CrossMark

ORIGINAL ARTICLE

The Charlson Comorbidity Index as an Independent Prognostic Factor in Older Colorectal Cancer Patients

Tetsuro Tominaga [1] · Takashi Nonaka [1] · Hiroaki Takeshita [1] · Masaki Kunizaki [1] ·
Yorihisa Sumida [1] · Shigekazu Hidaka [1] · Terumitsu Sawai [2] · Takeshi Nagayasu [1]

Abstract High-age patients have higher rates of comorbidity that are associated with a poor prognosis. It is important to correctly evaluate their preoperative status to avoid mortality. The aim of this study was to clarify whether the Charlson comorbidity index (CCI) was useful for predicting postoperative outcomes. This retrospective study collected data from 250 consecutive patients over 75 years of age. The CCI takes into account 19 comorbid conditions. Inflammation-based scores, including the Glasgow prognostic score (GPS) and the platelet to lymphocyte ratio (PLR), are other preoperative scoring systems. The relationships among these scores and postoperative outcomes were evaluated. The patients were classified according to their vital status (dead, $n = 30$ or alive, $n = 220$). Comorbidities, the presence of double cancer, and lymph node metastases were significantly different between the groups ($p < 0.01$, $p = 0.01$, and $p < 0.01$). In regard to the scoring systems, the CCI, GPS, and PLR were significantly different ($p = 0.02$, $p = 0.03$, and $p = 0.05$). Multivariate analysis identified CCI ≥ 2 (hazard ratio (HR) = 5.24, 95 % confidence interval (CI) = 1.30–12.1, $p = 0.01$) as a significant determinant of postoperative outcome ($p < 0.01$). The overall survival tended to be lower in patients with high CCI scores group ($p = 0.03$). The CCI was useful to predict postoperative outcomes in high-age colorectal cancer patients.

Keywords Charlson comorbidity index · Colorectal cancer · Older patients · Overall survival

✉ Terumitsu Sawai
  sawai@nagasaki-u.ac.jp

1 Department of Surgical Oncology, Graduate School of Biomedical Science, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

2 Department of Cardiopulmonary Rehabilitation Science, Graduate School of Biomedical Science, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

Introduction

Colorectal cancer is the third leading cause of cancer-related death in Japan. As the population ages, the number of elderly colorectal cancer patients is likely to increase. In general, high-age patients are said to have higher rates of comorbidity than younger patients [1]. In some reports, a number of past illnesses tended to be associated with increased postoperative complications and a poor prognosis [2]. It is important to correctly evaluate high-age patients' preoperative status to avoid poor outcomes. Until now, several scoring systems using preoperative information have been reported to predict postoperative outcomes. The Charlson comorbidity index (CCI) was reported to classify comorbid conditions that might alter the risk of mortality for use in longitudinal studies [3]. The index takes into account 19 comorbid conditions, including cardiovascular disease, diabetes mellitus, liver disease, and pulmonary disease.

On the other hand, there is a strong relationship between malignant disease and inflammation [4]. In colorectal cancer, inflammatory bowel diseases such as ulcerative colitis and Crohn's disease are known as premalignant disease [5]. Today, several inflammatory-based scores using preoperative data have been reported. C-reactive protein (CRP) is an acute phase protein produced in the liver that is recognized as a systemic inflammation marker [6]. Albumin has been shown to be a marker of nutrition, and hypoalbuminemia could show

a declining health status or malnutrition [7]. The Glasgow prognostic score (GPS) is one of the inflammatory-based scores that can be calculated from the CRP and the serum albumin level, and it has been reported to be effective for predicting postoperative mortality [8].

The platelet to lymphocyte ratio (PLR) is another inflammation score that consists of the platelet count and the lymphocyte count [9]. Platelets play an important role in the coagulation system and the inflammatory response, and they are known to correlate with tumor growth, invasion, and angiogenesis [10]. Lymphocytes play an important role in antitumor immunity and are important factors for the host immune system [11]. Therefore, a low lymphocyte level is considered to be associated with recurrence [12].

Several reports have shown the effectiveness of these preoperative scoring systems, including the CCI, GPS, and PLR, for predicting postoperative outcomes in various cancers [13–15]. However, few reports have examined their use in high-age patients.

The aim of this study was to evaluate whether preoperative scoring systems, including the CCI, GPS, and PLR, are useful prognostic factors in older colorectal cancer patients.

