Postoperative Serum Albumin is a Potential Prognostic Factor for Older Patients with Gastric Cancer

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ABSTRACT

Background   The incidence of gastric cancer (GC) among older adults is increasing. Therefore, determining postoperative age-associated prognostic factors is clinically important. This study retrospectively investigated the prognostic significance of serum albumin level in older GC patients.

Methods   We enrolled 135 patients aged ≥ 75 years, who underwent gastrectomies with histopathological diagnoses of gastric adenocarcinoma.

Results   Preoperative albumin (pre-Alb) levels in patients with advanced GC and stage III/IV GC were significantly lower than those in patients with early GC ($P = 0.0032$) and stage I/II GC ($P = 0.006$), respectively. Postoperative albumin (post-Alb) levels (measured 1 month after surgery) in male patients and in patients with advanced GC were significantly lower than those in female patients ($P = 0.024$) and those with early GC ($P = 0.044$), respectively. Post-Alb levels of patients who died of other diseases were significantly lower than those who were still living ($P = 0.0004$). Prognosis of patients with high post-Alb levels (≥ 4g/dL) was significantly better than that of patients with low post-Alb levels (< 4g/dL; $P = 0.045$); and in multivariate analysis, post-Alb level was an independent prognostic indicator.

Conclusion   Post-Alb level is a useful predictive factor for the prognosis of older GC patients. Postoperative nutritional support might help improve the prognosis of older GC patients.

Key words   age; albumin; gastric cancer; malnutrition; prognosis

Gastric cancer (GC) is one of the most common cancers worldwide. In fact, 989,600 new GC cases and 738,000 GC deaths were estimated to have occurred in 2008, thus accounting for 8% of the total cancer cases and 10% of the total cancer deaths.[1] The incidence of GC among the older population is increasing in Japan owing to the extended life span of the current population.[2] Therefore, determining postoperative, age-associated prognostic factors are clinically important.

Accumulating evidence indicate that markers that reflect nutrition are associated with prognosis of cancer patients.[3–9] Although various methods for evaluating nutritional status are available, serum albumin level is still the conventional and standard indicator in routine clinical settings. Serum albumin is produced in the liver and is the most abundant blood plasma protein. Low serum albumin levels reportedly indicate an increased risk of mortality and morbidity among hospitalized patients.[10–13] Furthermore, preoperative serum albumin (pre-Alb) level has been shown to be a prognostic indicator in various cancers, including GC.[14] However, these studies focused on the correlation between prognosis and pre-Alb level. As gastrectomy, which is a common treatment for GC, decreases stomach volume, some patients' postoperative nutritional status worsens in comparison with their preoperative nutritional status. Therefore, poor postoperative nutritional status might be related to poor prognosis in patients with GC. However, little research has been undertaken to examine the correlation between postoperative nutritional status and the prognosis of GC patients thus far.

Compared with younger people, the metabolic rate of older patients is altered; the cells undergo deformation and functional impairment, and major organs show reduced function or cell loss. In addition, with increasing age, tissue and cell regeneration is reduced, leading to slower recovery of bodily functions. Because adequate nutrition is vitally important for patients who undergo surgery, older patients may be more sensitive to malnutrition than younger patients. In the current study, we therefore examined the prognostic significance of not only pre-Alb level but also postoperative serum albumin (post-Alb) level in older GC patients.

