of the time points. **(A)** Recipients were categorized into two groups those with age ≤50 years and >50 years. **(B)** Recipients were categorized into two groups those with BMI ≤25 and >25.

Figure 4. The approximate straight line for all the recipients.

An approximate line of weight gain or loss, based on the time of discharge, was extrapolated.

Tables

Table 1. Recipient characteristics

Table 2. Univariate and Multivariate Analyses of Predictive Factors Affecting Recipient Weight Gain Trend

Table 1. Recipient Characteristics

Variables	Median (Range) or No. (%)
Age (y)	52 (17-65)
Gender (male/female)	6/23
MELD score	25 (17-34)
ALBI score	-1.14 (-2.70- -0.15)
BMI	23.7 (20.3-26.4)
NASH	5 (17)
Alb (mg/dL)	3.0 (1.8-5.4)
T-Cho (mg/dL)	144 (23-425)
Intraoperative ascites (ml)	10 (0-5880)
Length of ICU stay (day)	7 (4-18)

Qualitative variables are presented as number and percentage of patients; quantitative variables are presented as median and range.

MELD, model of end-stage liver disease; ALBI, albumin-bilirubin; BMI, body mass index; NASH, nonalcoholic steatohepatitis; Alb, albumin; T-Cho, total cholesterol; ICU, intensive care unit.

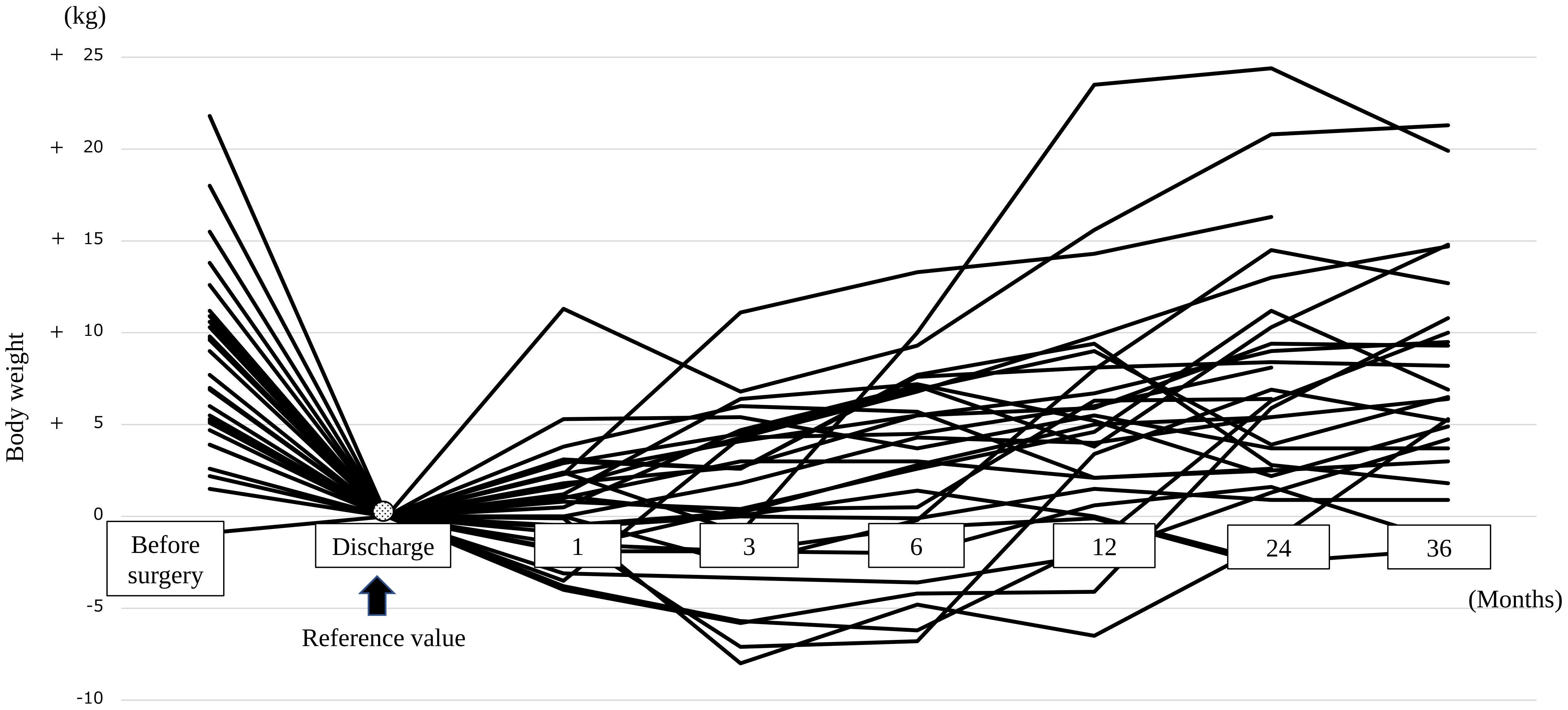
Table 2. Univariate and Multivariate Analyses of Predictive Factors Affecting Recipient Weight Gain Trend

