Albumin-globulin ratio indicates the survival outcome of pancreatic cancer cases who underwent preoperative treatment and curative surgical resection

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Short running head:

Albumin-globulin ratio for pancreatic cancer

Keywords

Albumin-globulin ratio; pancreatic cancer; pre-operative chemotherapy; pancreatectomy

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We have nothing to declare.

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Synopsis The albumin-globulin ratio is a simple and essential serum marker that infers the patient's nutritional and inflammatory status. The ratio was typically decreased in the duodenum- or bile duct-invaded cases in our consecutive surgically treated pancreatic cancer cohort following neoadjuvant chemotherapy. Moreover, a low level of the pre-treatment ratio significantly predicted poor patients' survival outcomes. It may be critical to avoid severe malnutrition or inflammation for the management during neoadjuvant treatment.

Abstract

Background: The pre-treatment albumin–globulin ratio (AGR) is a frequently used inflammation-associated factor that has been reported to have associations with the survival outcomes of various malignancies.

Methods: We retrospectively analyzed 162 patients with pancreatic cancer who underwent pre-operative treatment followed by curative surgery at Nagoya University Hospital between April 2010 and December 2020. Representative nutritional status indicators of neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), prognostic nutritional index (PNI) and albumin–globulin ratio (AGR) were calculated for each case.

Results: Among pre-treatment blood examination parameters, only AGR (cut-off: 1.33) showed a significant difference in overall survival time (OS) and progression-free survival time (PFS) from the beginning of the pre-operative treatment. Median PFS was 22.3 months in high AGR cases and 17.1 months in low AGR cases (P = 0.019). Median OS was 48.7 months in high AGR cases and 32.9 months in low AGR cases (P = 0.043).

Conclusion: High pre-treatment AGR may be a favorable prognostic factor for pancreatic cancer patients who received pre-operative multimodal therapy followed by curative cancer resection. It may imply that nutritional status and inflammation control before the multimodal treatment affect the survival outcomes of pancreatic cancer cases and needs to be optimized.

Introduction

Pancreatic cancer is one of the most lethal malignancies worldwide, ranked as the fourth leading cause of cancer-related mortality(1). Although surgical resection is the primary treatment, a substantial proportion of patients develop local recurrence or distal metastasis postoperatively. The recurrence rate is reported to be approximately 80%, and the 5-year survival rate is 10%-20%(2, 3). Surgical treatment alone sometimes makes extending the pancreatic cancer-free lifetime difficult, especially in advanced cases. Instead, multimodal treatment is currently applied to most pancreatic cancer patients. Pre-operative chemotherapy induction is performed for most pancreatic cancer cases according to resectability status. Thus, pre-operative prognostic factors for cases intended for surgery need to be evaluated regarding cancer resectability status and host nutritional and immunological conditions.

It has been reported that cancer prognosis is related to host conditions, including nutrition and inflammation(4). Malnutrition is associated with the immune-compromised status of cancer patients(5, 6), and pre-operative nutritional status influences the survival outcomes(5, 7) and tumor recurrence(8, 9) of several malignancies(5, 7). Furthermore, pre-treatment serum levels of inflammatory indicators, such as the Glasgow prognostic score (GPS)(10), prognostic nutritional index (PNI)(11), and controlling nutritional status (CONUT)(12), have also been frequently applied to predict survival outcomes in various cancers(13).

Like these host condition indexes, the albumin-globulin ratio (AGR) can also be calculated from blood examination data. AGR reflects the ratio of the circulating quantity of albumin and globulin. A healthy status usually maintains an albumin-rich condition and AGR scores over 1.0, while liver damage or chronic hepatitis results in an AGR score under 1.0 due to albumin reduction and globulin production. AGR has been frequently reported as an independent prognostic marker in gastric cancer(14), chronic kidney disease(15), and laryngeal squamous cell carcinoma(16). As for pancreatic cancer, Shinde et al. (17) reported that pre-operative AGR was not associated with survival outcomes in patients who underwent pancreaticoduodenectomy. However, their cohort consisted of a mixture of

pancreatic or periampullary adenocarcinoma cases without neoadjuvant treatment. Thus, oncological malignant tumor features may have influenced their prognosis. In the current study, we attempted to apply AGR to a consecutive pancreatic cancer-only cohort with all neoadjuvant treatment settings of our institution.

MATERIALS AND METHODS

Patients

We retrospectively analyzed 175 pancreatic cancer patients who underwent curative R0/R1 resection after pre-operative chemotherapy at Nagoya University Hospital (Nagoya, Japan) from April 2010 to December 2020. After 13 patients were excluded because of incomplete medical records, a total of 162 patients were included in this study. Radical resections with D2 lymphadenectomy were performed for all patients, followed by six months of adjuvant chemotherapy with gemcitabine or S-1, an oral 5-fluorouracil prodrug tegafur combined with oteracil and gimeracil. All patients were routinely observed by serum tumor markers and computed tomography examination every 3 or 6 months. The hospital ethics committee approved this study (2021-0296), and informed consent was obtained from all patients for the subsequent use of their clinical data.

Data collection

All clinicopathological data were retrieved from the electronic medical record system and were analyzed retrospectively. We calculated nutritional indexes from the blood examination just before the initial chemotherapy or chemoradiotherapy (pre-treatment status), such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), PNI, albumin, globulin, and AGR data. We excluded GPS because of its categorical scoring system, and CONUT because of considerable missing data at the preoperative therapy induction date. AGR was calculated using the following equation: serum albumin (g/dl) / [serum total protein (g/dl) − serum albumin (g/dl)]. We set the cut-off value of each nutritional

index as the median value.

We also calculated the average relative dose intensity (RDI) for each patient in accordance with the method proposed by Hryniuk and Bush(18). RDI was defined by the total administered drug dosage divided by the standard dosage. The average RDI (ARDI) of individual administered chemotherapy drugs was also calculated. Because the mean value of the ARDI was 87%, we set a cut-off value of 87%.

Histological findings were assessed by the 8th edition of the Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) classification. Resectability status was routinely classified at the diagnosis of pancreatic cancer by the radiologist using dynamic CT images following National Comprehensive Cancer Network (NCCN) guidelines for pancreatic adenocarcinoma (version 3. 2017).

Preoperative treatment regimens

We performed pre-operative chemotherapy in 112 patients and chemoradiotherapy in 50 patients. The pre-operative chemotherapy regimen included gemcitabine and nab-paclitaxel (GnP) therapy (n = 44), gemcitabine and tegafur/gimeracil/oteracil (S-1) combination (GS) therapy (n = 39), FOLFIRINOX (folinic acid, fluorouracil, irinotecan, and oxaliplatin; n = 21), and others (n = 8). The chemoradiotherapy regimen included S-1 and radiation (n = 42) and GnP and radiation (n = 8).

Statistical analysis

Continuous data were compared using t-tests, and categorical data were compared using a chi-squared test. Survival time was estimated using the Kaplan–Meier method, and survival outcomes were compared using log-rank tests. Overall survival (OS) was defined as the interval from the neoadjuvant therapy start date to death from any cause or last follow-up, whichever occurred first. Progression-free survival (PFS) was calculated from the neoadjuvant therapy start date to the first

observation of recurrence or last follow-up without recurrence evidence. Cox proportional hazards regression analysis was used for univariate analyses. Nutritional markers such as NLR, PLR, PNI, and AGR were included in the multivariate analysis. All statistical analyses were conducted using JMP version 13.0 software (SAS Institute; Cary, NC, USA). The threshold for significance was $P < 0.05$.