Table 1. Correlation between clinicopathologic factors and serum albumin levels

	Pre-Alb (g/dL)[c]	P value	Post-Alb (g/dL)[d]	P value
Gender		0.32		0.024
Male (n = 93)	3.87 ± 0.53		3.51 ± 0.57	
Female (n = 42)	3.8 ± 0.48		3.72 ± 0.53	
Histology [a]		0.22		0.5
Differentiated (n = 83)	3.8 ± 0.53		3.63 ± 0.56	
Undifferentiated (n = 52)	3.93 ± 0.47		3.49 ± 0.55z	
Depth of invasion [b]		0.0032		0.044
T1 (n = 67)	3.97 ± 0.48		3.65 ± 0.59	
T2 / 3 / 4 (n = 68)	3.73 ± 0.51		3.50 ± 0.52	
Lymph node metastasis		0.051		0.36
Absence (n = 88)	3.91 ± 0.5		3.61 ± 0.53	
Presence (n = 47)	3.74 ± 0.51		3.51 ± 0.62	
Peritoneal metastasis		0.23		0.33
Absence (n = 126)	3.87 ± 0.5		3.59 ± 0.56	
Presence (n = 9)	3.62 ± 0.63		3.39 ± 0.58	
Stage of disease		0.006		0.072
I / II (n = 99)	3.92 ± 0.49		3.63 ± 0.54	
III / IV (n = 36)	3.66 ± 0.53		3.41 ± 0.59	
Lymphatic invasion		0.7		0.5
Absence (n = 41)	3.88 ± 0.51		3.6 ± 0.6	
Presence (n = 94)	3.84 ± 0.51		3.57 ± 0.55	
Venous invasion		0.5		0.067
Absence (n = 46)	3.89 ± 0.51		3.66 ± 0.6	
Presence (n = 89)	3.83 ± 0.51		3.53 ± 0.54	
Child-Pugh classification		< 0.0001		0.0082
A (n = 121)	3.95 ± 0.41		3.62 ± 0.54	
B (n = 14)	3.02 ± 0.55		3.16 ± 0.64	

All albumin measurements are expressed as mean ± standard deviation.

[a] Differentiated (papillary or tubular adenocarcinoma) or undifferentiated (poorly differentiated or mucinous adenocarcinoma, or signet-ring cell carcinoma).

[b] T1, Tumor invasion of the *lamina propria* or submucosa; T2, tumor invasion of the *muscularis propria*; T3, tumor invaded the subserosa; T4, tumor invasion is contiguous with or extends beyond the serosa or the tumor invades adjacent structures.

[c] Pre-Alb, preoperative serum albumin level

[d] Post-Alb, postoperative serum albumin level

MATERIALS AND METHODS

Patients

This study was based on a retrospective analysis of 135 patients with gastric adenocarcinoma who were ≥ 75 years of age and underwent gastrectomy at our institution between January 2001 and December 2011. The clinicopathologic findings were determined according to the Japanese Classification of Gastric Carcinoma.[15] All patients underwent either distal partial, proximal partial, or total gastrectomy with regional dissection of the lymph nodes. Patients were periodically checked for early recurrence by diagnostic imaging (chest X-ray, upper gastrointestinal fiberscopy, ultrasonography, and computed tomography). Cause of death and patterns of recurrence were determined by reviewing their medical records, including laboratory data, ultrasonography, computed tomography, scintigrams, peritoneal punctures, and laparotomies, or by direct inquiry with family members. We collected data of serum concentration of albumin from blood tests performed preoperatively and 1 month postoperatively. This study was approved by our institutional review board (17A075), and informed consent requirement was waived for this retrospective study.

Statistical analysis

Differences between the two groups were evaluated using the Mann–Whitney U test. Receiver operating characteristic (ROC) curves were constructed for patients' survival status; area under the curve (AUC) values were compared to assess the discrimination ability of pre- and post-Alb levels. Survival curves were calculated

(a)