Variables	Positive Slope (n = 18)	Negative Slope (n = 11)	*P* Value	
			Univariate	Multivariate
Age (y) ≤56	14 (78%)	5 (45)	.076	
Gender (female)	15 (83%)	8 (73%)	.499	
MELD score ≤24	10 (56%)	3 (27%)	.198	
ALBI score ≥-1.02	8 (44%)	2 (18%)	.138	
BMI ≤23	11(61%)	2 (18%)	.020	.042
NASH	5 (28%)	2 (18%)	.552	
Alb (mg/dL) ≤2.4	5 (28%)	1 (9%)	.182	
T-Cho (mg/dL) ≥147	9 (50%)	4 (36%)	.472	
Intraoperative ascites (ml) ≤720	15 (83%)	8 (72%)	.502	
Length of ICU stay (day) ≤8	12 (67%)	6 (55%)	.511	

Variables are presented as number and percentage of patients.

MELD, model of end-stage liver disease; ALBI, albumin-bilirubin; BMI, body mass index; NASH, nonalcoholic steatohepatitis; Alb, albumin; T-Cho, total cholesterol; ICU, intensive care unit.

Figure 1


(kg)
+ 25
+ 20
+ 15
+ 10
+ 5
0
-5
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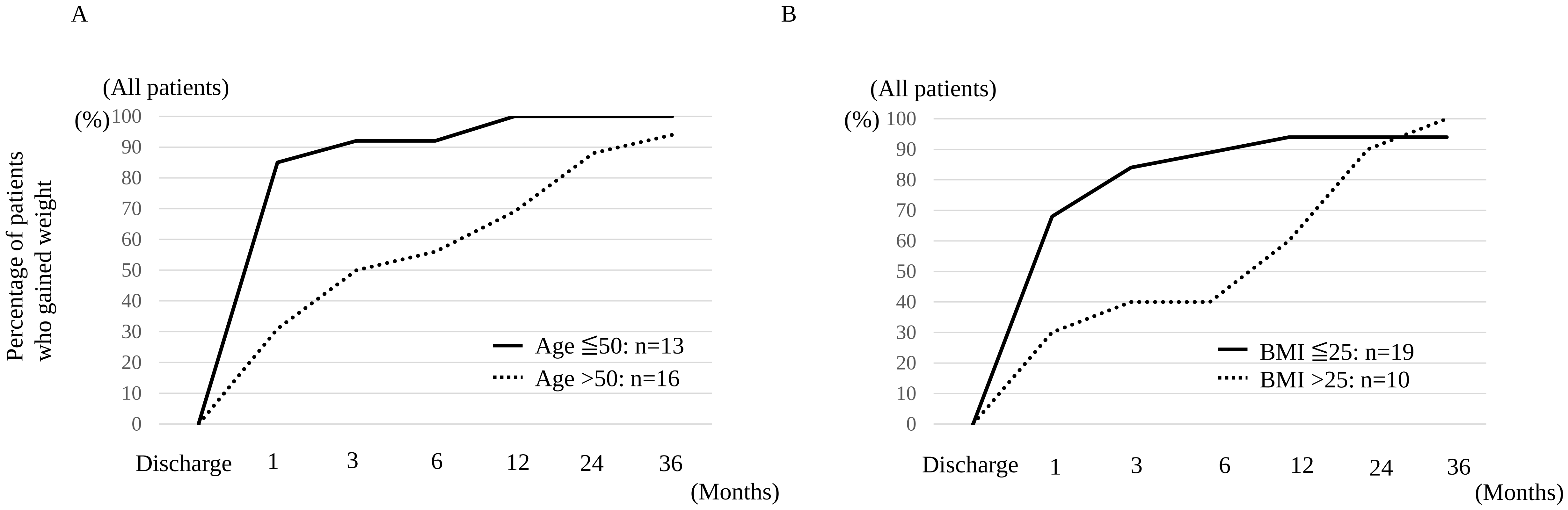
Body weight
Before surgery
Discharge
1
3
6
12
24
36
(Months)
Reference value