RESULTS

Patients' characteristics

The baseline demographic characteristics of the 162 patients eligible for this study are summarized in **Table 1**. This retrospective study included 71 women and 91 men aged 40-86 (mean, 66.8 ± 8.9 years). The mean body mass index was 20.9 ± 0.27 kg/m^2. Tumors were located in the pancreatic head in 127 patients and the pancreas body and tail in 35 patients. We performed 130 pancreaticoduodenectomies, 29 distal pancreatectomies, and three total pancreatectomies. The histological stage of the 162 patients was classified following the International Union for Cancer Control TNM classification 8th edition staging system as follows: Stage 0 in five cases, IA in eight cases, IIA in 72 cases, IIB in 66 cases, III in six cases, and IV in four cases. Sixty-three cases were resectable, 66 cases were borderline resectable, and 32 cases were unresectable at the time of diagnosis. Preoperative therapy regimens varied depending on the NCCN resectability status. For example, resectable cases were followed by a GS regimen for six weeks, while borderline resectable cases were typically treated by GnP or FOLFIRINOX for two months(19). As for unresectable cases, GnP or FOLFIRINOX were used for eight months(20). In the early phase of this study period, S-1 based NACRT regimen was dominantly performed(21). Although there was no significant regimen selection difference between high and low AGR groups (Table 2), the number of GS regimen-applied resectable cases was relatively high in the low AGR group. Regarding the nutritional index, all patients were divided into high and low groups based on the median value.

Nutritional indexes and survival outcomes

Among the candidate pre-treatment nutritional indexes of NLR, PLR, PNI and AGR using the median cut-off value, only AGR showed a significant difference in both OS and PFS survival outcomes in this cohort (**Figure 1**). The median PFS time was 22.3 months in high AGR cases and 17.1 months in low AGR cases, with a significant difference (P = 0.019). Furthermore, the median OS time was 48.7 months in high AGR cases and 32.9 months in low AGR cases (P = 0.043). AGR consists of two elements, albumin and globulin. However, neither becomes a significant prognostic factor for PFS and OS (**Supplementary Figure S1**, **Supplementary Figure S2**).

AGR and clinicopathological characteristics

The associations between AGR and clinicohistological characteristics are shown in **Table 2**. Low AGR cases were significantly associated with pancreatic head tumor cases (P = 0.013) and higher serum tumor markers DUPAN-2 (P = 0.005) and SPAN-1 (P = 0.011). However, the two groups had no significant differences in age, sex, body mass index, and tumor size. Regarding histological factors, low AGR cases showed significant retroperitoneum invasion (P = 0.010), bile duct invasion (P = 0.001), duodenum invasion (P = 0.001), and lymph node metastasis (P = 0.034). Cancer resectability and other nutritional indexes, except for PNI (P < 0.0001), indicated no association with high or low AGR.

In subgroup analyses, the associations between each component of AGR, albumin or globulin, and clinicopathological characteristics were shown. Because both low albumin and high globulin reduce the AGR value, clinicohistological factors of these were examined separately. Interestingly, low albumin cases were significantly associated with pancreatic head tumor lesions (P = 0.022) and positive bile duct invasion (P = 0.001), while no serum tumor marker showed a correlation with the low albumin group (**Supplementary Table 1**). However, high globulin cases indicated a significant association with duodenal invasion (P = 0.032) and relatively high tumor markers (DUPAN-2, P = 0.043; SPAN-1, P = 0.001) (**Supplementary Table 2**).

In the additional subgroup analysis, we focused only on cases with the pancreatic head lesion to see whether low AGR is associated with bile duct invasion or duodenal invasion (**Supplementary Table 3**). Low AGR cases were associated again with bile duct invasion (P = 0.013) and duodenum invasion (P = 0.012).

Univariate analysis of pre-operative prognostic factors of pancreatic cancer cases treated with pre-operative chemotherapy and surgery

Among pre-operative factors only, proportional hazards model analysis identified that AGR was the sole significant risk factor of both PFS (Hazard ratio: 0.63, 95% confidence interval: 0.42-0.93, P = 0.020) and OS (Hazard ratio: 0.62, 95% confidence interval: 0.38-0.99, P = 0.045) (**Table 3**). Tumor size, tumor markers, and other nutritional indexes were not precise predictors of cases with pre-operative treatment. Even tumor resectability was not a predictor of survival outcomes from the beginning of neoadjuvant therapy.

To identify the advantages of the high AGR status at the diagnosis, we examined the ARDI of preoperative therapy regimens. As shown in **Figure 2**, AGR and ARDI did not show a significant correlation in all cases. However, the high AGR status scored a significantly high ARDI of S-1 based regimens (P = 0.011), which might lead to favorable survival outcomes.

DISCUSSION

This study examined several nutritional indexes of 162 pancreatic cancer patients at the beginning of multimodal treatment, including pre-operative chemotherapy or chemoradiotherapy and subsequent curative pancreatectomy at our hospital. Among them, high AGR was solely associated with favorable survival outcomes, which means the sum of pre-operative treatment duration and postoperative times in this study. Pre-operative treatment tolerability or effectiveness also reflects the outcomes.

Azab et al. (22) first reported in 2013 that the AGR is considered a powerful prognostic marker in patients with colorectal cancer. Low AGR is induced by lower serum albumin and/or higher serum globulin. Lower serum albumin frequently reflects the poor nutritional status and the existence of systemic inflammatory response in patients(23). In contrast, higher serum globulin indicates the activation of immunity or inflammation as a primary cortisol-binding protein(24). Both decreased albumin and increased globulin have been widely reported as prognostic indicators for survival in patients with several types of tumors(25-27).

Serum albumin level quickly changes in perioperative patients because of the changes in body fluid level. Malnutrition and inflammation could also impair the synthesis of albumin. In particular, interleukin-6 activation decreases protein synthesis in the acute phase of inflammation reactions in human hepatocytes(28). Tumor necrosis factor also downregulates albumin synthesis and increases the microvasculature permeability(29). In **Supplementary Table 1**, we also found that low serum albumin was closely correlated with the tumor's histological invasion of the common bile duct (P = 0.001). Because hepatocytes produce albumin, their damage results in a low serum albumin status. It also reflects the amount of skeletal muscle and is decreased by inflammatory mediators(30) (31). Obstructive jaundice-induced liver function damage would reduce the synthetic capacity of albumin(32).

The inflammatory status also produces acute-phase protein and immunoglobulin aggregation, leading to increased serum globulin(16). Additional analysis in **Supplementary Table 2** indicated that high globulin level was significantly associated with the histological result of cancer invasion of the duodenum (P = 0.032). Generally, gamma-globulin, deeply related to immune function among the globulins, is called immunoglobulin. There are five types of immunoglobulins: G, M, A, D, and E. Immunoglobulin A (IgA) is mainly responsible for gut immunity. Peyer's patches are unique and vital immune organs localized in the intestinal wall. Primary immune cells such as dendritic cells, T cells, and B cells are concentrated in the Peyer's patch region. These intestinal immune cell groups work

together to produce IgA against the invading antigen and prevent it from entering the body. Such a mechanism may affect the association between globulin and duodenum invasion.

Patients with pancreatic cancer often have pre-operative inflammatory diseases such as cholangitis and pancreatitis due to the tumor invasion. Aziz et al.(33) reported that pre-operative biliary drainage for obstructive jaundice improved immune-nutritional status. This emphasizes the importance of maintaining a non-inflammatory condition during preoperative therapy. Whether early nutritional support and inflammation might lead to better patient outcomes remains controversial. However, Chao et al.(34) reported that patients with nutritional support exhibited more favorable clinical outcomes than those without support. This may be partially because a satisfactory pre-operative immune-nutritional status would improve tolerance to preoperative therapy (35). **Figure 2** shows a significant association between AGR and ARDI of S-1 based regimens (GS and NACRT (S-1)).

