Original Article

Preoperative Laboratory Neutrophil-lymphocyte Ratio, Serum Carcinoembryonic Antigen Level, and Serum Albumin Level Predict Overall Survival in Stage II Colon Cancer

Kuan-Chu Ho[1]
Cheng-Yi Huang[1]
Chih-Jung Chen[1]
Yi-Hung Kuo[1,3]
Jeng-Fu You[2]
Chih-Chien Chin[1,3]
Wen-Shih Huang[1,3]
[1]*Division of Colon and Rectal Surgery, Department of Surgery, Chang Gung Memorial Hospital, Chiayi,*
[2]*Division of Colon and Rectal Surgery, Department of Surgery, Chang Gung Memorial Hospital,*
[3]*Graduate Institute of Clinical Medicine, Chang Gung University, Linkuo, Taiwan*

Key Words
Stage II colon cancer;
Neutrophil-lymphocyte ratio;
Carcinoembryonic antigen;
Hypoalbuminemia;
Overall survival

Background. Systemic inflammation and immune response may be associated with the conventional high-risk features of stage II colon cancer and are crucial in cancer treatment. High preoperative neutrophil-lymphocyte ratio (NLR), carcinoembryonic antigen (CEA) level, and preoperative hypoalbuminemia may facilitate the objective assessment of stage II colon cancer prognosis.
Methods. In this observational study, we analyzed 1180 patients with stage II colon cancer who had undergone curative colon cancer surgery between January 1995 and December 2005 at a single institution. All the patients were followed up until December 2009.
Results. The patients with high preoperative NLR (≥ 3.5) had a higher tendency to develop T4-stage cancer; higher probability of exhibiting preoperative anemia, hypoalbuminemia (< 3.5 g/dL), and high CEA level (≥ 5 ng/mL); and a higher possibility of requiring emergency surgery with a higher postoperative morbidity rate than the other patients. Multivariate analysis revealed that postoperative morbidity and preoperative characteristics – high NLR, high CEA level, and hypoalbuminemia – were independent risk factors for low 5-year overall survival in all patients with colon cancer and in patients who had undergone elective colon cancer surgery. We stratified the patients into subgroups according to the presence or absence of independent factors such as postoperative morbidity and preoperative characteristics (high NLR, high CEA level, and hypoalbuminemia). Among the patients who exhibited independent adverse factors, those who had received adjuvant chemotherapy showed significantly higher overall survival than did those who had not received adjuvant therapy (p = .024). Among the patients who did not exhibit the adverse factors, the overall survival did not differ significantly between those who had and had not received adjuvant chemotherapy (p = .654).
Conclusion. High NLR, high CEA level, and hypoalbuminemia are cost-effective objective data that can efficiently predict the overall survival of patients with stage II colon cancer. The adverse effects of these factors may be normalized after adjuvant chemotherapy.
[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2018;29:168-179*]

Received: February 21, 2018. Accepted: July 6, 2018.
Correspondence to: Dr. Yi-Hung Kuo, Division of Colon and Rectal Surgery, Department of Surgery, Chang Gung Memorial Hospital, Chiayi Branch, No. 6, Sec. West, Chia-Pu Road, Putz City, Chiayi 613, Taiwan. Tel: 886-5-362-1000 ext. 2862, 2736; Fax: 886-5-362-3002; E-mail: kuoyihung@cgmh.org.tw

Colorectal cancer is a growing health problem worldwide. The oncological outcomes of patients with stage III colon cancer have improved considerably owing to the introduction of an advancements in adjuvant chemotherapy.[1,2] However, patients with stage II colon cancer appear to be unsatisfied with the benefits or outcomes of adjuvant chemotherapy. In a previous study, survival outcomes improved by approximately 3% to 5% after the administration of a 5-fluorouracil (5-FU)-based regimen to patients with stage II colon cancer.[3-5] The determination of objective and reliable markers for identifying patients with stage II colon cancer at high risk of cancer relapse may facilitate early initiation of adjuvant chemotherapy in these patients. Currently, in clinical practice, lymphovascular invasion, poor tumor differentiation, cancer-related obstruction or perforation, TNM-T4 stage or the presence of < 12 nodes, and positive resection margin are the risk factors for stage II colon cancer, which were identified in the latest edition of the National Comprehensive Cancer Network guideline. Adjuvant chemotherapy is generally recommended for patients with adverse clinical features.[6] Nevertheless, this recommendation has been challenged because in a retrospective cohort study, adjuvant chemotherapy did not significantly improve overall survival in patients with stage II colon cancer with the aforementioned adverse features.[7] Therefore, other reliable markers may be required to facilitate patient selection regarding the administration of adjuvant chemotherapy.

