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# Poor Nutritional Status Before and During Chemotherapy Leads to Worse Prognosis in Unresectable Advanced or Recurrent Colorectal Cancer

Keisuke Ihara, Satoru Yamaguchi, Yosuke Shida, Hideo Ogata, Yasushi Domeki, Kentaro Okamoto, Masanobu Nakajima, Kinro Sasaki, Takashi Tsuchioka, Hiroyuki Kato

*Department of Surgical Oncology, Dokkyo Medical University, Mibu, Tochigi, Japan*

**This study aimed to clarify the relationship between host nutritional status prior to first-line chemotherapy and therapeutic effect, and, whether these nourishment indexes could become factors that predict long-term convalescence in metastatic or recurrent colorectal cancer. It has previously been reported that postoperative complications and long-term prognosis of patients with gastrointestinal malignancies may be affected by their nutritional status. But, there is little information regarding the relationship between prognosis, nutritional status, and immunocompetence in metastatic or recurrent colorectal cancer. Ninety patients who had measurable target lesions underwent resection for primary colorectal cancer in our institution, between April 2007 and March 2013. The indicators of host nutritional status were body weight (BW), body mass index (BMI), serum albumin, Onodera's prognostic nutritional index (OPNI), and Glasgow Prognostic Score (GPS). The indicators of host immunocompetence were total lymphocyte counts, total neutrophil counts, and granulocytes/lymphocytes ratio (G/L ratio). The median overall survival (OS) was 32.5 months, and the median progression-free survival was 10.9 months. The relative change of target lesions was associated with BW, BMI, and OPNI. Furthermore, there was strong correlation between the change ratio of the serum carcinoembryonic antigen (CEA) level before and after chemotherapy administration and BMI. BW, BMI, serum albumin level, OPNI, and GPS were**

Corresponding author: Keisuke Ihara, MD, Department of Surgical Oncology, Dokkyo Medical University, 880 Kitakobayashi, Mibu, Tochigi 321-0293, Japan.
Tel.: +81 282 872157; Fax: +81 282 866213; E-mail: k-ihara@dokkyomed.ac.jp

**significantly associated with overall survival (OS). Poor nutritional status and suppressive immunocompetence are associated with ineffective chemotherapy.**

*Key words:* Colorectal cancer – Nutrition – Immunocompetence – Prognosis

In recent years, there has been rapid progress in the development of the chemotherapy for metastastic or recurrent colorectal cancer. Combination chemotherapy, such as FOLFOX and FOLFIRI, and several molecular targeting agents have contributed to prolonged survival.[1,2] Because of an increasing number of treatment options, factors that can predict treatment effects and side effects in chemotherapy are of great interest.[3,4]

Cancer-bearing patients have poor prognosis because they have decreased tolerance to cancer treatment as a result of protein-energy malnutrition and cachexia. TNF-α, IL-6, and several humoral factors cause cachexia.[5] Therefore, there may be a strong relationship between nutritional status and immunocompetence.

It has previously been reported that postoperative complications and long-term prognosis of patients with gastrointestinal malignancies may be affected by their nutritional status.[6–10] Onodera's prognostic nutritional index (OPNI) is thought to be a simple parameter to determine the nutritional and immunological status of patients.[11] McMillan *et al* reported that the presence of elevated systemic inflammatory response, as evidenced by elevated circulating concentrations of C-reactive protein and hypoalbuminemia [termed the Glasgow Prognostic Score (GPS)], was associated with poor survival in patients undergoing curative resection for colorectal cancer. Moreover, the GPS has been found to be a useful prognostic factor in several types of cancer.[12]

There is little information regarding the relationship between prognosis, nutritional status, and immunocompetence in metastastic or recurrent colorectal cancer. This study aimed to clarify the relationship between host nutritional status prior to first-line chemotherapy and therapeutic effect, and, whether these nourishment indexes could become factors that predict long-term convalescence in metastastic or recurrent colorectal cancer.