(b)
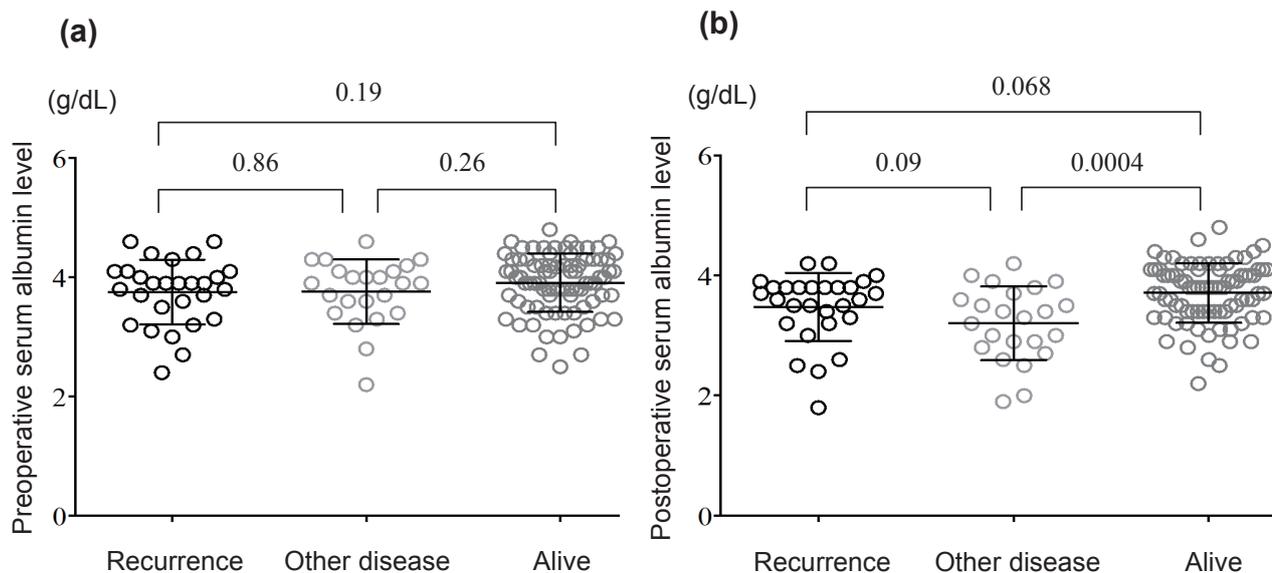
Fig. 1. Comparison of preoperative serum albumin levels (**a**) and postoperative serum albumin levels (**b**) to the cause of patient death.

according to the Kaplan–Meier method. Differences between survival curves were examined with the log rank test. We used multivariate analysis of factors considered prognostic of either overall survival (OS) or disease-specific survival (DSS), with Cox's proportional hazards model and a stepwise procedure. Covariates included in this analysis were age, sex, tumor size, histology, depth of invasion, lymph node metastasis, lymphatic vessel invasion, blood vessel invasion, presence of distant metastasis, pre-Alb level, post-Alb level, Child–Pugh classification, and ASA score. The accepted level of significance was $P < 0.05$. GraphPad Prism (GraphPad Software, La Jolla, CA) and Stat View (Abacus Concepts, Berkeley, CA) software were used for the statistical analyses.

RESULTS

The mean pre- and post-Alb levels were 3.9 ± 0.51 g/dL and 3.6 ± 0.56 g/dL, respectively. Compared with the pre-Alb levels, post-Alb levels were lower in 83 patients and equivalent or greater in 52 patients. Table 1 shows the correlation between the various clinicopathologic factors and serum Alb levels. The pre-Alb levels of the patients with advanced GC patients and those with stage III/IV cancers were significantly lower than those of the patients with early GC patients ($P = 0.0032$) and those with stage I/II cancers ($P = 0.006$), respectively. In addition, the pre-Alb levels of patients with Child–Pugh grade B disease were significantly lower than those of patients with grade A disease ($P < 0.0001$). Post-Alb levels of male patients and those with advanced GC were significantly lower than those of female patients ($P =$

0.024) and those with early GC ($P = 0.044$), respectively. Furthermore, post-Alb levels of patients with Child–Pugh grade B disease were significantly lower than those of patients with grade A disease ($P = 0.0082$).

Among the 153 patients, 28 patients died of recurrent GC, and 23 patients died of other diseases. There was no statistical difference between the pre-Alb levels of the patients who died of recurrent GC, and those who were either still living or who had died of other diseases (Fig. 1a). However, post-Alb levels of patients who died of other diseases were significantly lower than levels of patients who were still alive ($P = 0.0004$; Fig. 1b). Furthermore, post-Alb levels of patients who died of recurrent GC tended to be lower than levels of patients who were still alive ($P = 0.068$; Fig. 1b).

ROC curves were then constructed for patient survival status, and AUC values were compared to assess the discrimination ability of pre- and post-Alb levels. For both OS and DSS, the AUC value of the post-Alb level was higher than that of the pre-Alb level, indicating that the post-Alb level was more predictive of OS and DSS than the pre-Alb level (Fig. 2).