Conversely, cases without preoperative therapy showed no advantage of high AGR in their survival outcomes (**Supplementary Figure S3**). It also supports the hypothesis that the AGR index may reflect the patient's tolerance to preoperative therapy, a current standard strategy of PDAC treatment. Moreover, both nutritional support by pancrelipase tablets or amino acid-rich nutrients and intensive infection control arising from cholangitis or duodenal stenosis before preoperative therapy may improve the ARDI of preoperative therapy and prolong the survival outcomes.

We have previously reported the importance of presurgical CONUT score, GPS, and PNI in pancreatic cancer(10, 12) (36). Even in this study, high AGR was significantly associated with high PNI in Table 2. However, PNI did not show the impact in **Table 3** as a prognostic factor. We think it may be because the total lymphocyte counts, one of the factors of PNI, were influenced by both nutritional status and chemotherapy damage of bone marrow suppression. Therefore, this irregular period of the preoperative therapy cohort may weaken the impact of the PNI index. Kato et al. (12) reported that the CONUT score was a better immune-nutritional prognostic factor because of the

addition of the total cholesterol level in the PNI. However, in many cases in this cohort, serum cholesterol data were lacking before the start of pre-operative treatment. This is why we could not compare the index power with the CONUT score.

Our study has certain limitations. First, this was a single-institution retrospective study with relatively few patients. Further investigation using other cohorts is required. Second, we set the median value as a cut-off for several nutritional indexes. Different cohorts may require different cut-off values, although the AGR cut-off value in this study was similar to that of other reports(37-39). Third, we focused on surgically resected cases only, and pre-operative chemotherapy regimens and durations varied in the cohort. Therefore, if we recruit a larger cohort, we must assess each regimen separately.

In conclusion, AGR may be a simple scoring system and an independent survival outcome predictor of pancreatic cancer cases with multimodal treatments. To maintain AGR high, it may be essential to keep albumin high with adequate medication or amino acid loading or control inflammation by antibiotics treatment and endoscopic intervention. If these intensive treatments before preoperative therapy do not work enough, pre-operative therapy induction may not be favorable for those patients.

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Author Contributions

M.H. designed the project. M.H., D.K., H.T. and Y.I. collected and analyzed clinical and blood examination data. M.H., H.T., Y.I., N.T. and K.K. performed pancreatectomy and followed up the patients. K.N., S.U., D.S., N.H., M.K, C.T., G.N and Y.K. reviewed the manuscript. M.K. and Y.K. prepared the materials and analytic tools. M.H. and D.K. wrote the manuscript.

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Figure legends

Figure 1. Survival outcomes of 162 cases with pre-operative treatment are shown. **a:** PFS curves of high and low AGR cases. **b:** OS curves of high and low AGR cases.

Figure 2. Pre-operative chemotherapy treatment ARDI was compared with AGR by the correlation coefficient analysis.

Supplementary Figure S1. Survival outcomes of 162 cases with pre-operative treatment are shown. **a:** PFS curves of high and low albumin cases. **b:** OS curves of high and low albumin cases.

Supplementary Figure S2. Survival outcomes of 162 cases with pre-operative treatment are shown. **a:** PFS curves of high and low globulin cases. **b:** OS curves of high and low globulin cases.

Supplementary Figure S3. Survival outcomes of 429 cases without pre-operative treatment are shown. **a:** PFS curves of high and low AGR cases. **b:** OS curves of high and low AGR cases.

Table 1. Patients' characteristics

Variable	n=162
Age, mean ± SD (years)	66.8 ± 8.9
Sex	
Male	91 (56.2)
Female	71 (43.8)
Body mass index, mean ± SD (kg/m^2)	20.9 ± 3.5
Tumor location	
Head	127 (78.4)
Body or tail	35 (21.6)
Resectability at the diagnosis	
Resectable	63 (39.1)
Borderline resectable	66 (41.0)
Unresectable	32 (19.9)
CEA, mean ± SD (ng/mL)	5.4 ± 22.2
CA19-9, mean ± SD (U/mL)	676 ± 1783
DUPAN-2, mean ± SD (U/mL)	934 ± 2696
SPan-1, mean ± SD (U/mL)	84.3 ± 143.7
NLR	
High (> 2.33)	83 (51.2)
Low (< 2.33)	79 (48.8)
PLR	
High (> 160)	80 (49.4)
Low (< 160)	82 (50.6)
PNI	
High (> 45)	79 (48.8)
Low (< 45)	83 (51.2)
AGR	
High (> 1.33)	80 (49.4)
Low (< 1.33)	82 (50.6)
Preoperative therapy	
FFX	21 (13.0)
GnP	44 (27.2)
GS	39 (24.1)
NACRT (S-1)	42 (25.9)
Others	16 (9.8)
RDI (%)	
High (> 80)	114 (70.4)
Low (< 80)	48 (29.6)
Operative procedure	
Pancreaticoduedenectomy	130 (80.2)
Distal pancreatectomy	29 (17.9)
Total pancreatectomy	3 (1.9)
Tumor size, mean ± SD (mm)	24.1 ± 8.9
Pathological TNM stage	
0	5 (3.1)
IA	8 (5.0)
IIA	72 (44.7)
IIB	66 (41.0)
III	6 (3.7)
IV	4 (2.5)

NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio;
PNI, prognostic nutritional index; AGR, albumin–globulin ratio;
FFX, FOLFIRINOX; GnP, gemcitabine and nab-paclitaxel;
GS, gemcitabine and tegafur/gimeracil/oteracil (S-1);
NAT, neoadjuvant therapy; RDI: relative dose intensity
continuous variables: average ± standard deviation

Table 2. Association of AGR and clinicopathological characteristics in 162 patients treated with preoperative therapy and surgical resection