Increasing evidence demonstrates that the oncological outcome of patients with cancer is affected by tumor characteristics as well as the host immune environment and inflammatory responses.[8] In the human immune system, neutrophils and lymphocytes control systemic inflammation and cell-mediated immunity, respectively. An increase in the levels of C-reactive protein or cytokine as well as hypoalbuminemia may indicate systemic inflammation; these characteristics thus may be used as biomarkers for colon cancer.[9-11] The neutrophil-lymphocyte ratio (NLR), which is a combined indicator of the inflammatory response as well as of cell-mediated immune activity, has been recently reported to be a prognostic predictor of survival in patients with colon and rectal cancer.[12-15] The NLR can predict the oncological outcomes of patients with stage II-IV colon cancer; therefore, it may be a sensitive biomarker in many situations encountered in patients at various stages of colon cancer.

We hypothesized that a high NLR is correlated with colon-cancer-related obstruction or perforation. This ratio may substitute for some previously identified risk factors including T4-stage and colon-cancer-related obstruction or perforation. To examine whether objective laboratory data are possible prognostic factors for predicting the overall survival of patients with stage II colon cancer, we analyzed oncological outcomes in relation to the following preoperative conditions: high NLR, high carcinoembryonic (CEA) level, and low serum albumin level.

Patients and Methods

Information on patients who had undergone surgery at Chang Gung Memorial Hospital between January 1995 and December 2005, including their tumor characteristics and clinical follow-ups, was obtained from the hospital's registry. The necessary approval for this observational study was obtained from the Institutional Review Board of Chang Gung Memorial Hospital. We enrolled 1180 patients with sufficiently detailed data for analyzing the NLR and other objective laboratory factors after curative surgery for stage II colon cancer. All included patients had accepted regular postoperative surveillance until December 2009. The following patient characteristics were analyzed: sex; age; preoperative data such as CEA level, serum albumin level, and NLR; surgical timing; postoperative morbidity; colon cancer location; examined lymph nodes; histology; and tumor grade. Laboratory data recorded within 1 week before surgery were used in our study. The NLR was calculated using the differential count derived from routine blood analysis by dividing the neutrophil count by the lymphocyte count. An NLR of 3-5 can predict the oncological outcomes in patients with colon cancer.[12-18] A high NLR cutoff may be associated with emergency surgery requirement for colon cancer, and it may not reflect the prognostic value of elective colon cancer surgery. Based

on a literature review, we used an NLR cutoff of 3.5 – which is generally accepted in clinical practice – to distinguish between patients who required elective and those who required emergency surgery for colon cancer.

We also included patients who had received 5-FU-based adjuvant chemotherapy (n = 256) to analyze the survival benefit of adjuvant chemotherapy among subsets of patients with or without risk factors such as high preoperative CEA level, hypoalbuminemia, high NLR, and presence of postoperative morbidity. Postoperative morbidity was defined using the Clavien-Dindo classification of surgical complications.[19] In our data, morbidity included wounds (infection or dehiscence), respiratory complications (atelectasis or pneumonia), cardiovascular system complications (embolism, myocardial infarction, or cerebrovascular accident), anastomosis (leakage), abdominal complications (peritonitis or intra-abdomen infection), bowel dysfunction (ileus or bleeding), and bladder dysfunction with or without infection. We simplified the postoperative morbidity data as "yes" or "no" morbidity because our focus was the NLR and other laboratory data. Nevertheless, patients with coexisting hematological disorders, double primary cancer, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer were excluded from our analysis. The median follow-up duration for this cohort was 60 (range, 1-139) months.

The patients were followed up every 3 months for the first 5 years and then every 6 months. The patients underwent a physical examination and assessment of serum CEA level at each follow-up in the outpatient department of the hospital. Complete colonoscopy was performed 1 year after surgery and then every 2 to 3 years, depending on the previous colonoscopy findings. Abdominal computed tomography (CT) along with chest radiography or chest CT was performed once yearly if no abnormal findings were noted during physical examination or CEA follow-up. Local or distant cancer relapse was defined using a combination of clinical, radiological, and laboratory data as well as chemotherapy administration.