## Materials and Methods

### *Patients*

Ninety patients with metastastic or recurrent colorectal cancer who had measurable target lesions such as hepatic, pulmonary, lymphatic, and peritoneal metastases, underwent resection for primary colon and rectal cancer in our institution, between April 2007 and March 2013. All patients underwent combination chemotherapy followed by primary surgery.

### *Detection of nutritional status and immunocompetence*

The indicators of host nutritional status were body weight (BW), body mass index (BMI), serum albumin, OPNI, and GPS. GPS was defined that patient with both an elevated level of C-reactive protein (>1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL) were allocated a score of 2. Patients with only 1 of the aforementioned 2 abnormalities were allocated a score of 1. Patients with neither of the aforementioned two abnormalities were allocated a score of 0.[12] The indicators of host immunocompetence was total lymphocyte counts, total neutrophil counts, and granulocytes/lymphocytes ratio [granulocytes/lymphocytes (G/L) ratio]. All blood samples were collected 1 or 2 days prior to administration of first-line chemotherapy.

### *Assessments*

Descriptions of the therapeutic effects were evaluated using the best overall response of first-line chemotherapy using RECIST version 1.1. Changes in tumor size were expressed as a relative change of the sum of the longest diameters of the target lesions. Nontarget lesions and newly occurring lesions were not considered in the measurement of change in tumor size.[13]

The endpoints of the long-term outcome study were overall survival (OS) and progression-free survival (PFS). OS was calculated by death from any causes, and PFS was calculated by progression of target lesions as the only events for survival analyses.

### *Statistical analysis*

Spearman's method was performed for rank correlation. Survival curves were plotted according to the

*Table 1 Characteristics of patients and tumor*

| Characteristics (n = 90) | |
|---|---|
| Age | 64.5 |
| Sex | |
| Men | 56 |
| Female | 34 |
| Location | |
| Right | 24 |
| Left | 66 |
| Tumor size (mm) | 50 |
| Histology | |
| Well differentiated | 26 |
| Moderately differentiated | 53 |
| Poorly differentiated | 5 |
| Others | 6 |
| Site of metastases | |
| Liver | 51 |
| Lung | 26 |
| Peritoneum | 11 |
| Lymph node | 13 |
| Bone | 1 |
| The number of metastasized organs | |
| 1 | 61 |
| 2 | 22 |
| 3 | 7 |
| Surgery before chemotherapy | |
| Palliative surgery | 64 |
| Radical surgery | 26 |
| Regimen | |
| mFOLFOX6 + bevacizumab | 47 |
| CapeOX + bevacizumab | 20 |
| FOLFIRI + bevacizumab | 3 |
| FOLFIRI + antiEGFR | 5 |
| mFOLFOX6 | 8 |
| Others | 7 |
| Treatment session number | 10 |
| Overall survival (months) | 32.5 |
| Progression-free survival (months) | 10.9 |

Kaplan–Meier method and any differences were analyzed using the log-rank test. A multivariate analysis with Cox proportional hazards model was adopted to clarify the independent prognostic factors. Differences were considered to be significant if the *P* value was less than 0.05.

## Results

Patient clinical characteristics are detailed in Table 1. The median age was 64.5 years, and the cohort consisted of 56 males and 34 females. The median overall was 32.5 months, and the median progression-free survival was 10.9 months. Thirty-one patients had recurrent disease after they received radical surgery. The median recurrent period was