Variables	High AGR (n=80)	Low AGR (n=82)	P value
Age, years	65.8 ± 9.3	67.8 ± 8.5	0.156
Sex			0.754
Male	46 (57.5)	45 (54.9)	
Female	34 (42.5)	37 (45.1)	
Body mass index (kg/m^2)	21.1 ± 4.0	20.6 ± 3.0	0.468
Tumor location			0.013*
Head	56 (70.0)	71 (86.6)	
Body or tail	24 (30.0)	11 (13.4)	
Resectability at the diagnosis			0.053
Resectable	25 (31.3)	38 (46.9)	
Borderline resectable	35 (42.5)	32 (39.5)	
Unresectable	21 (26.2)	11 (13.6)	
CEA, mean ± SD (ng/mL)	6.6 ± 3.5	4.3 ± 3.5	0.498
CA19-9, mean ± SD (U/mL)	412 ± 951	933 ± 2303	0.063
DUPAN-2, mean ± SD (U/mL)	334 ± 564	1519 ± 3665	0.005*
SPan-1, mean ± SD (U/mL)	54.3 ± 61.9	113.6 ± 188.6	0.011*
NLR			0.271
High (> 2.33)	37 (46.3)	46 (56.1)	
Low (< 2.33)	43 (53.8)	36 (43.9)	
PLR			0.877
High (> 160)	39 (48.8)	41 (50.0)	
Low (< 160)	41 (51.2)	41 (50.0)	
PNI			<0.0001*
High (> 45)	52 (65.0)	27 (32.9)	
Low (< 45)	28 (35.0)	55 (67.1)	
Preoperative therapy			0.508
FFX	11 (13.8)	10 (12.2)	
GnP	23 (28.8)	21 (25.6)	
GS	14 (17.5)	25 (30.5)	
NACRT (S-1)	21 (26.3)	21 (25.6)	
Others	11 (13.6)	5 (6.1)	
ARDI, mean ± SD (ng/mL)	89.4 ± 15.8	85.7 ± 18.9	0.180
Operative procedure			0.122
Pancreaticoduedenectomy	59 (73.8)	71 (86.6)	
Distal pancreatectomy	19(23.8)	10 (12.2)	
Total pancreatectomy	1 (2.5)	1 (1.2)	
Postoperative hospital stay period (days)	24.2 ± 9.6	25.8 ± 13.6	0.393
Pathological findings			
Tumor size (mm)	23.6 ± 9.8	24.6 ± 7.9	0.482
Serosal invasion			0.468
(+)	58 (72.5)	64 (78.1)	
(-)	22 (27.5)	18 (21.9)	
Retroperitoneal invasion			0.010*
(+)	61 (76.3)	75 (91.5)	
(-)	19 (23.7)	7 (8.5)	
Bile duct invasion			0.001*
(+)	22 (27.5)	43 (52.4)	
(-)	58 (72.5)	39 (47.6)	
Duodenum invasion			0.001*
(+)	19 (23.8)	40 (48.8)	
(-)	61 (76.2)	42 (51.2)	
Portal venous system invasion			0.748
(+)	33 (41.3)	31 (37.8)	
(-)	47 (58.7)	51 (62.2)	
Regional artery invasion			0.058
(+)	14 (17.5)	6 (7.3)	
(-)	66 (82.5)	76 (92.7)	
Nerve plexus invasion			0.506
(+)	13 (16.3)	10 (12.2)	
(-)	67 (83.7)	72 (87.8)	
Lymphatic invasion			0.057
(+)	27 (33.8)	40 (48.8)	
(-)	53 (66.2)	42 (51.2)	
Venous invasion			0.198
(+)	26 (32.5)	35 (42.7)	
(-)	54 (67.5)	47 (57.3)	
Lymph node metastasis			0.034*
(+)	22 (27.5)	36 (43.9)	
(-)	58 (72.5)	46 (56.1)	
Peritoneal cytology			0.403
(+)	5 (6.3)	9 (11.0)	
(-)	75 (93.2)	73 (89.0)	
Pathological TNM stage			0.086
0 or I or IIA	48 (60.0)	38 (46.3)	
IIB or III or IV	32 (40.0)	44 (53.7)	
Adjuvant chemotherapy			0.826
(+)	69 (86.3)	69 (84.2)	
(-)	11 (13.7)	13 (15.8)	
Adjuvant chemotherapy course completion			0.701
(+)	49 (71.0)	52 (75.4)	
(-)	20 (29.0)	17 (24.6)	

NLR, neutrophil–lymphocyte ratio; PLR, platelet-lymphocyte ratio;
PNI, prognostic nutritional index; AGR, albumin–globulin ratio;
FFX, FOLFIRINOX; GnP, gemcitabine and nab-paclitaxel;
GS, gemcitabine and tegafur/gimeracil/oteracil (S-1); CEA, carcinoembryonic antigen;
CA19-9, carbohydrate antigen 19-9; ARDI, average relative dose intensity
continuous variables: average ± standard deviation
*Statistically significant

Table 3. Clinicopathological factors of survival outcomes in 162 patients treated with preoperative therapy and surgical resection

Variables	PFS Univariate analysis		OS Univariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (> 70 years vs. ＜70 years)	1.23 (0.83-1.84)	0.299	1.56 (0.97-2.51)	0.069
Sex (male vs. female)	0.98 (0.66-1.45)	0.936	1.07 (0.67-1.72)	0.766
Tumor location (head vs. body or tail)	0.94 (0.59-1.50)	0.803	0.97 (0.55-1.69)	0.911
Resectability at the diagnosis (R vs. BR / UR)	1.45 (0.96-2.20)	0.075	1.39 (0.83-2.32)	0.209
CEA (> 5.0 IU/ml vs. < 5.0 IU/ml)	0.92 (0.56-1.51)	0.734	0.96 (0.54-1.71)	0.897
CA19-9 (> 37 IU/ml vs. ＜ 37 IU/ml)	1.15 (0.71-1.85)	0.581	1.11 (0.62-2.00)	0.728
DUPAN-2 (> 150 IU/ml vs. ＜ 150 IU/ml)	1.12 (0.76-1.66)	0.565	1.28 (0.80-2.05)	0.300
Span-1 (> 30 IU/ml vs. ＜ 30 IU/ml)	1.20 (0.79-1.83)	0.401	1.52 (0.89-2.58)	0.121
NLR (> 2.33 vs. ＜ 2.33)	1.06 (0.72-1.57)	0.776	0.91 (0.57-1.46)	0.707
PLR (> 160 vs. < 160)	1.10 (0.75-1.63)	0.625	0.92 (0.58-1.48)	0.739
PNI (> 45 vs. < 45)	0.84 (0.57-1.25)	0.385	1.09 (0.68-1.75)	0.716
AGR (> 1.33 vs. < 1.33)	0.63 (0.42-0.93)	0.020*	0.62 (0.38-0.99)	0.045*
ARDI (＞ 80 vs. < 80)	0.83 (0.54-1.27)	0.393	0.77 (0.50-1.28)	0.309
Tumor size (> 20mm vs. < 20mm)	1.29 (0.85-1.96)	0.240	1.28 (0.76-2.16)	0.349

PFS, progression-free survival; OS, overall survival; NAT, neoadjuvant therapy; RDI, average relative dose intensity
NLR: neutrophil lymphocyte ratio, PLR: platelet-lymphocyte ratio,
PNI: prognostic nutritional index, AGR: Albumin-Globulin ratio,
CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9
continuous variables: average ± standard deviation
*Statistically significant

Supplementary Table 1. Association of albumin and clinicopathological characteristics in 162 patients treated with preoperative therapy and surgical resection

Variables	High Albumin (n=78)	Low Albumin (n=84)	P value
Age, years	65.7 ± 9.1	67.9 ± 8.7	0.117
Sex			0.017*
Male	36 (46.2)	55 (65.5)	
Female	42 (53.8)	29 (34.5)	
Body mass index (kg/m^2)	21.7 ± 3.9	20.1 ± 2.8	0.003*
Tumor location			0.022*
Head	55 (70.5)	72 (85.7)	
Body or tail	23 (29.5)	12 (14.3)	
Resectability at the diagnosis			0.022*
Resectable	22 (28.6)	41 (48.8)	
Borderline resectable	35 (45.5)	31 (36.9)	
Unresectable	20 (25.9)	12 (14.3)	
CEA, mean ± SD (ng/mL)	6.9 ± 3.6	4.1 ± 3.4	0.433
CA19-9, mean ± SD (U/mL)	572 ± 1139	772 ± 2224	0.476
DUPAN-2, mean ± SD (U/mL)	702 ± 2205	1148 ± 3081	0.297
SPan-1, mean ± SD (U/mL)	61.4 ± 55.9	105.5 ± 190.2	0.061
NAT RDI	89.6 ± 15.5	85.6 ± 19.0	0.153
Operative procedure			0.085
Pancreaticoduedenectomy	57 (73.1)	73 (86.9)	
Distal pancreatectomy	19 (24.4)	10 (11.9)	
Total pancreatectomy	2 (2.5)	1 (1.2)	
Pathological findings			
Tumor size (mm)	25.0 ± 9.4	23.3 ± 8.3	0.219
Serosa invasion			0.717
(+)	60 (76.9)	62 (73.8)	
(-)	18 (23.1)	22 (26.2)	
Retroperitoneum invasion			0.669
(+)	64 (82.1)	72 (85.7)	
(-)	14 (17.9)	12 (14.3)	
Bile duct invasion			0.001*
(+)	21 (26.9)	44 (52.4)	
(-)	57 (73.1)	40 (47.6)	
Duodenum invasion			0.327
(+)	25 (32.1)	34 (40.5)	
(-)	53 (67.9)	50 (59.5)	
Portal venous system invasion			0.011*
(+)	39 (50.0)	25 (29.8)	
(-)	39 (50.0)	59 (70.2)	
Regional artery invasion			0.151
(+)	13 (16.7)	7 (8.3)	
(-)	65 (83.3)	77 (91.7)	
Nerve plexus invasion			0.822
(+)	12 (15.4)	11 (13.1)	
(-)	66 (84.6)	73 (86.9)	
Lymphatic invasion			0.75
(+)	31 (39.7)	36 (42.9)	
(-)	47 (60.3)	48 (57.1)	
Venous invasion			1
(+)	29 (37.2)	32 (38.1)	
(-)	49 (62.8)	52 (61.9)	
Lymph node metastasis			0.139
(+)	23 (29.5)	35 (41.7)	
(-)	55 (70.5)	49 (58.3)	
Peritoneal cytology			1
(+)	7 (8.9)	7 (8.3)	
(-)	71 (91.1)	77 (91.7)	
Pathological TNM stage			0.159
0 or I or IIA	46 (58.9)	40 (47.6)	
IIB or III or IV	32 (41.1)	44 (52.4)	

NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio;
PNI, prognostic nutritional index; AGR, albumin–globulin ratio;
PD, pancreaticoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy;
CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9;
NAT, neoadjuvant therapy; RDI, relative dose intensity
continuous variables: average ± standard deviation
*Statistically significant

Supplementary Table 2. Association of globulin and clinicopathological characteristics in 162 patients treated with preoperative therapy and surgical resection

Variables	High globulin (n=69)	Low globulin (n=93)	P value
Age, years	68.3 ± 8.4	65.7 ± 9.2	0.074
Sex			0.873
Male	38 (55.1)	53 (57.0)	
Female	31 (44.9)	40 (43.0)	
Body mass index (kg/m^2)	21.2 ± 4.1	20.6 ± 2.9	0.255
Tumor location			0.335
Head	57 (82.6)	70 (75.3)	
Body or tail	12 (17.4)	23 (24.7)	
Resectability at the diagnosis			0.446
Resectable	30 (44.1)	33 (35.5)	
Borderline resectable	27 (39.7)	39 (41.9)	
Unresectable	11 (16.2)	21 (22.6)	
CEA, mean ± SD (ng/mL)	3.9 ± 3.1	6.6 ± 3.0	0.437
CA19-9, mean ± SD (U/mL)	799 ± 1563	585 ± 1934	0.451
DUPAN-2, mean ± SD (U/mL)	1435 ± 3531	564 ± 1787	0.043*
SPan-1, mean ± SD (U/mL)	129.4 ± 202.7	51.7 ± 60.4	0.001*
NAT RDI	86.6 ± 18.3	88.2 ± 16.9	0.581
Operative procedure			0.798
Pancreaticoduedenectomy	57 (82.6)	73 (78.5)	
Distal pancreatectomy	11(15.9)	18 (19.4)	
Total pancreatectomy	1 (1.5)	2 (2.1)	
Pathological findings			
Tumor size (mm)	25.9 ± 8.4	22.8 ± 9.0	0.031*
Serosa invasion			0.854
(+)	51 (73.9)	71 (76.3)	
(-)	18 (26.1)	22 (23.7)	
Retroperitoneum invasion			0.087
(+)	62 (89.9)	74 (79.6)	
(-)	7 (10.1)	19 (20.4)	
Bile duct invasion			0.105
(+)	33 (47.8)	32 (34.4)	
(-)	36 (52.2)	61 (65.6)	
Duodenum invasion			0.032*
(+)	32 (46.4)	27 (29.0)	
(-)	37 (53.6)	66 (71.0)	
Portal venous system invasion			0.627
(+)	29 (42.0)	35 (37.6)	
(-)	40 (58.0)	58 (62.4)	
Regional artery invasion			1
(+)	8 (11.6)	12 (12.9)	
(-)	61 (88.4)	81 (87.1)	
Nerve plexus invasion			0.652
(+)	11 (15.9)	12 (12.9)	
(-)	58 (84.1)	81 (87.1)	
Lymphatic invasion			1
(+)	29 (42.0)	38 (40.9)	
(-)	40 (58.0)	55 (59.1)	
Venous invasion			1
(+)	26 (37.7)	35 (37.6)	
(-)	43 (62.3)	58 (62.4)	
Lymph node metastasis			0.508
(+)	27 (39.1)	31 (33.3)	
(-)	42 (60.9)	62 (66.7)	
Peritoneal cytology			0.271
(+)	8 (11.6)	6 (6.5)	
(-)	61 (88.4)	87 (93.5)	
Pathological TNM stage			0.635
0 or I or IIA	35 (50.7)	51 (54.8)	
IIB or III or IV	34 (49.3)	42 (45.2)	

NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio;
PNI, prognostic nutritional index; AGR, albumin–globulin ratio;
PD, pancreaticoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy;
CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9;
NAT, neoadjuvant therapy; RDI, relative dose intensity
continuous variables: average ± standard deviation
*Statistically significant

Supplementary Table 3. Association of AGR and clinicopathological characteristics in 127 patients treated with preoperative therapy and pancreatic head resection

Variables	High AGR (n=56)	Low AGR (n=71)	P value
Age, years	66.9 ± 9.5	67.5 ± 8.8	0.744
Sex			0.722
Male	32 (57.1)	38 (53.5)	
Female	24 (42.9)	33 (46.5)	
Body mass index (kg/m^2)	21.1 ± 4.1	20.7 ± 3.1	0.692
Resectability at the diagnosis			0.020*
Resectable	14 (25.0)	32 (45.7)	
Borderline resectable	27 (48.2)	30 (42.9)	
Unresectable	15 (26.8)	8 (11.4)	
CEA, mean ± SD (ng/mL)	8.2 ± 5.0	4.1 ± 3.4	0.420
CA19-9, mean ± SD (U/mL)	381 ± 620	914 ± 2437	0.080
DUPAN-2, mean ± SD (U/mL)	285 ± 380	1628 ± 3898	0.005*
SPan-1, mean ± SD (U/mL)	58.4 ± 68.7	111.8 ± 196.0	0.043*
NLR			0.155
High (> 2.33)	24 (42.9)	40 (56.3)	
Low (< 2.33)	32 (57.1)	31 (43.7)	
PLR			0.375
High (> 160)	26 (46.4)	39 (54.9)	
Low (< 160)	30 (53.6)	32 (45.1)	
PNI			<0.0001*
High (> 45)	36 (64.3)	20 (28.2)	
Low (< 45)	20 (35.7)	51 (71.8)	
Preoperative therapy			0.553
FFX	7 (12.5)	8 (11.2)	
GnP	13 (23.2)	17 (23.9)	
GS	10 (17.9)	21 (29.6)	
NACRT (S-1)	17 (30.4)	19 (26.8)	
Others	9 (16.0)	6 (8.5)	
ARDI, mean ± SD (ng/mL)	89.8 ± 16.9	85.5 ± 18.7	0.182
Postoperative hospital stay period (days)	24.7 ± 7.7	25.8 ± 14.3	0.577
Pathological findings			
Tumor size (mm)	23.7 ± 9.7	25.0 ± 7.7	0.432
Serosal invasion			0.167
(+)	37 (66.1)	55 (77.5)	
(-)	19 (33.9)	16 (22.5)	
Retroperitoneal invasion			0.002*
(+)	40 (71.4)	66 (93.0)	
(-)	16 (28.6)	5 (7.0)	
Bile duct invasion			0.013*
(+)	21 (37.5)	43 (60.6	
(-)	35 (62.5)	28 (39.4)	
Duodenum invasion			0.012*
(+)	18 (32.1)	39 (54.9)	
(-)	38 (67.9)	32 (45.1)	
Portal venous system invasion			0.579
(+)	22 (39.3)	24 (33.8)	
(-)	34 (60.7)	47 (66.2)	
Regional artery invasion			0.630
(+)	1 (1.8)	3 (4.2)	
(-)	55 (98.2)	68 (95.8)	
Nerve plexus invasion			0.806
(+)	9 (16.1)	10 (14.1)	
(-)	47 (83.9)	61 (85.9)	
Lymphatic invasion			0.070
(+)	18 (32.1)	35 (49.3)	
(-)	38 (67.9)	36 (50.7)	
Venous invasion			0.192
(+)	16 (35.6)	29 (64.4)	
(-)	40 (48.8)	42 (51.2)	
Lymph node metastasis			0.042*
(+)	15 (26.8)	32 (45.1)	
(-)	41 (73.2)	39 (54.9)	
Peritoneal cytology			0.754
(+)	4 (7.1)	7 (9.9)	
(-)	52 (92.9)	64 (90.1)	
Pathological TNM stage			0.032*
0 or I or IIA	37 (66.1)	33 (46.5)	
IIB or III or IV	19 (33.9)	38 (53.5)	
Adjuvant chemotherapy			0.806
(+)	47 (83.9)	61 (85.9)	
(-)	9 (16.1)	10 (14.1)	
Adjuvant chemotherapy course completion			0.830
(+)	35 (74.5)	44 (72.1)	
(-)	12 (25.5)	17 (27.9)	