All statistical analyses were performed using SPSS (version 17). Pearson's chi-squared test was used to analyze differences among the groups of patients with high and normal NLR. The 5-year overall survival was calculated as the number of months from primary cancer resection to death. The univariate analysis of the overall survival was estimated using the Kaplan-Meier method. A stepwise Cox proportional hazards regression model was used for multivariate analysis to identify the independent prognostic factors of overall survival. Statistical significance was defined at $p <$ .05.

Results

Table 1 presents the baseline characteristics of the 1180 enrolled patients. The median age of the patients was 65 (range, 22-93) years, and 624 (52.9%) patients were men. Based on the World Health Organization criteria, we defined anemia as follows: hemoglobin level < 12 g/dL in premenopausal women and < 13 g/dL in men and postmenopausal women. The median values (range) of preoperative serum albumin level, CEA level, hemoglobin level, and NLR were 3.9 (1.5-5.9) g/dL, 3.4 (0.5-590) ng/mL, 11.4 (4.3-17.9) g/dL, and 2.87 (0.12-89), respectively. The patients in the high-NLR group had higher likelihood of an abnormal CEA (≥ 5 ng/mL) level, hypoalbuminemia, anemia, stage IIb cancer, emergency surgery requirement, and postoperative morbidity; they were also likely to be aged ≥ 65 years with poor tissue grade and histology (Table 2).

The patients with objective laboratory data such as abnormal CEA level (≥ 5 ng/mL), hypoalbuminemia (< 3.5 g/dL), anemia, and high NLR (≥ 3.5) had significantly poor 5-year overall survival in the univariate analysis. Other clinical features such as emergency surgery requirement, surgical morbidity, age of ≥ 65 years, and non-receipt of postoperative adjuvant chemotherapy could also predict poor 5-year overall survival in these patients (Table 1). All factors significant to overall survival in the univariate analysis were included in multivariate analysis. The multivariate analysis, conducted using Cox regression, revealed that age of ≥ 65 years, high CEA level (≥ 5 ng/mL), hypoalbuminemia (< 3.5 g/dL), high NLR (≥ 3.5),

Table 1. Patient characteristics and univariate analysis of the prognostic factors for 5-year overall survival in stage II colon cancer (univariate analysis: Kaplan-Meier method)

	Number, (%)	5-year OS rate (%)	*p* value
Sex			
Male/female	624/556, (52.9/47.1)	80.0/84.2	0.104
Age			
≥ 65/< 65 year-old	600/580, (50.8/49.2)	75.8/88.5	< 0.001
Pretreatment CEA			
≥ 5/< 5 ng/ml	405/734, (34.3/62.2)	75.7/85.8	< 0.001
Loss data	41, (3.5)		
Pretreatment serum ALB			
≥ 3.5/< 3.5 g/dl	89/250, (75.7/21.2)	85.8/68.3	< 0.001
Loss data	37, (3.1)		
Pretreatment NLR			
High (≥ 3.5)/low (< 3.5)	455/725, (38.6/61.4)	75.9/85.9	< 0.001
Pretreatment anemia			
Presence/absence	779/401, (66/34)	79.4/87.2	0.001
Tumor location			
Proximal/distal colon	519/661, (44/56)	83.9/80.4	0.215
Operative timing			
Elective/emergent	1065/115, (90.3/9.7)	83.4/68.4	< 0.001
Operative method			
Right hemicolectomy	455, (37.7)	--	--
Left hemicolectomy	97, (8.2)	--	--
Anterior resection	525, (44.5)	--	--
Segmental colectomy	17, (1.4)	--	--
Total or subtotal colectomy	79, (6.7)	--	--
Hartmann resection	17, (1.4)	--	--
Postoperative morbidity			
Presence/absence	135/1045, (11.4/88.6)	64.4/84.2	< 0.001
TNM stage			
IIA/IIB	632/548, (53.6/46.4)	86.2/78.1	0.035
Histology type			
Adenocarcinoma	1068, (90.5)	82.1	0.972
Mucinous and signet ring cell	112, (9.5)	81.4	
Histology grade			
G1 and G2	1100 (93.2)	82.5	0.234
G3	80, (6.8)	75.1	
Number of ELN			
≥ 12/< 12 nodes	1005/175, (85.2/14.8)	82.4/79.3	0.261
5-FU based adjuvant therapy			
Yes/no	256/924, (21.7/78.3)	85.6/81	0.016