Figure 2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(All patients)
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Percentage of patients who gained weight
Age ≦50: n=13
Age >50: n=16
Discharge
1
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12
24
36
(Months)
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(All patients)
(%)
100
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BMI ≦25: n=19
BMI >25: n=10
Discharge
1
3
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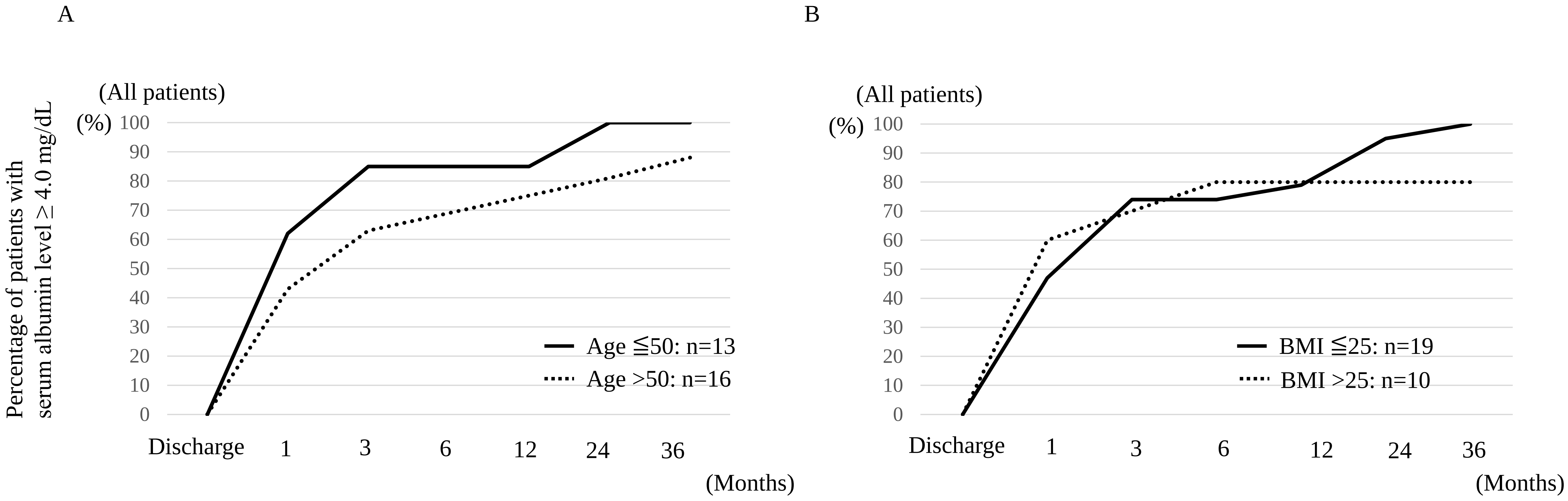
36
(Months)