For both pre-Alb and post-Alb levels, patients were then divided into two groups: those with Alb level ≥ 4 g/dL (Alb[High]), and Alb level < 4 g/dL (Alb[Low]). Five-year OS rates did not significantly differ between the pre-Alb[High] group (53.9%) and the pre-Alb[Low] group (49.4%; $P = 0.27$; Fig. 3a); nor did the 5-year DSS rates (pre-Alb[High]: 78.9%, pre-Alb[Low]: 67.2%; $P = 0.23$; Fig. 3b). However, 5-year OS rates significantly differed between the post-Alb[High] group (78.6%) and post-Alb[Low] group
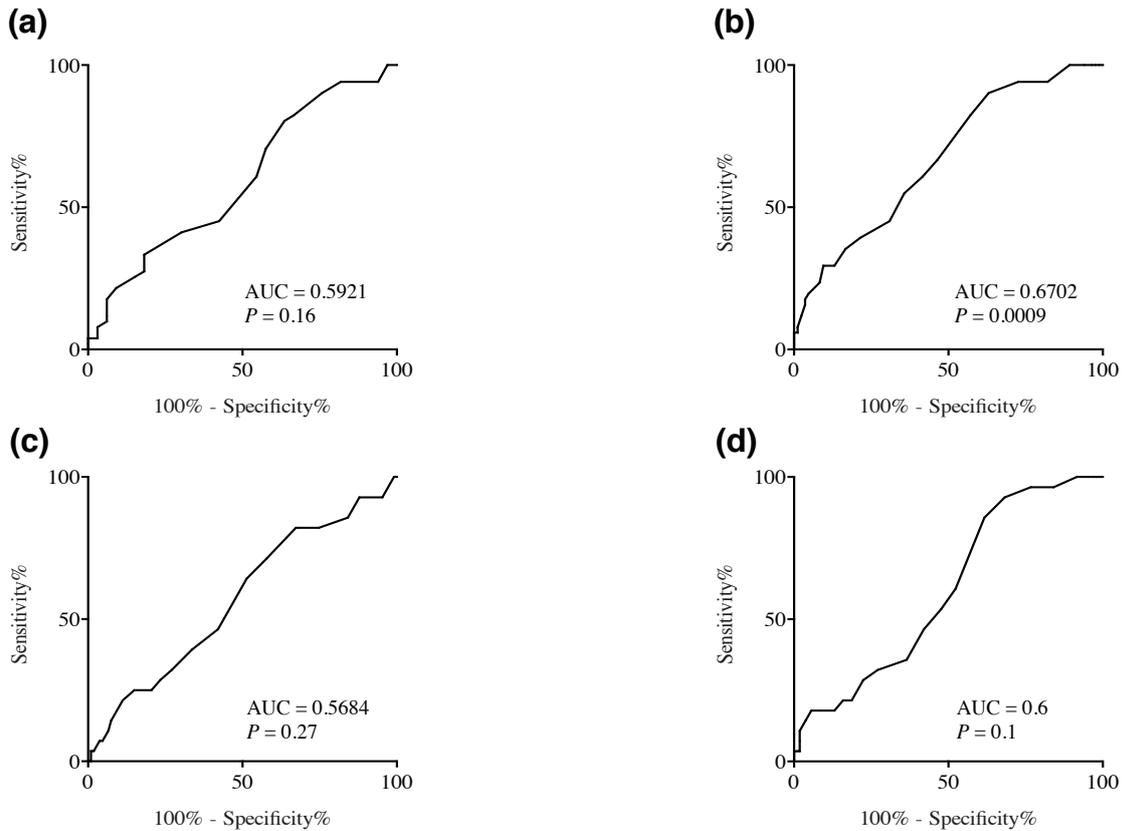
Fig. 2. Comparison of areas under the receiver operating curves (AUC) for outcome prediction. (**a**) Preoperative serum albumin level for overall survival (OS), (**b**) postoperative serum albumin level for OS (**c**) preoperative serum albumin level for disease-specific survival (DSS), and (**d**) postoperative serum albumin level for DSS.
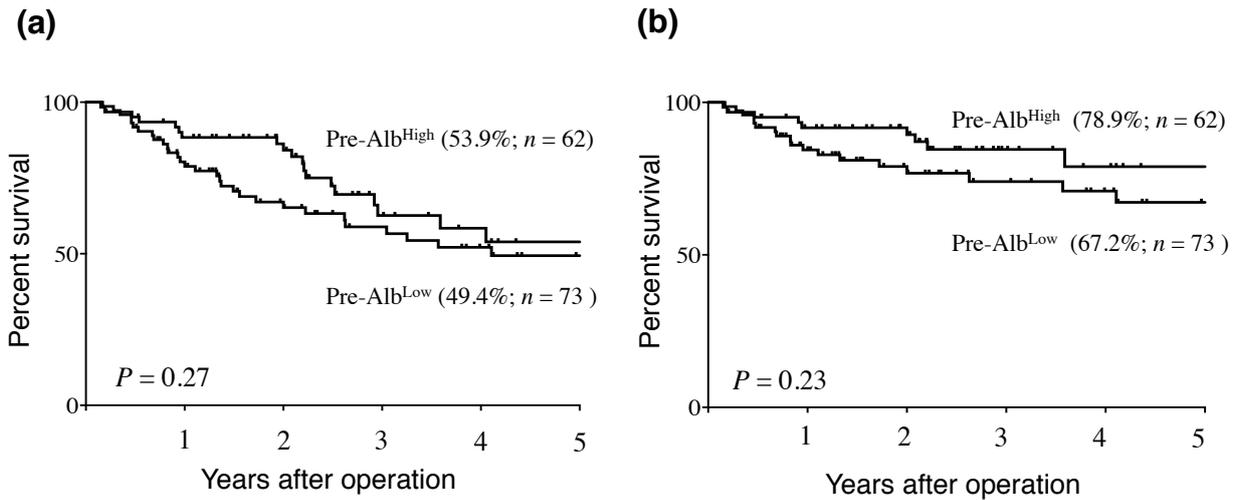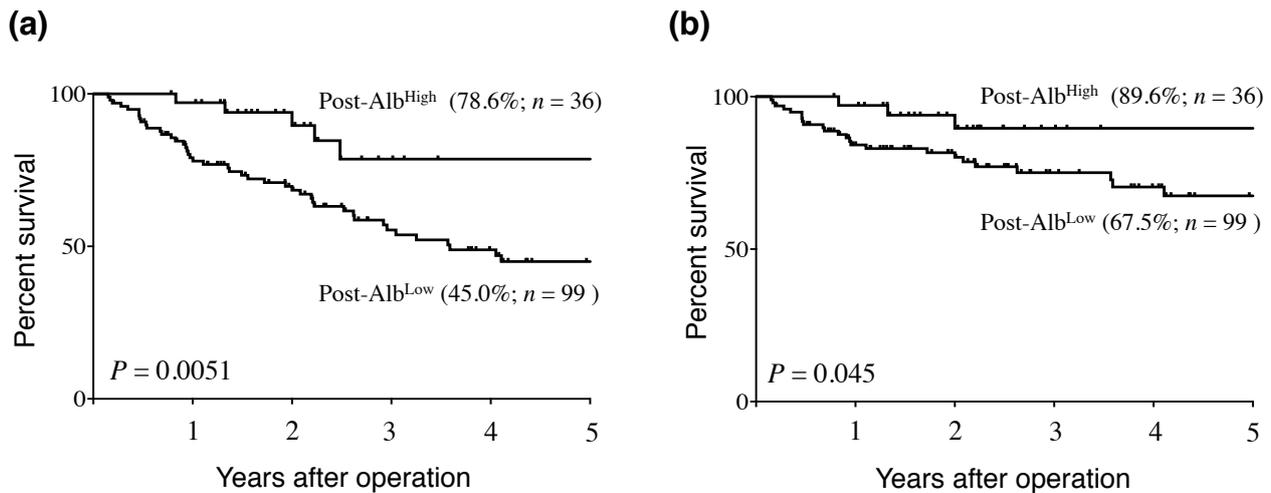