Patients and Methods

Patients

A total of 506 colorectal cancer patients who underwent colorectal resection of primary cancer at the Department of Surgical Oncology, Nagasaki University Graduate School of Biological Sciences from January 2009 to December 2014 were evaluated. This retrospective study collected data from 250 consecutive patients over 75 years of age. The median follow-up time was 24.0 months (range, 0.2–69.2 months).

Before surgery, the appropriateness of resection was determined by abdominal CT and colonoscopy. Data for age, sex, body mass index, performance status, tumor markers including CEA and CA19-9, International Union Against Cancer tumor staging, operation time, amount of blood loss, and postoperative data including pathology, depth of tumor invasion, and hospital stay were retrospectively collected. Postoperative complications were graded according to the Clavien-Dindo classification, categorizing surgical complications from grades 1 to 5 based on the invasiveness of the treatment required. In the present study, complications were defined as conditions that required treatment (Clavien-Dindo classification grades 2–5).

Colectomy, anterior resection, and abdominoperineal resection plus lymph node resection were performed according to the guideline of the Japanese Society for Cancer of the Colon and Rectum (JSCCR). A hand-sewn or an end-to-end anastomosis using double-stapling technique was performed

according to tumor location. Mortality and morbidity data were collected from the database of our department and collaborating hospitals.

Scoring Systems Evaluated

The components of the CCI are shown in Supplementary Table 1. Weights were assigned for each condition the patients had, and their total was the score.

The GPS was established in the following manner. Patients with both hypoalbuminemia (<3.5 g/dL) and an elevated CRP level (>1.0 mg/dL) were allocated a score of 2; patients with only one of the two abnormalities were allocated a score of 1; and patients with neither of the above-mentioned two abnormalities were allocated a score of 0. The PLR was defined as the absolute platelet count divided by the absolute lymphocyte count.

Statistical Analysis

Data of different groups were compared using Student's t test. Continuous data are expressed as means ± standard deviation (SD). On univariate analysis, comparisons of categorical variables were performed using the chi-square test or Fisher's exact test. $p < 0.05$ was considered significant. Overall survival and disease-free survival were calculated according to Kaplan-Meier methods, and the differences between groups were tested for significance using the log-rank test. Statistical analysis was performed using SPSS ver. 22 (Chicago, IL,

Table 1 Clinicopathological characteristics of 250 colorectal cancer patients

Number	250
Age (year)	79 (75–92)
Sex (male/female)	128:122
Comorbidity (no/yes)	161:89
Performance status (0/1/2/3)	164:64:20:0
Double cancer (no/yes)	187:63
Location (C/A/T/D/S/R)	27:56:27:11:55:74
Tumor size (mm)	40 (3–105)
Tumor depth (Tis/T1/T2/T3/T4)	21:47:40:99:19
Lymph node metastasis (N0/N1/N2)	169:51:30
Histological type (well/mod/poor)	126:103:21
TNM stage (0/I/II/III)	21:80:68:81
Operation time (min)	240 (63–860)
Blood loss (g)	122 (5–1550)
Laparoscopic surgery (no/yes)	95:155
Perioperative chemotherapy (no/yes)	206:44
Postoperative complication (no/yes)	162:88
Hospital stay (days)	25.5 (12–112)

USA). Cox proportional hazard model was used to determine significant factors affecting the mortality.

Results

Baseline Patient Demographic Data

Table 1 shows the patient demographic data. The median age was 79.8 years (75–92 years), and 51.2 % of the patients were male. Patients' performance status levels (0/1/2/3) were 164, 64, 20, and 0. Overall, 89 patients (35.6 %) had comorbidities, 63 had double cancer, 61 patients had rectal cancer, and the others had colon cancer. Average tumor size was 40.0 mm (3–105 mm). Lymph node metastases were present in 88 patients. TMN stages (0/1/2/3) were 21, 80, 68, and 81. Histological types were as follows: well differentiated, 126; moderately differentiated, 103; and poorly differentiated, 21. The average operation time was 240.2 min (63–860 min), and the average

blood loss was 122.3 g (5–1550 g). A total of 155 patients underwent laparoscopic surgery, and 44 patients received perioperative chemotherapy. Postoperative complications occurred in 88 patients (35.2 %).