NLR, neutrophil–lymphocyte ratio; PLR, platelet-lymphocyte ratio;
PNI, prognostic nutritional index; AGR, albumin–globulin ratio;
FFX, FOLFIRINOX; GnP, gemcitabine and nab-paclitaxel;
GS, gemcitabine and tegafur/gimeracil/oteracil (S-1); CEA, carcinoembryonic antigen;
CA19-9, carbohydrate antigen 19-9; ARDI, average relative dose intensity
continuous variables: average ± standard deviation
*Statistically significant

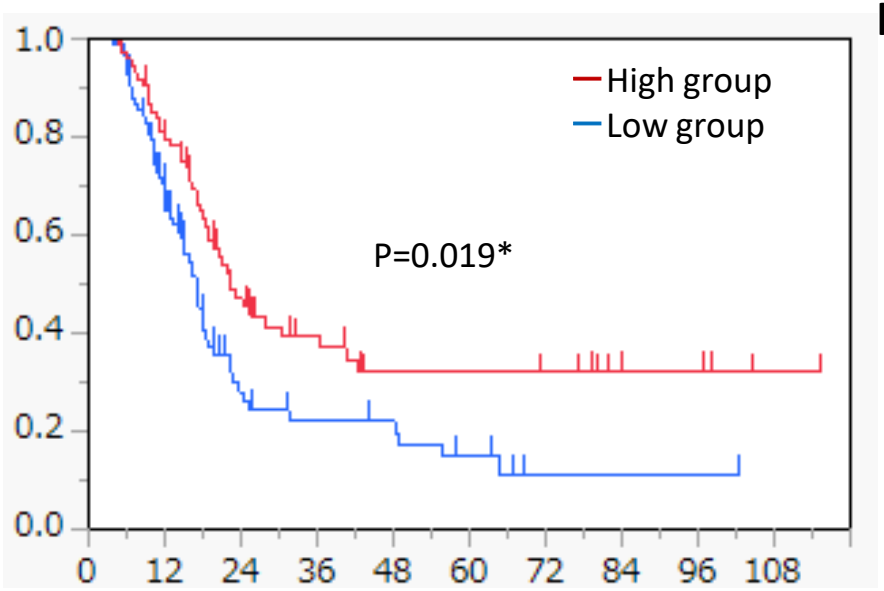
Median PFS time

AGR High group 22.3

AGR Low group 17.1

PFS survival rate

a



Months after therapy induction

Number at risk

AGR High group

80 58 28 18 12 12 11 6 6 2

AGR Low group

82 53 16 11 10 6 2 2 1 1

Recurrence-free survival

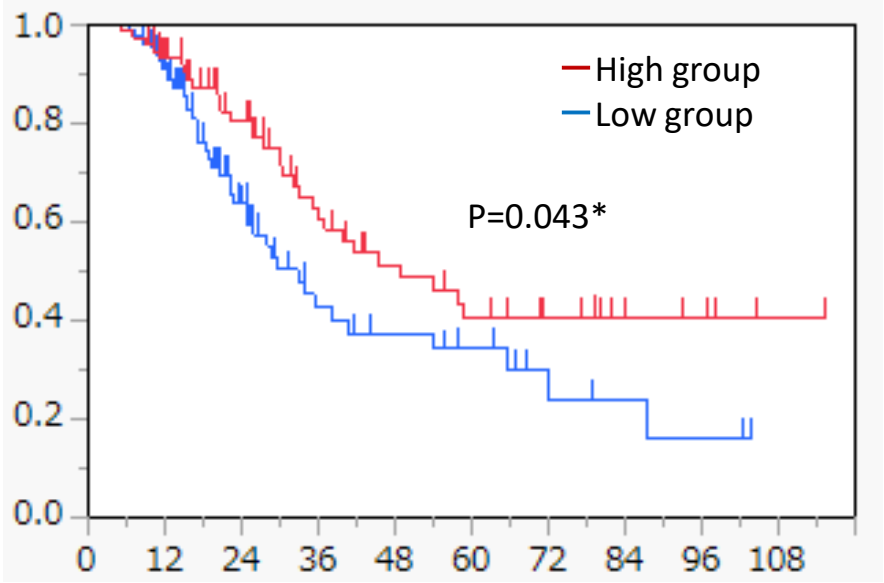
Median OS time

AGR High group 48.7

AGR Low group 32.9

OS survival rate

b



Months after therapy induction

Number at risk

AGR High group

80 69 48 29 21 16 12 7 6 2

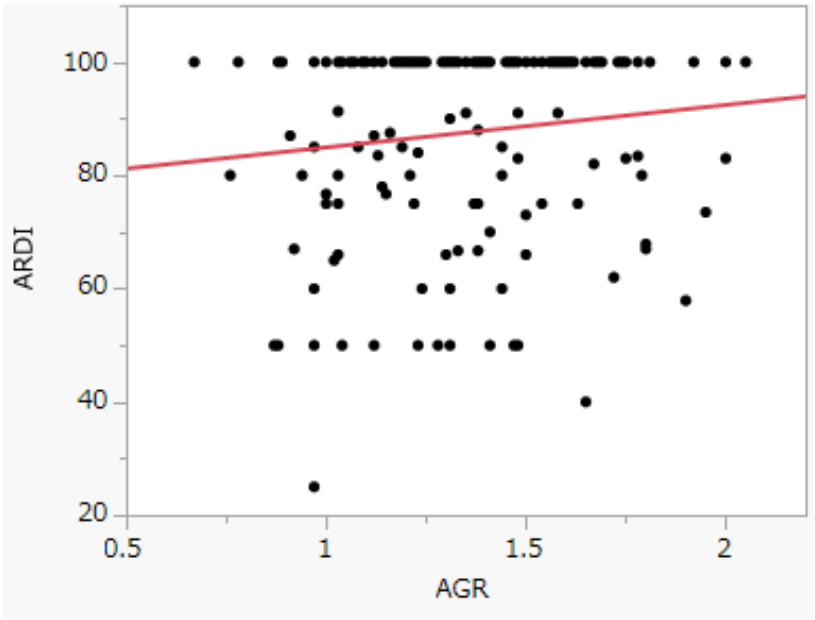
AGR Low group