Fig. 3. Comparison of overall survival (**a**) and disease-specific survival (**b**) according to preoperative serum albumin levels. Pre-Alb^High, serum albumin level ≥ 4 g/ dL; Pre-Alb^Low, serum albumin level < 4 g/dL.

(45.0%; $P = 0.0051$; Fig. 4a); as did the 5-year DSS rates (post-Alb^Low: 67.5%; post-Alb^High: 89.6%; $P = 0.045$; Fig. 4b).

Finally, multivariate analysis indicated that in addi- tion to lymph node metastasis, distant metastasis, histol- ogy, venous invasion, and ASA score, the post-Alb level was also an independent prognostic indicator for OS (Table 2), but not for DSS (Table 3).

(a)

(b)

Fig. 4. Comparison of overall survival (**a**) and disease-specific survival (**b**) according to postoperative serum albumin levels. Post-Alb[High], serum albumin level ≥ 4 g/ dL; Post-Alb[Low], serum albumin level < 4 g/dL.

Table 2. Association of various factors with overall survival determined by the Cox proportional hazards model and a stepwise procedure

	HR [f]	95% CI [g]	P value
Histology (Differentiated vs. undifferentiated) [a]	0.508	0.286–0.903	0.021
Lymph node metastasis (n0–3) [b]	1.812	1.385–2.370	< 0.0001
Distant metastasis (Absent vs. present)	6.387	2.702–15.096	< 0.0001
Venous invasion (v0–3) [c]	1.61	1.119–2.316	0.01
Postoperative serum albumin level [d]	0.508	0.346–0.953	0.0318
ASA score [e]	1.832	1.107–3.031	0.0185

[a] Differentiated (papillary or tubular adenocarcinoma) or undifferentiated (poorly differentiated or mucinous adenocarcinoma, or signet-ring cell carcinoma).
[b] Lymph node metastasis: N0, no regional lymph node metastasis; N1, metastasis in 1–2 regional lymph nodes; N2, metastasis in 3–6 regional lymph nodes; N3, metastasis in 7 or more regional lymph nodes
[c] Venous invasion: v0–v3, grade of lymphatic invasion
[d] Continuous variable
[e] American Society of Anesthesiologists (ASA) score: I, normal healthy patient; II, patient with mild systemic disease; III, patient with severe systemic disease; IV, patient with severe systemic disease that is a constant threat to life; V, moribund patient who is not expected to survive without surgery; VI, patient who has been declared brain-dead.
[f] HR, hazard ratio
[g] CI, confidence interval

Table 3. Association of various factors with disease specific survival determined by the Cox proportional hazards model and a stepwise procedure

	HR [d]	95% CI [e]	P value
Histology (Differentiated vs. undifferentiated) [a]	0.419	0.188–0.933	0.0332
Lymph node metastasis (n0–3) [b]	2.438	1.662–3.577	< 0.0001
Distant metastasis (Absent vs. present)	7.875	2.965–20.921	< 0.0001
Venous invasion (v0–3) [c]	3.041	1.696–5.453	0.0002

[a] Differentiated (papillary or tubular adenocarcinoma) or undifferentiated (poorly differentiated or mucinous adenocarcinoma, or signet-ring cell carcinoma).
[b] Lymph node metastasis: N0, no regional lymph node metastasis; N1, metastasis in 1–2 regional lymph nodes; N2, metastasis in 3–6 regional lymph nodes; N3, metastasis in 7 or more regional lymph nodes
[c] Venous invasion: v0–v3, grade of lymphatic invasion
[d] HR, hazard ratio
[e] CI, confidence interval

DISCUSSION

Because older patients with GC often have severe co-morbidities, they may be high-risk surgical candidates; nevertheless, several studies have shown that the risk can be minimized by intensive care.[16, 17] Advances in surgical techniques, and in anesthetic and postoperative intensive care, have increased the likelihood of these patients safely undergoing surgery.