Figure 3


A
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Percentage of patients with serum albumin level ≥ 4.0 mg/dL
Discharge
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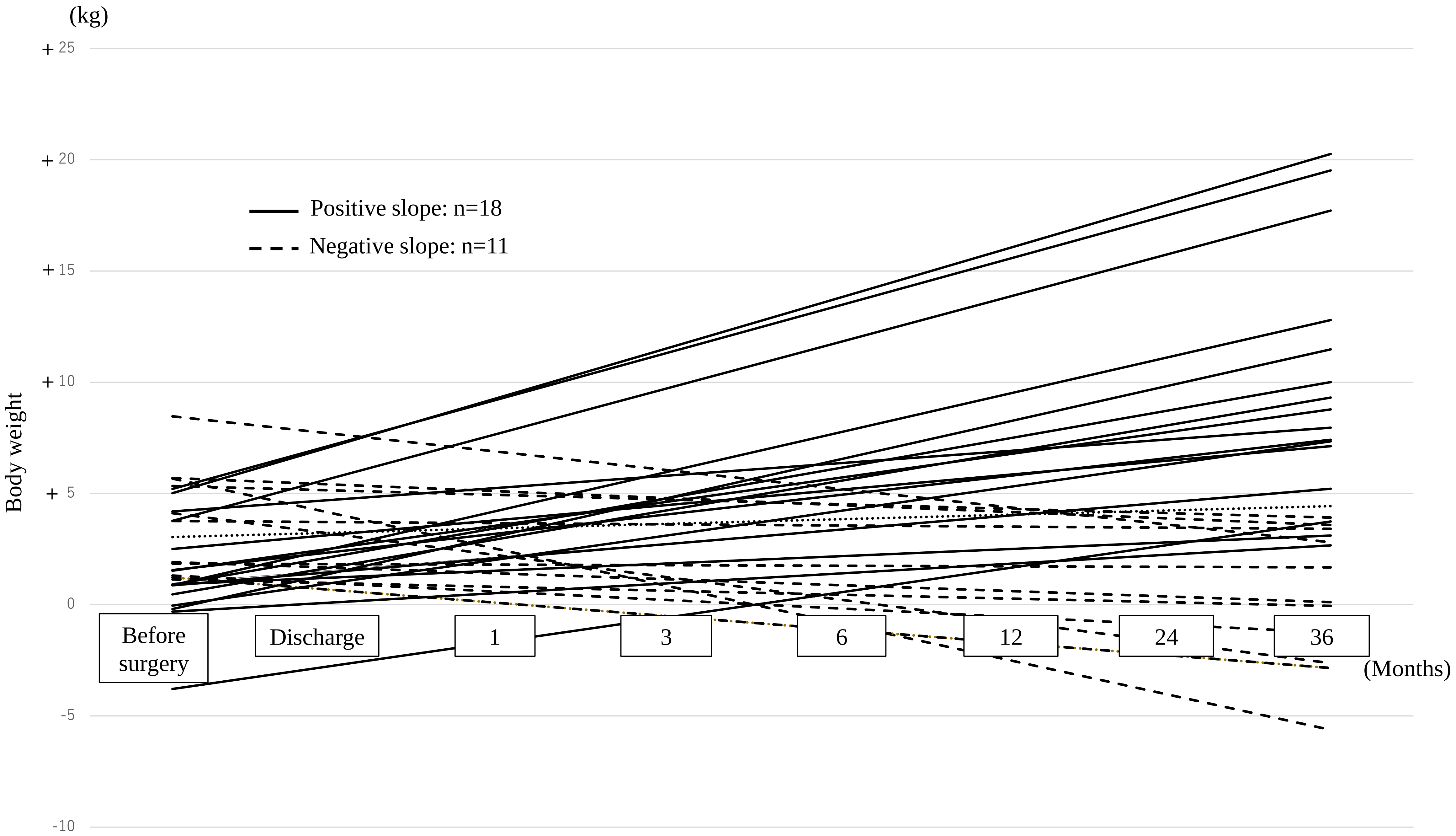
36
(Months)
Age ≦50: n=13
Age >50: n=16
BMI ≦25: n=19
BMI >25: n=10

Figure 4


(kg)
+ 25
+ 20
+ 15
+ 10
+ 5
0
-5
-10
Body weight
Positive slope: n=18
Negative slope: n=11
Before surgery
Discharge
1
3
6
12
24
36
(Months)