Relationships between Patient Outcomes and Clinicopathological Features

Of the 250 patients, 30 patients died during the observation period. The patients were subdivided into two groups (dead, $n = 30$ or alive, $n = 220$). Table 2 shows the characteristics of each group. Age, sex, body weight, body mass index, performance status, tumor location, tumor size, tumor depth, and tumor markers including CEA and CA19-9 were not significantly different between the two groups. Comorbidities, the presence of double cancer, and lymph node metastases were significantly different between the groups ($p < 0.01$, $p = 0.01$, and $p < 0.01$).

Table. 2 Relationship between patient outcomes and clinicopathological features

	Dead	Alive	p value
Number	30	220	
Age (year)	79.6	77.9	0.96
Sex (male/female)	11:19	117:113	0.08
Body weight (kg)	50.5	52.6	0.76
Body mass index (kg/m^2)	23.3	23.5	0.91
Comorbidity (no/yes)	9:21	123:97	<0.01
Performance status (0/1, 2, 3)	14:16	80:140	0.27
Double cancer (no/yes)	17:13	170:50	0.01
Location (C/A/T/D/S/R)	6:12:4:0:4:6	21:44:23:11:51:68	0.58
Tumor size (mm)	41.5	39.7	0.63
Tumor depth (Tis/T1/T2/T3/T4a/T4b)	3:3:3:17:2:2	20:50:42:90:13:5	0.35
Lymph node metastasis (N0/1/2a/2b)	8:8:14:1	161:43:14:1	<0.01
CEA	8.1	9.1	0.69
CA19-9	26.1	21.4	0.97
Histological type (well/mod/poor)	11:15:4	117:92:11	0.08
Lymphatic invasion (no/yes)	4:26	64:156	0.07
Vessel invasion (no/yes)	6:24	75:145	0.12
Dukes classification (A/B/C)	8:8:14	98:61:61	0.07
Operation time (min)	200.3	246.3	0.06
Blood loss (g)	127	81.3	0.04
Laparoscopic surgery (no/yes)	15:15	92:128	0.39
Complication ablation (no/yes)	27:3	196:24	0.88
Perioperative chemotherapy (no/yes)	24:6	182:38	0.71
Postoperative complication (no/yes)	16:14	144:76	0.19
Hospital stay (days)	25.7	25.5	0.93
Prognostic score			
GPS (0/1, 2)	13:17	55:165	0.03
PLR	185.6	157.2	0.05
CCI (0, 1/≥2)	14:16	60:160	0.02

Table 3 Baseline characteristics of patients stratified by GPS, PLR, and CCI

		GPS			PLR			CCI		
		0, 1	≥2	p	<136.4	>136.4	p	0, 1	≥2	p
Sex	Male	113	15		67	61		82	46	
	Female	109	13	0.68	59	64	0.42	96	28	0.01
Location	Colon	158	18		86	90		121	55	
	Rectum	64	10	0.89	39	35	0.55	55	19	0.18
Tumor	Tis-T2	113	7		75	45		83	37	
	T3-T4	109	21	<0.01	50	80	<0.01	93	37	0.68
Dukes	A	98	8		66	40		73	33	
	B	61	14		32	43		49	26	
	C	63	6	0.07	28	41	<0.01	52	17	0.65
CEA	<5	165	15		91	81		122	50	
	≥5	57	13	0.08	36	44	0.14	54	24	0.97
CA19-9	<37	197	19		111	105		156	60	
	≥37	25	9	0.2	14	20	0.17	20	14	0.32
Histology	Well	115	11		70	56		87	39	
	Mod	95	16		50	61		80	31	
	Por	12	1	0.26	5	8	0.16	9	4	0.8
Lymph nodes	N0	153	16		91	78		118	51	
	N1–3	69	12	0.53	34	47	0.06	58	23	0.53
ly	0–1	153	17		92	78		122	48	
	2–3	69	11	0.91	33	47	0.04	54	26	0.66
v	0–1	163	14		96	81		126	51	
	2–3	59	14	0.03	29	44	0.02	50	23	0.92
Stage	I-II	153	16		91	78		118	51	
	III	69	12	0.53	34	47	0.06	58	23	0.53
Chemotherapy	yes	41	3		23	31		31	13	
	no	186	22	0.09	102	104	0.7	145	61	0.44
Operation time (min)		243	203	0.09	260	221	0.01	246	225	0.23
Bleeding (g)		117	181	0.3	122	131	0.41	126	110	0.49
Laparoscopic surgery (no/yes)	no	84	11		34	61		70	25	
	yes	138	17	0.63	91	64	0.02	106	49	0.24
Combined resection (no/yes)	no	210	20		119	111		163	67	
	yes	12	8	<0.01	7	14	0.2	13	7	0.92