82 68 33 17 13 10 6 4 3 1

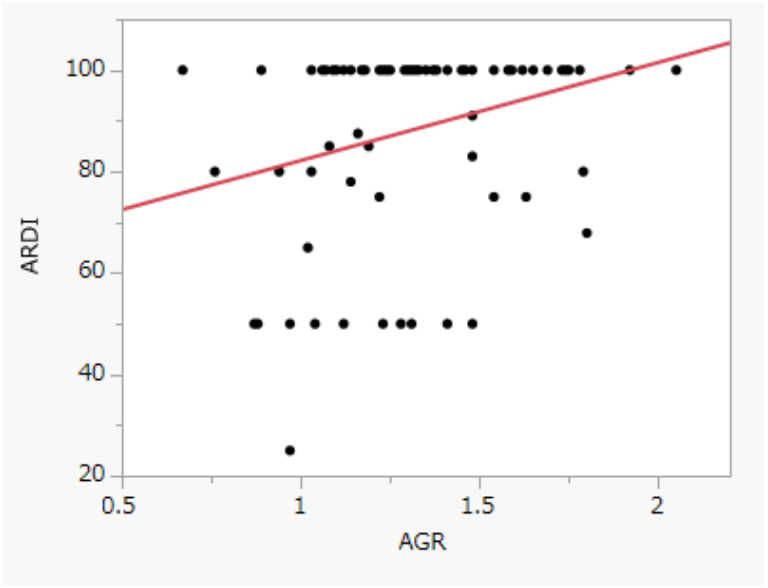
Overall survival

Figure 1

All cases (n=162) R^2<0.5, P=0.131



S-1 based regimens (n=81) R^2<0.5, P=0.011*



Other regimens (n=81) R^2<0.5, P=0.532

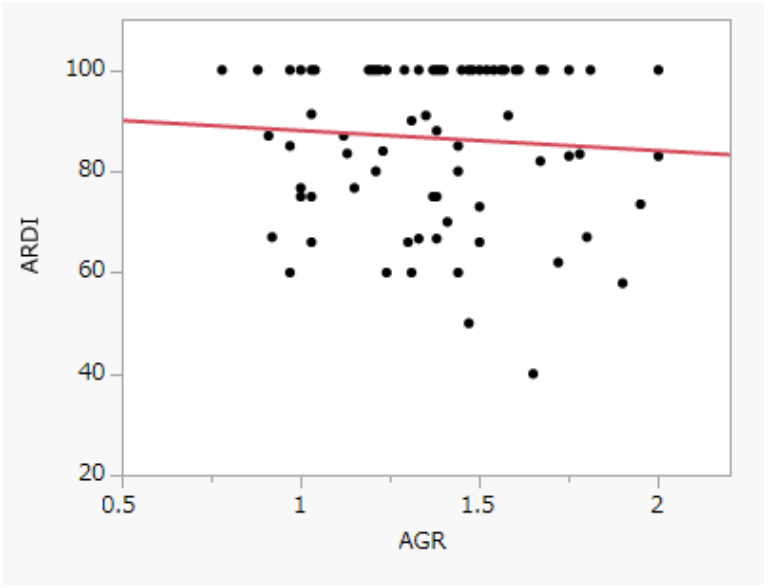


Figure 2

Median PFS time

Albumin High group 18.8

Albumin Low group 18.4

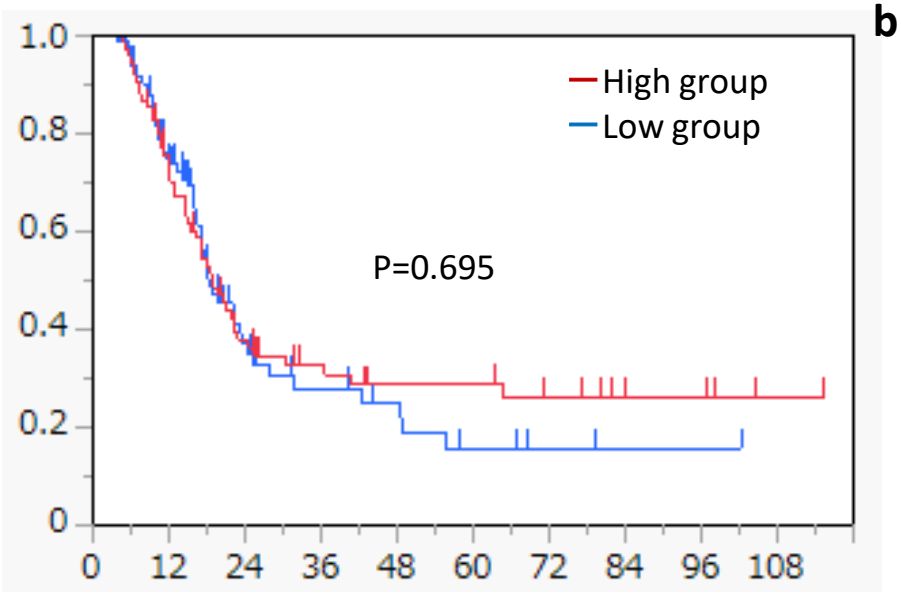
Median OS time

Albumin High group 37.0

Albumin Low group 57.9

a

PFS survival rate



Months after therapy induction

Number at risk

Albumin High group

78 55 25 17 13 13 10 6 6 2

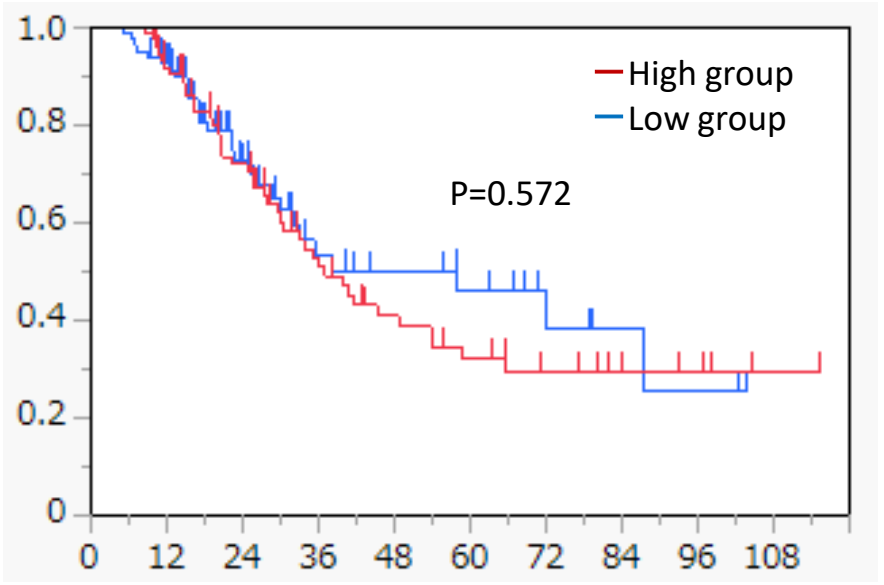
Albumin Low group

84 56 19 12 9 5 3 3 3 1

Recurrence-free survival

b

OS survival rate



Months after therapy induction

Number at risk

Albumin High group

78 65 47 28 20 15 11 7 6 2

Albumin Low group

84 72 34 18 14 12 7 4 3 1

Overall survival

Supplementary Figure S1

Median PFS time

Globulin High group 17.3

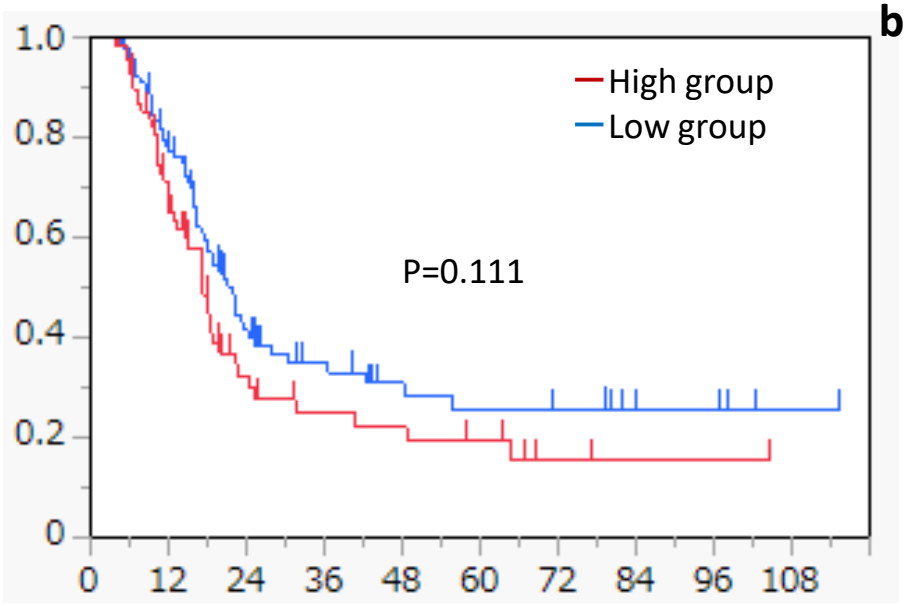