CEA: carcinoembryonic antigen; ALB: albumin; NLR: neutrophil-lymphocyte ratio; TNM: TNM classification of malignant tumors; G1: well differentiated; G2: moderately differentiated; G3: poorly differentiated; ELN: examined lymph nodes; 5-FU: fluorouracil.

presence of postoperative morbidity, and non-receipt of adjuvant chemotherapy administration were independent predictors of the 5-year overall survival (Table 3). In the present study, the NLR remained an independent predictor of overall survival in the patients with stage II colon cancer when the patients who had undergone elective colon cancer surgery were isolated from the entire patient population (Table 4). However, the cutoff of the NLR in this study was not an independent factor in the patients who had undergone emergency surgery; in that group, the patients who had received adjuvant chemotherapy exhibited signifi-

Table 2. Association between neutrophil-lymphocyte ratio and other variables (Pearson's chi-squared test)

Variable category	NLR (≥ 3.5), *n* = 455 No (%)	NLR (< 3.5), *n* = 725 No (%)	*p* value
Age			
≥ 65 years	241 (53)	359 (49.5)	.249
< 65 years	214 (47)	366 (50.5)	
Sex			
Male	256 (56.3)	368 (50.8)	.065
Female	199 (43.7)	357 (49.2)	
Pretreatment CEA			
≥ 5 ng/mL	178 (41.2)	227 (32.1)	.002
< 5 ng/mL	254 (58.8)	480 (67.9)	
Pretreatment serum ALB			
≥ 3.5 g/dL	265 (61.2)	628 (88.5)	< .001
< 3.5 g/dL	168 (38.8)	82 (11.5)	
Pretreatment anemia			
Presence	335 (73.6)	444 (61.2)	< .001
Absence	120 (26.4)	281 (38.8)	
Operative timing			
Elective	352 (77.4)	713 (98.3)	< .001
Emergent	103 (22.6)	12 (1.7)	
Postoperative morbidity			
Presence	71 (15.6)	64 (8.8)	< .001
Absence	384 (84.4)	661 (91.2)	
Histology type			
Adenocarcinoma	397 (87.3)	671 (92.6)	.003
Mucinous and signet ring cell	58 (12.7)	54 (7.4)	
Histology grade			
G1	60 (13.2)	112 (15.4)	.012
G2	352 (77.4)	576 (79.4)	
G3	43 (9.4)	37 (5.2)	
TNM stage			
IIA	206 (45.3)	426 (58.8)	< .001
IIB	249 (54.7)	299 (41.2)	
Number of ELN			
≥ 12nodes	391 (85.9)	614 (84.7)	.558
< 12 nodes	64 (14.1)	111 (15.3)	
5-FU based adjuvant therapy			
Yes	117 (25.7)	139 (19.2)	.008
No	338 (74.3)	586 (80.8)	

CEA: carcinoembryonic antigen; ALB: albumin; TNM: TNM classification of malignant tumors; NLR: neutrophil-lymphocyte ratio; G1: well differentiated; G2: moderately differentiated; G3: poorly differentiated; ELN: examined lymph nodes; 5-FU: fluorouracil.

cantly lower survival risk than those who had not.

Independent prognostic factors – namely age, abnormal CEA level, hypoalbuminemia, high NLR, and presence of postoperative morbidity – were analyzed separately to evaluate the difference in survival benefit after adjuvant chemotherapy administration. The CEA cutoff of 5 ng/mL remained a significant prognostic factor for overall survival after adjuvant chemotherapy administration. However, the other factors did not differ significantly in their effect on survival after adjuvant chemotherapy administration (Fig. 1). The relative benefit of adjuvant chemotherapy might be visible when patients preoperatively exhibit high CEA level, hypoalbuminemia, and a high NLR as well as exhibit postoperative morbidity. In patients with high NLRs, a significant difference in overall survival

Table 3. Multivariate analysis of the prognostic factors for 5-year overall survival in patients with stage II colon cancer (stepwise Cox proportional hazards regression model)