GPS Glasgow prognostic score, *PLR* platelet to lymphocyte ratio, *CCI* Charlson comorbidity index

Surgical Features, Outcomes, and Scoring Systems

There were no significant differences in operation time, blood loss, the performance of laparoscopic surgery,

Table 4 Predictors of mortality on logistic regression analysis

	HR	95 % CI, lowest-highest CI	p value
Sex male vs. female	3.24	0.76–13.7	0.11
Dukes b/c vs. a	7.32	0.90–59.2	0.06
CCI ≥2 vs. 0,1	5.24	1.30–12.1	0.01

HR hazard ratio, *CI* confidence interval, *CCI* Charlson comorbidity index

perioperative chemotherapy, and postoperative complications. The pathological features including histological type, lymphatic invasion, and vessel invasion were not significantly different between the groups. In regard to the scoring systems, GPS, PLR, and CCI were significantly different ($p = 0.03$, $p = 0.05$, and $p = 0.02$).

Baseline Characteristics of Colorectal Cancer Patients Stratified by GPS, PLR, and CCI

As shown in Table 3, tumor depth, vessel invasion, and combined resection were significantly different according to the GPS score. Tumor depth, Dukes classification, lymphatic

invasion, vessel invasion, operation time, and laparoscopic surgery were significantly different according to the PLR score. With the CCI score, only sex was significantly different.

Predictors of Mortality by Logistic Regression Analysis

Multivariate analysis using the clinicopathological factors that were selected according to the backward elimination method identified CCI ≥ 2 (hazard ratio [HR] = 5.24, 95 % confidence interval [CI] = 1.30–12.1, p = 0.01) as a significant determinant of postoperative complications ($p < 0.01$) (Table 4).

### Kaplan-Meier Curves of DFS, OS, and CSS for CCI

The Kaplan-Meier method and log-rank tests showed that overall survival tended to be lower in patients with a high CCI score than in those with a low CCI score (Fig. 1a; p = 0.03). Disease-free survival was not significantly different between the groups (Fig. 1b; p = 0.63).

Discussion

This study verified that preoperative scoring systems could predict postoperative outcomes in high-age

Fig. 1 Overall survival (OS) (**a**) and disease-free survival (DFS) (**b**) after colorectal resection, according to the CCI score. There are significant differences in OS (p = 0.03). DFS shows no significant difference between the two groups (p = 0.63). *HR* hazard ratio; *CI* confidence interval

colorectal cancer patients and showed that CCI was the independent prognostic factor. This result supports the previous reports that showed the usefulness of the CCI score for predicting mortality in cancer of the digestive system. Dias-Santos and colleagues examined 497 pancreas cancer patients who underwent curative resection and they calculated the CCI scores. A high CCI score was a predictor of postoperative complications, longer hospital stay, and mortality within 1 year of pancreas resection [16]. In colorectal cancer, the CCI score was reported to correlate with long-term outcomes [17]. Colonic cancer patients with high CCI scores had a 28 % greater risk of death within 5 years. Rectal cancer patients with high CCI scores also had 14 times greater risk of death within 5 years. As previously described, high-age patients had several comorbidities prior to surgery. The CCI score could be useful for predicting patient prognosis in the older patient group. In the present study, however, the CCI score was not significantly correlated with postoperative complications (p = 0.72). With respect to postoperative complications, several reports showed the importance of operative factors, including operation time, severity, and amount of blood loss [18, 19]. The scoring of this study included only the preoperative factors, which is why the CCI was not significantly correlated with postoperative complications.