Globulin Low group 21.8

Median OS time

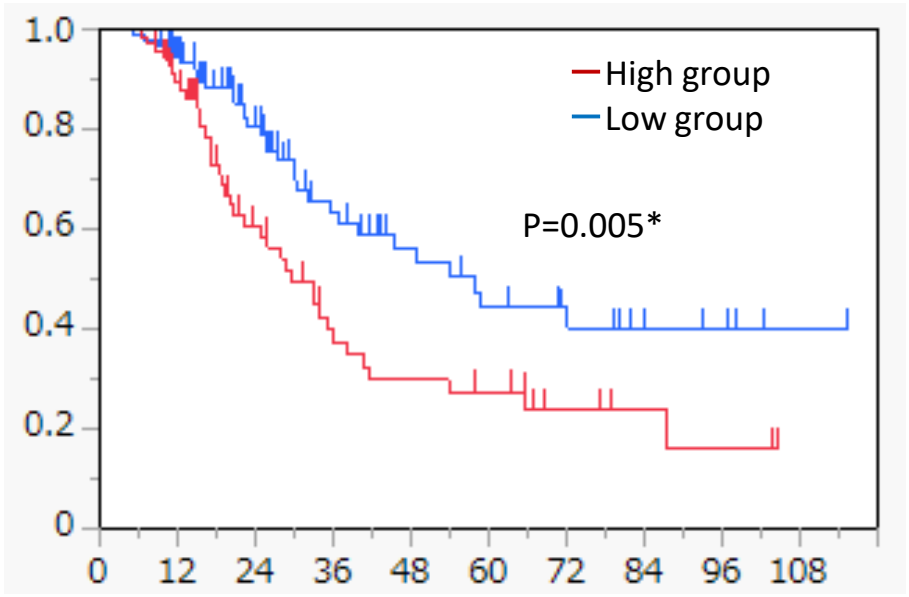
Globulin High group 29.7

Globullin Low group 57.9

a



b



Number at risk

Globulin High group

69 44 15 10 9 7 3 2 2 1

Globulin Low group

93 66 29 19 13 11 10 6 6 2

Recurrence-free survival

Number at risk

Globulin High group

69 56 29 16 13 11 6 4 3 1

Globulin Low group

93 81 52 30 21 15 12 7 6 2

Overall survival

Supplementary Figure S2

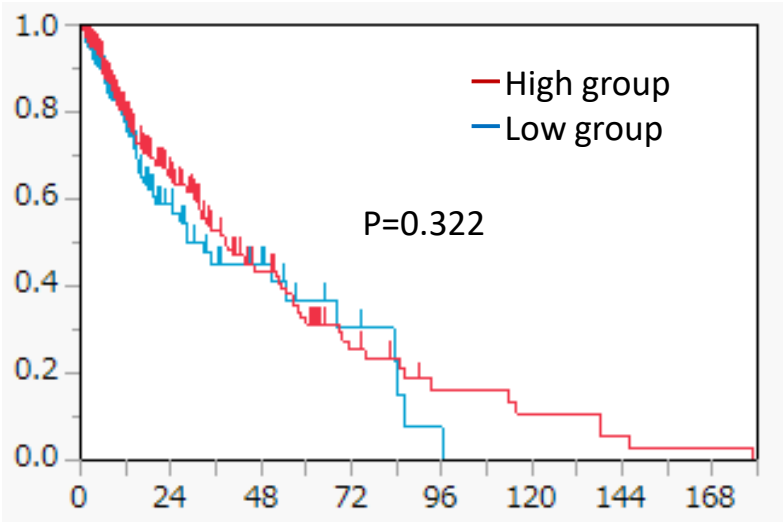
Median PFS time

AGR High group 38.6

AGR Low group 33.0

a

PFS survival rate



Months after surgery

Number at risk

AGR High group

267 84 36 14 7 5 3 2

AGR Low group

162 31 15 6 2 0 0 0

Recurrence-free survival

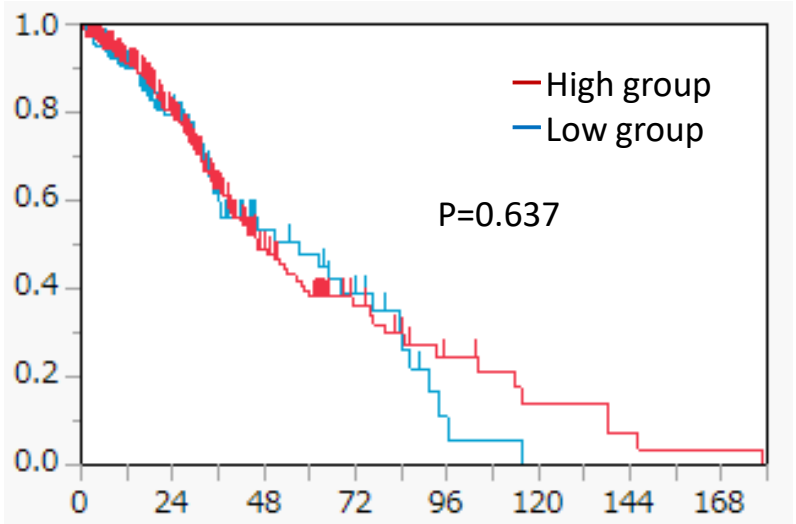
Median OS time

AGR High group 46.2

AGR Low group 57.2

b

OS survival rate



Months after surgery

Number at risk

AGR High group

267 133 45 19 9 5 3 2

AGR Low group

162 66 21 12 3 0 0 0

Overall survival

Supplementary Figure S3