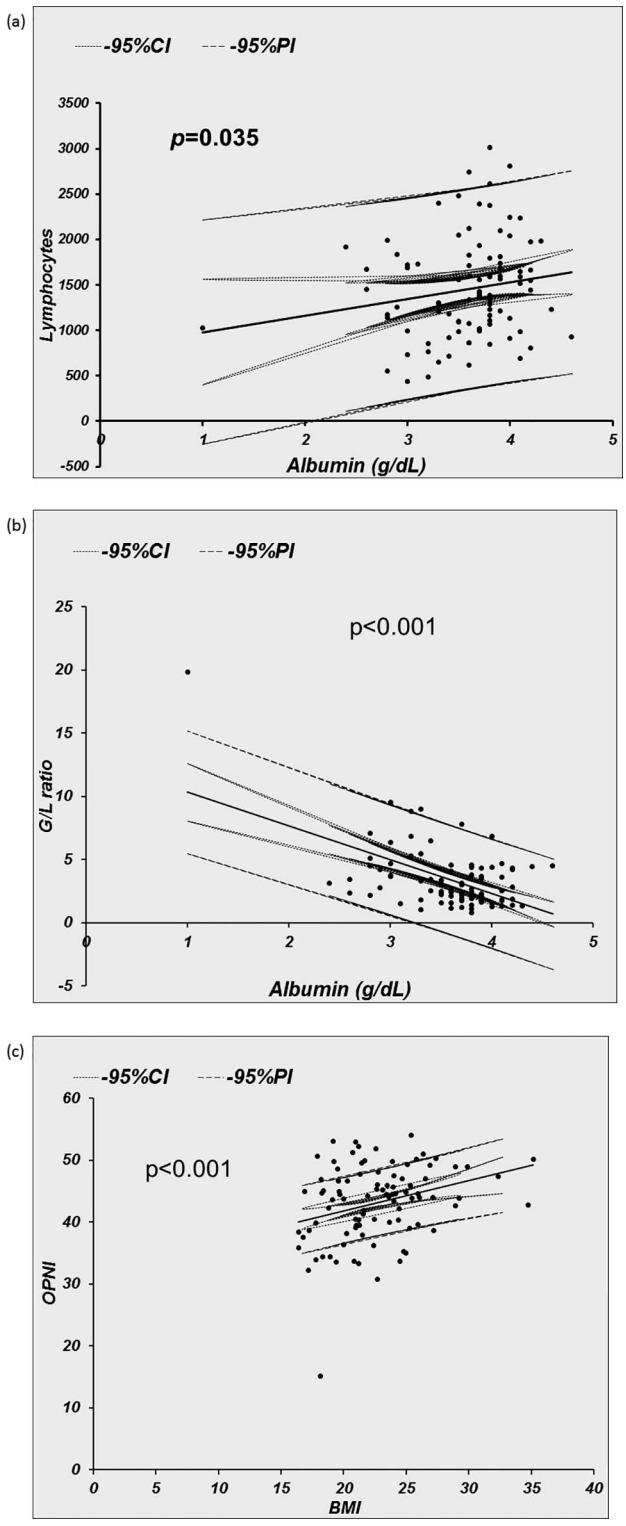


**Fig. 1** The correlation of host nutritional status and immunocompetence prior to chemotherapy administration. (a) The correlation between the serum albumin level and the number of the total lymphocytes ($P = 0.035$). (b) The correlation between the serum albumin level and the G/L ratio ($P < 0.001$). (c) The correlation between BMI and Onodera's PNI ($P < 0.001$).