The GPS score that is calculated from the CRP and albumin levels has been demonstrated to be of prognostic value in several solid cancers [20]. In colorectal cancer, Choi and colleagues reported that patients with a high GPS score (GPS = 2) had poorer cancer-specific survival than those with a low GPS score (GPS = 0, 1) [21]. On multivariate analysis, GPS was identified as an independent prognostic factor in colorectal cancer (GPS 2; GPS 0 or 1; HR 5.168; p = 0.003). Contrary to the previous report, in the present study, the GPS score was not correlated with patient prognosis. There were relatively younger patients (72.3 % of patients were under 70 years) in Choi's report. However, all patients in the present study were over 75 years. It has been reported that the older the individual, the higher the CRP level [22]. Cytokines such as IL-6 stimulate the production of CRP in hepatocytes [23]. High-age patients usually have more hypercytokinemia than younger patients because of comorbidities, including lung disease, heart disease, and malignancy [24]. It has been reported that serum albumin levels change with age, with a progressive reduction of the serum albumin concentration of between 0.08 and 0.17 g/L/year [25–27]. The same as the CRP level, hypercytokinemia also affects hypoalbuminemia [28]. In addition to high cytokine levels, several factors including low oral intake, loss of muscle mass, and many comorbidities, which were strongly correlated with high age,
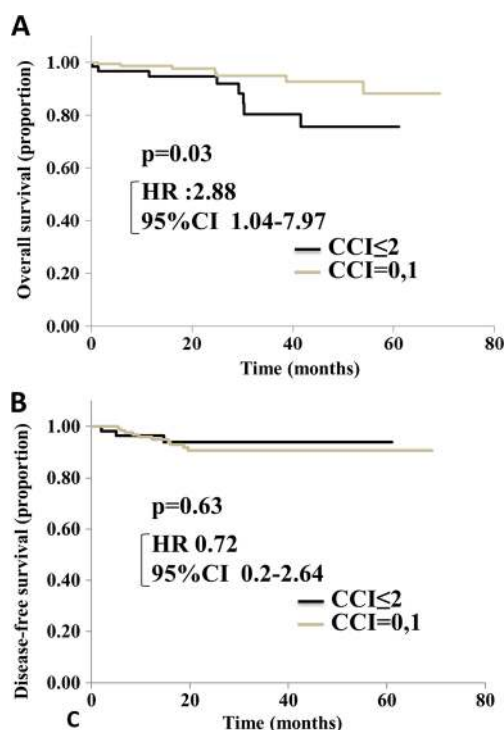
were related to a low level of albumin. This is because the GPS score, which consists of the CRP and albumin levels, could have some bias in high-age patients.

In fact, a high PLR level is reported to be associated with reduced OS and decreased time to recurrence [29]. However, the present result showed no significant correlation between the PLR level and mortality. The platelet count was not affected by age. However, the lymphocyte count has been reported to decrease with age because of weakness of the immune system [30]. For these reasons, inflammatory-based scores including the GPS and PLR could be less effective as prognostic markers in elderly patients than in younger patients.

There were some limitations in this study. First, the number of patients was relatively small, and the follow-up period was limited. Second, this was a retrospective, single-institution study. Third, prognosis was evaluated using only some inflammatory-based scores. There are other inflammatory-based scores such as the neutrophil to lymphocyte ratio, the derived neutrophil to lymphocyte ratio, and the lymphocyte to monocyte ratio [15]. Further large-scale studies and analyses are needed to clarify which score is most relevant for old individuals.

The CCI was useful to predict postoperative outcomes in high-age colorectal cancer patients. Inflammatory-based scores could be biased in older patients because of abnormalities in the immune, coagulation, and inflammatory systems.

Compliance with Ethical Standards   The work presented herein is original, has not been previously published in whole or in part, and is not under consideration for publication at any other journal.

Conflicts of Interest   No financial or other potential conflicts of interest exist for any of the authors.

Financial Disclosure   None.

References

1. Teriokhin AT, Budilova EV, Thomas F, et al. (2004) World wide variation in life-span sexual dimorphism and sex-specific environmental mortality rates. Hum Biol 76:623–641
2. Alves A, Panis Y, Mathieu P, et al. (2005) Postoperative mortality and morbidity in French patients undergoing colorectal surgery: result of a prospective multicenter study. Arch Surg 140:278–283
3. Mary EC, Peter P, Kathy LA, et al. (1987) A new method of classifying prognostic comorbity in longitudinal studies: development and validation. J Chron Dis 40:373–383
4. Trinchieri G (2012) Cancer and inflammation: an old intuition with rapidly evolving new concept. Annu Rev Immunol 30:677–706
5. Triantafillidis JK, Nasioulas G, Kosmidis PA (2009) Colorectal cancer and inflammatory bowel disease: epidemiology,risk factors, mechanism of carcinogenesis and prevention strategies. Anticancer Res 29:2727–2737
6. Marnell L, Mold C, Du Cos TW (2005) C-reactive protein: ligands, receptors and role in inflammation. Clin Immunol 117:104–111