However, GC often leads to malnutrition, owing to obstruction and bleeding from the tumor. Because malnutrition increases the rate of postoperative complications, accurately evaluation of the preoperative nutritional status of all GC patients is important. Various methods have been developed for evaluating patients' nutritional status, including the prognostic nutritional index (PNI) and controlling nutrition status (CONUT) score. These measurements are reported to be closely

associated with the prognosis of cancer patients, which indicates that nutritional status has a critical bearing on cancer outcomes.[3–9] Visceral proteins, such as albumin, prealbumin, and transferrin, are also examined in clinical practice. Because those protein levels can be quickly and easily determined, they are frequently used to evaluate patients' nutritional status. Pre-Alb levels have been shown to correlate with the clinical outcomes of medical and surgical patients.[18–20] Because of its convenience, the current study used serum albumin level to assess the nutritional status and determined the correlation between serum albumin levels and prognosis in older GC patients. Our findings showed that the post-Alb level, but not pre-Alb level, was significantly correlated with OS and DSS. Furthermore, post-Alb level was an independent prognostic factor in OS, but not for DSS. With regard to the correlation between serum albumin levels and cause of death, post-Alb level was significantly lower in patients who died of other diseases compared with those who were still alive. These results clearly indicate that post-Alb level is an indicator for risk of death by other diseases for older patients. Previously, Migita et al. used the PNI to evaluate patients' preoperative immunonutritional status and found that a low PNI score was associated with a higher risk of non-cancer death in GC patients.[21] A similar study has shown that for older patients with gastric cancer, low PNI scores increases their chances of respiratory failure owing to pneumonia compared with patients with high PNI scores.[22] Taken together, these findings suggest that low nutritional status in older patients increases their risk of death from other diseases after surgery. Our results showed the importance of postoperative nutrition in terms of prognosis in older patients with GC, whereas preoperative nutritional status did not affect their outcomes. Post-Alb levels were low in 83 patients and equal or higher in 52 patients compared with the same patients' pre-Alb levels. These results indicate that 60% of the older patients had gastrectomy-induced malnutrition. Unlike other procedures, gastrectomy can cause patients to become malnourished after their surgeries because of poor food intake as a result of decreased stomach volume. Therefore, prolonged malnutrition after gastrectomy, which can be evaluated by post-Alb level, may make patients susceptible to death from other diseases.

Older populations are usually associated with high comorbidity rates. Comorbidities are likely to worsen both short-term and long-term outcomes. Therefore, we included ASA score as a covariate in multivariate analysis, which showed ASA score was an independent prognosis indicator for OS.

Liver dysfunction might affect the serum albumin level because albumin is produced in the liver. In this regard, both pre- and post Alb levels in patients with Child–Pugh grade B disease were significantly lower than those in patients with grade A disease, which implies that serum albumin levels are associated with liver function in addition to nutritional status. However, Child-Pugh classification was not an independent prognostic indicator in our multivariate analysis, which indicates that post-Alb levels are associated with the prognosis of older GC patients, independently of liver function or comorbidity.

Preoperative nutritional support is known to be effective for moderate-to-severe malnutrition,[23, 24] and postoperative complications are significantly decreased by nutritional support after gastrointestinal surgery.[25] In contrast, our results clearly demonstrated that low post-Alb levels were significantly associated with poor prognosis. Therefore, postoperative nutritional support might be effective in improving the prognosis of older gastric cancer patients. Recently, body weight loss was shown to be the most important risk factor with regard to the patient compliance with adjuvant S-1 chemotherapy in patients who underwent D2 gastrectomy for GC.[26] Therefore, postoperative nutritional support may improve patient compliance with adjuvant S-1 chemotherapy, which may further improve their prognosis.

The present study has a few limitations. First, some bias was present because the study was retrospective. Second, we measured the serum albumin levels 1 month after surgery and used it as the postoperative parameter; however, the best time to measure the post-Alb level remains unclear. Third, the number of patients included in the current study was small; therefore, a large-scale, prospective randomized controlled trial is needed to confirm the results.

In conclusion, the post-Alb level is useful for predicting the prognosis of older gastric cancer patients. Postoperative nutritional support might be effective in improving the prognosis of older gastric cancer patients.

Human rights statement and informed consent: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent from patients was waived because of the retrospective design of this study.

The authors declare no conflict of interest.

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