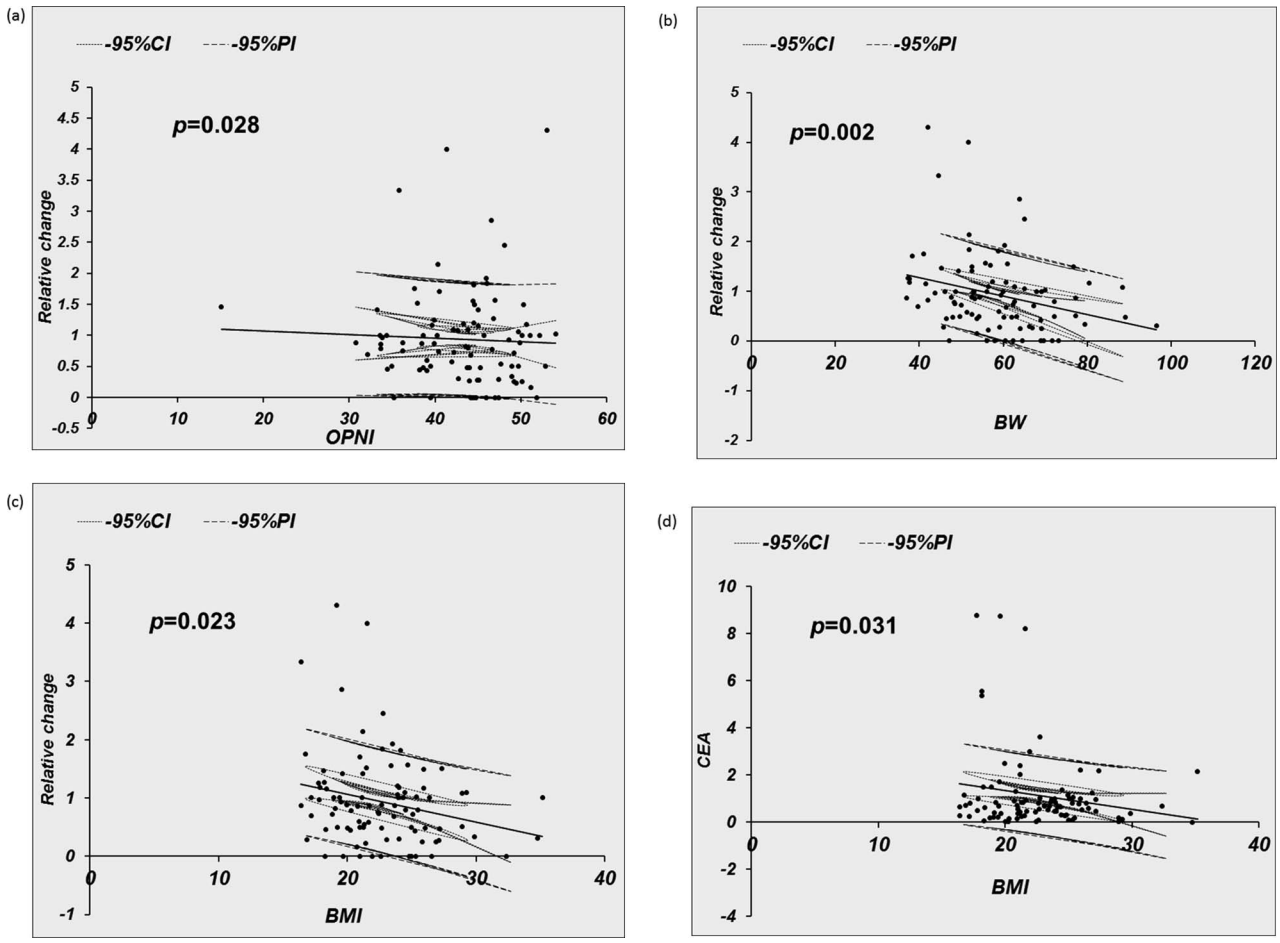


**Fig. 2** The correlation between curative effect and host nutritional status or immunocompetence. (a) The correlation between OPNI and relative change ($P = 0.028$). (b) The correlation between BW and relative change ($P = 0.002$). (c) The correlation between BMI and relative change ($P = 0.023$). (d) The correlation between BMI and the change ratio before and after the chemotherapy enforcement of the serum CEA level ($P = 0.031$).

17 months. We first examined the correlation between nutritional status and immunocompetence prior to chemotherapy administration (Fig. 1). Serum albumin level and the number of the total lymphocytes showed equilateral correlation, and the G/L ratio showed negative correlation. These results suggested that there was correlation between nutritional status and immunocompetence.

Next, we examined the relationship between curative effect and host nutritional status or immunocompetence (Fig. 2). The relative change of target lesions were associated with BW, BMI, and OPNI. Furthermore, there was strong correlation between the change ratio of the serum carcinoembryonic antigen (CEA) level before and after chemotherapy administration and BMI. These results demonstrated the relationship between nutritional status prior to chemotherapy administration and therapeutic effect.

The association between clinicopathologic characteristics, host nutritional status, immunocompetence, and OS is shown in Table 2. BW, BMI, serum albumin level, OPNI, and GPS were significantly associated with OS (Fig. 3). Furthermore, the treatment session number of first-line chemotherapy and relative change, and the change ratio of the serum CEA level before and after chemotherapy were related to OS.