7. McMillan DC (2009) Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opin Clin Nutr Metab Care 12:223–226
8. Roxburgh CS, McMillan DC (2010) Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol 6:146–163
9. Xie X, Luo KJ, Hu Y, et al. (2014) Prognostic value of preoperative platelet-lymphocyte and neutrophil-lymphocyte ratio in patients undergoing surgery for esophageal squamous cell carcinoma. Di Esophagus 19:10
10. Trousseau A, Phlegmasia AD (1865) Lectures on clinical medicine, delivered at the Holte-Dieu. Paris 5:281–332
11. Katayama J, Yasuda K, Kawai K, et al. (2011) Circulating lymphocyte is an important determinant of the effectiveness of preoperative radiotherapy in advanced rectal cancer. BMC Cancer 11:16
12. Ceze N, Thibault G, Goujoin G, et al. (2011) Pretreatment lymphopenia as a prognostic biomarker in colorectal cancer patients receiving chemotherapy. Cancer Chemother Pharmacol 68:1305–1313
13. Birim O, Kappetein AP, Bogers AJ (2005) Charlson cormorbidity index as a predictor of long term outcome after surgery for non-small cell lung cancer. Eur J Cardiothoracic Surg 28:759–762
14. Smith RA, Bosonnet L, Raraty M, et al. (2009) Preoperative platelet lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. Am J Surg 197:466–472
15. McMillan DC, Crozier JE, Canna K, et al. (2007) Evaluation of an inflammation-based prognostic score (GPS) in patients undergoing resection for colon and rectum cancer. Int J Color Dis 22:881–886
16. Santos DD, Ferrone CR, Sheng H, et al. (2015) The Charlson age comorbidity index predicts early mortality after surgery for pancreatic cancer. Sirgery 157:881–887
17. Wu CC, Hsu TW, Chang CM, et al. (2015) Age-adjusted Charlson comorbidity index scores as predictor of survival in colorectal cancer patients who underwent surgical resection and chemoradiation. Medicine 94:431
18. Haga Y, Ikei S, Ogawa M (1999) Estimation of physiologic ability and surgical stress (E-PASS) as a new prediction scoring system for postoperative morbidity and mortality following elective gastrointestinal surgery. Surg Today 29:219–225
19. Prytherch DR, Whiteley MS, Higgins B, et al. (1998) POSSUM and Portsmouth POSSUM for predicting mortality. Physiological and operative severity score for the enumeration of mortality and morbidity. Br J Surg 85:1217–1220
20. Forrest LM, McMillan DC, McArdle CS, et al. (2003) Evaliiation of cumulative prognostic scores based on the systemic inflammatory response I patients with inoperable non-small-cell lung cancer. Br J Cancer 89:1028–1030
21. Choi KW, Hong SW, Chang YG, et al. (2014) Inflammation-based score (Glasgow prognostic score) as an independent prognostic factor in colorectal cancer patients. Ann Surg Treat Res 86:309–313
22. Aparecida SC, Fattori A, Sousa AL, et al. (2010) Determining the C-reactive protein level in patients with different clinical forms of Chagas disease. Rev Esp Cardiol 63:1096–1099
23. McMillan DC, Canna K, McArdle CS (2003) Systemic inflammatory response predicts survival following curative resection of colorectal cancer. Br J Surg 90:215–219
24. Cheng CC, Sun CF, Pai Wang WK, et al. (2010) Preoperative serum C-reactive protein and gastric cancer ; clinical-pathological correlation and prognostic significace. Chang Gung Med J 33:301–311
25. Cooper JK, Gardner C (1989) Effect of aging on serum albumin. J Am Geriaty Soc 37:1039–1042
26. Gom I, Fukushima H, Shiraki M, et al. (2007) Relationship between serum albumin level and aging in community-dwelling self-supported elderly populations. J Nutr Sci Vitaminol 53:37–42

27. Sahyoun NR, Jacques PF, Dallal G, et al. (1996) Use of albumin as a predictor of mortality in community dwelling and institutionalized elderly populations. J Clin Epidemiol 49:981–988

28. Cabrerizo S, Cuadras D, Gomez-Busto F, et al. (2015) Serum albumin and health in older people: review and meta analysis. Maturitas 81:17–27

29. Kwon HC, Kim SH, Oh SY (2012) Clinical significance of preoperative neutrophil-lymphocyte versus platelet-lymphocyte ratio in patients with operable colorectal cancer. Biomarkers 17:216–222

30. Jain S, Harris J, Ware J (2010) Platelets: linking hemostasis and cancer. Arterioscler Thromb Vasc Biol 30:2362–2367