*Table 2 Relationship between clinicopathologic characteristics, host nutritional status, immunocompetence, and OS*

| Factors | Number | Median | *P*-value |
|---|---|---|---|
| Age | | | |
| <65 | 50 | 33 | 0.999 |
| ≥65 | 40 | 32.5 | |
| Gender | | | |
| Male | 56 | 36.3 | 0.987 |
| Female | 34 | 29.9 | |
| Location | | | |
| Right | 24 | 25.8 | 0.136 |
| Left | 66 | 33 | |
| Tumor size (mm) | | | |
| <50 | 36 | 33.0 | 0.440 |
| ≥50 | 54 | 32.3 | |
| Treatment session number | | | |
| <10 | 46 | 27.4 | 0.021** |
| ≥10 | 44 | 38.9 | |
| BW (kg) | | | |
| ≤50 | 25 | 20 | 0.011** |
| >50 | 65 | 38.1 | |
| BMI | | | |
| <20 | 24 | 19.6 | 0.029** |
| ≥20 | 66 | 33.8 | |
| Albumin (g/dL) | | | |
| <3.5 | 27 | 22 | <0.001** |
| ≥3.5 | 63 | 38.1 | |
| Onodera's PNI | | | |
| <40 | 28 | 23.9 | 0.007** |
| ≥40 | 62 | 38.1 | |
| GPS | | | |
| 0 | 54 | 41.2 | <0.001** |
| 1 | 20 | 38.1 | |
| 2 | 16 | 17.2 | |
| G/L ratio | | | |
| <3.5 | 58 | 38.9 | 0.062* |
| ≥3.5 | 32 | 27.4 | |
| CEA change ratio | | | |
| <0.6 | 41 | 29.9 | 0.027** |
| ≥0.6 | 49 | 46.9 | |
| Relative change | | | |
| <0.7 | 37 | 41.2 | 0.010** |
| ≥0.7 | 53 | 29.9 | |

BMI, body mass index; BW, body weight; OS, overall survival; CEA, carcinoembryonic antigen; G/L, granulytes/lymphocytes; GPS, Glasgow Prognostic Score; PNI, prognostic nutritional index.

*$P < 0.1$.

**$P < 0.05$.

For multivariate analysis, the significant predictors from the univariate analysis were introduced into the Cox regression model (Table 3). According to these results, OPNI, the treatment session number of first- line chemotherapy, and the ratio of the serum CEA level before and after chemotherapy were independent prognostic factors.

*Table 3 Multivariate analysis of OS*

| | HR (95% CI) | *P*-value |
|---|---|---|
| BW, >50 (kg) | 0.46 (0.18–1.18) | 0.107 |
| BMI, ≥20 | 0.87 (0.33–2.30) | 0.785 |
| Albumin, ≥3.5 (g/dL) | 0.05 (0.003–0.90) | 0.042** |
| OPNI, <40 | 15.38 (1.17–201.77) | 0.037** |
| CEA change ratio, ≥0.6 | 0.50 (0.28–0.90) | 0.021** |
| Treatment session number, ≥10 | 0.44 (0.24–0.81) | 0.009** |
| GPS, 2 | 3.09 (0.67–14.37) | 0.149 |
| Relative change, <0.7 | 1.78 (0.92–3.44) | 0.088* |

BMI, body mass index; BW, body weight; GPS, Glasgow Prognostic Score, OPNI, Onodera's Prognostic Nutritional Index.

*$P < 0.1$.

**$P < 0.05$.

Second, the relationship between clinicopathologic characteristics, host nutritional status, immunocompetence, and PFS is shown in Table 4. Location, BW, serum albumin level, the treatment session number of first-line chemotherapy, and the G/L ratio were significantly associated with PFS (Fig. 4). According to the multivariate analysis, location, the treatment session number of first-line, and relative change were independent prognostic factors (Table 5).

## Discussion

The recent development of chemotherapy such as FOLFOX and FOLFIRI along with several molecular targeting agents has dramatically improved the survival of metastatic or recurrent colorectal cancer patients. A previous reports show that median survival time was prolonged to 11 to 26 months in metastatic or recurrent colorectal cancer.[14–16] Therefore, factors that can predict therapeutic effect and outcome have been noted, along with prognostic factors.

Past several reports showed relationship among nutritional status, postoperative outcomes, and long-term outcomes in gastrointestinal surgery.[6,17] Preoperative malnutrition is associated with postoperative complications, tumor progression, and poor clinical outcome.[18] Along with the relationship between nutritional status and prediction of long-term outcome in colorectal cancer, Boonpipattanapong *et al* showed that preoperative CEA and albumin were predictors of patient survival.[19] Furthermore, Nozoe *et al* showed that the OPNI can be a prognostic indicator in colorectal cancer.[20]

*Table 4 Relationship between clinicopathologic characteristics, host nutritional status, immunocompetence, and PFS*

| Factors | Number | Median | *P*-value |
|---|---|---|---|
| Age | | | |
| <65 | 50 | 11 | 0.635 |
| ≥65 | 40 | 10.9 | |
| Gender | | | |
| Male | 56 | 12.6 | 0.059* |
| Female | 34 | 9.4 | |
| Location | | | |
| Right | 24 | 9.8 | 0.002** |
| Left | 66 | 11.8 | |
| Tumor size (mm) | | | |
| <50 | 36 | 10.2 | 0.426 |
| ≥50 | 54 | 11.3 | |
| Treatment session number | | | |
| <10 | 46 | 7.7 | <0.001** |
| ≥10 | 44 | 14.4 | |
| BW (kg) | | | |
| ≤50 | 25 | 9.8 | 0.031** |
| >50 | 65 | 13.2 | |
| BMI | | | |
| <20 | 24 | 10.4 | 0.385 |
| ≥20 | 66 | 12.9 | |
| Albumin (g/dL) | | | |
| <3.5 | 27 | 10 | 0.009** |
| ≥3.5 | 63 | 13.5 | |
| Onodera's PNI | | | |
| <40 | 28 | 10.4 | 0.079* |
| ≥40 | 62 | 12.9 | |
| GPS | | | |
| 0 | 54 | 13.2 | 0.040** |
| 1 | 20 | 10.9 | |
| 2 | 16 | 9.3 | |
| G/L ratio | | | |
| <3.5 | 58 | 13.5 | 0.005** |
| ≥3.5 | 32 | 8.6 | |
| CEA change ratio | | | |
| <0.6 | 41 | 11.8 | 0.814 |
| ≥0.6 | 49 | 10.9 | |
| Relative change | | | |
| <0.7 | 37 | 18.4 | <0.001** |
| ≥0.7 | 53 | 8.8 | |

BMI, body mass index; BW, body weight; CEA, carcinoembryonic antigen; G/L, granulytes/lymphocytes; GPS, Glasgow Prognostic Score; PFS, progression-free survival; PNI, prognostic nutritional index.

*$P < 0.1$.

**$P < 0.05$.

*Table 5 Multivariate analysis of PFS*

| | HR (95% CI) | *P*-value |
|---|---|---|
| G/L ratio, ≥3.5 | 1.21 (0.70–2.09) | 0.487 |
| BW, ≥50 (kg) | 0.91 (0.53–1.55) | 0.717 |
| Albumin, ≥3.5 (g/dL) | 0.47 (0.16–1.39) | 0.171 |
| Treatment session number, ≥10 | 0.37 (0.23–0.61) | <0.001** |
| GPS, 2 | 1.14 (0.32–4.03) | 0.845 |
| Relative change, <0.7 | 2.87 (0.23–0.61) | <0.001** |
| Location, left | 0.54 (0.31–0.95) | 0.032** |

BW, body weight; G/L, granulytes/lymphocytes; GPS, Glasgow Prognostic Score; PFS, progression-free survival.

**$P < 0.05$.

McMillan *et al* showed that the GPS was associated with poor survival in patients undergoing resection for colorectal cancer.[21] However, little has been reported regarding the relationship between host nutritional status and reduction ratio of metastatic tumors. In our study, we examined that relationship using a relative change of target lesions followed by RECIST in patients who had measurable lesions. This revealed that poor nutritional status prior to chemotherapy administration is associated with worse relative change and prognosis. Furthermore, we showed that much numbers of treatment sessions and good therapeutic effects in first-line chemotherapy are associated with good prognosis. Because of this, we reasoned that maintenance of good nutritional status and appropriate immunocompetence leads to better therapeutic effects, fewer adverse events, and greater numbers of treatment sessions. Furthermore, we suggest that because maintenance of appropriate immunocompetence leads to precise immunoreactions, these patients experience better therapeutic effects. The results of our study show that appropriate nutritional management before and during treatment confers to better therapeutic effects.

## Conclusion

In conclusion, poor nutritional status and suppressive immunocompetence is associated with ineffective chemotherapy. Patient with better immunoreaction and nutritional status benefited from chemotherapy because maintenance of good nutritional status, and appropriate immunocompetence leads to fewer adverse events and greater numbers of treatment sessions.

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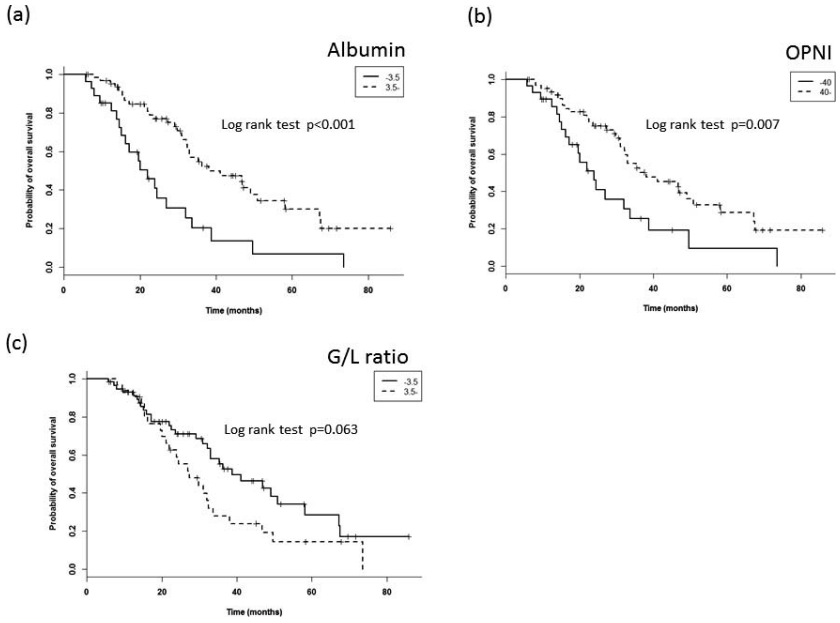


**Fig. 3** Kaplan–Meier overall survival curves of colorectal cancer patients stratified by (a) serum albumin level ($P < 0.001$), (b) OPNI ($P = 0.007$), (c) G/L ratio ($P = 0.063$).

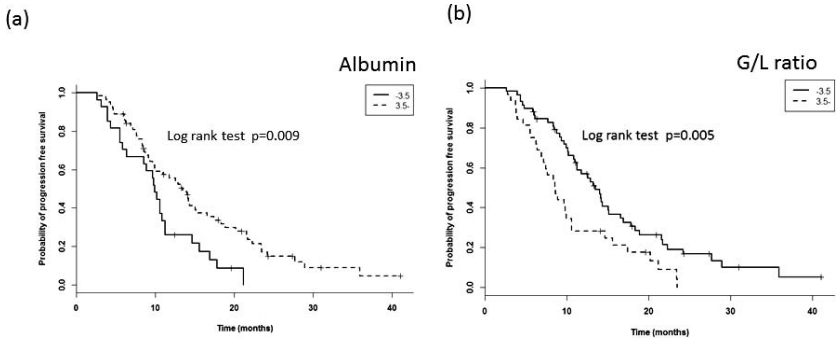


**Fig. 4** Kaplan–Meier progression-free survival curves of colon cancer patients (a) serum albumin level ($P = 0.009$), (b) G/L ratio ($P = 0.005$).

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