Variable category	HR	95% CI	*p* value
Sex, female vs. male	0.8	0.608-1.053	0.111
Age, ≥ 65 vs. < 65 year-old	1.885	1.407-2.526	< 0.001
Pretreatment CEA, < 5 vs. ≥ 5 ng/ml	0.665	0.507-0.871	0.003
Pretreatment serum ALB, ≥ 3.5 vs. < 3.5 g/dl	0.533	0.392-0.725	< 0.001
Pretreatment NLR, low (< 3.5) vs. high (≥ 3.5)	0.706	0.530-0.939	0.017
Pretreatment anemia, presence vs. absence	1.339	0.959-1.869	0.086
Operative timing, elective vs. emergent	0.785	0.520-1.185	0.249
Postoperative morbidity, absence vs. presence	0.508	0.363-0.710	< 0.001
TNM stage, IIA vs. IIB	0.816	0.615-1.083	0.158
Histology type			
Adenocarcinoma vs. mucinous and signet ring cell	0.974	0.605-1.569	0.915
Histology grade			
G1 vs. G3	0.799	0.439-1.454	0.463
G2 vs. G3	0.744	0.444-1.246	0.261
Number of ELN, ≥ 12 vs. < 12 nodes	0.854	0.613-1.190	0.352
5-FU based adjuvant therapy, yes vs. no	0.591	0.402-0.867	0.007

HR: hazard ratio; CI: confidence interval; CEA: carcinoembryonic antigen; ALB: albumin; NLR: neutrophil-lymphocyte ratio; TNM: The TNM classification of malignant tumors; G1: well differentiated; G2: moderate differentiated; G3: poorly differentiated; ELN: examined lymph nodes; 5-FU: fluorouracil.

Table 4. Multivariate analysis of the prognostic factors for 5-year overall survival in 1065 patients with stage II colon cancer who had received elective colon cancer surgery and 115 patients who had undergone emergency surgery (stepwise Cox proportional hazards regression model)

Variable category	HR	95% CI	*p* value
Patients with elective surgery (*n* = 1065)			
Sex, female vs. male	0.781	0.579-1.053	0.105
Age, ≥ 65 vs. < 65 year-old	2.005	1.456-2.759	< 0.001
Pretreatment CEA, < 5 vs. ≥ 5 ng/ml	0.646	0.483-0.865	0.003
Pretreatment serum ALB, ≥ 3.5 vs. < 3.5 g/dl	0.542	0.388-0.756	< 0.001
Pretreatment NLR, low (< 3.5) vs. high (≥ 3.5)	0.673	0.501-0.904	0.008
Pretreatment anemia, presence vs. absence	1.332	0.942-1.882	0.104
Postoperative morbidity, absence vs. presence	0.531	0.365-0.773	0.001
TNM stage, IIA vs. IIB	0.838	0.619-1.135	0.255
Histology type			
Adenocarcinoma vs. mucinous and signet ring cell	1.185	0.682-2.057	0.547
Histology grade			
G1 vs. G3	0.837	0.431-1.628	0.601
G2 vs. G3	0.786	0.434-1.422	0.425
Number of ELN, ≥ 12 vs. < 12 nodes	0.815	0.571-1.164	0.261
5-FU based adjuvant therapy, yes vs. no	0.853	0.567-1.283	0.445
Patients with emergency surgery (*n* = 115)			
Sex, female vs. male	1.075	0.458-2.522	0.867
Age, ≥ 65 vs. < 65 year-old	0.988	0.423-2.310	0.978
Pretreatment CEA, < 5 vs. ≥ 5 ng/ml	0.757	0.346-1.657	0.486
Pretreatment serum ALB, ≥ 3.5 vs. < 3.5 g/dl	0.360	0.138-0.937	0.036
Pretreatment NLR, low (< 3.5) vs. high (≥ 3.5)	0.634	0.208-1.934	0.423
Pretreatment anemia, presence vs. absence	2.187	0.475-10.064	0.315
Postoperative morbidity, absence vs. presence	0.578	0.234-1.425	0.233
TNM stage, IIA vs. IIB	0.661	0.257-1.697	0.389
Histology type			
Adenocarcinoma vs. mucinous and signet ring cell	0.432	0.138-1.350	0.149
Histology grade			
G1 vs. G3	0.704	0.096-5.170	0.730
G2 vs. G3	1.104	0.284-4.288	0.886
Number of ELN, ≥ 12 vs. < 12 nodes	0.795	0.289-2.190	0.658
5-FU based adjuvant therapy, yes vs. no	0.122	0.039-0.376	< 0.001

HR: hazard ratio; CI: confidence interval; CEA: carcinoembryonic antigen; ALB: albumin; NLR: neutrophil-lymphocyte ratio; TNM: TNM classification of malignant tumors; G1: well differentiated; G2: moderately differentiated; G3: poorly differentiated; ELN: examined lymph nodes; 5-FU: fluorouracil.

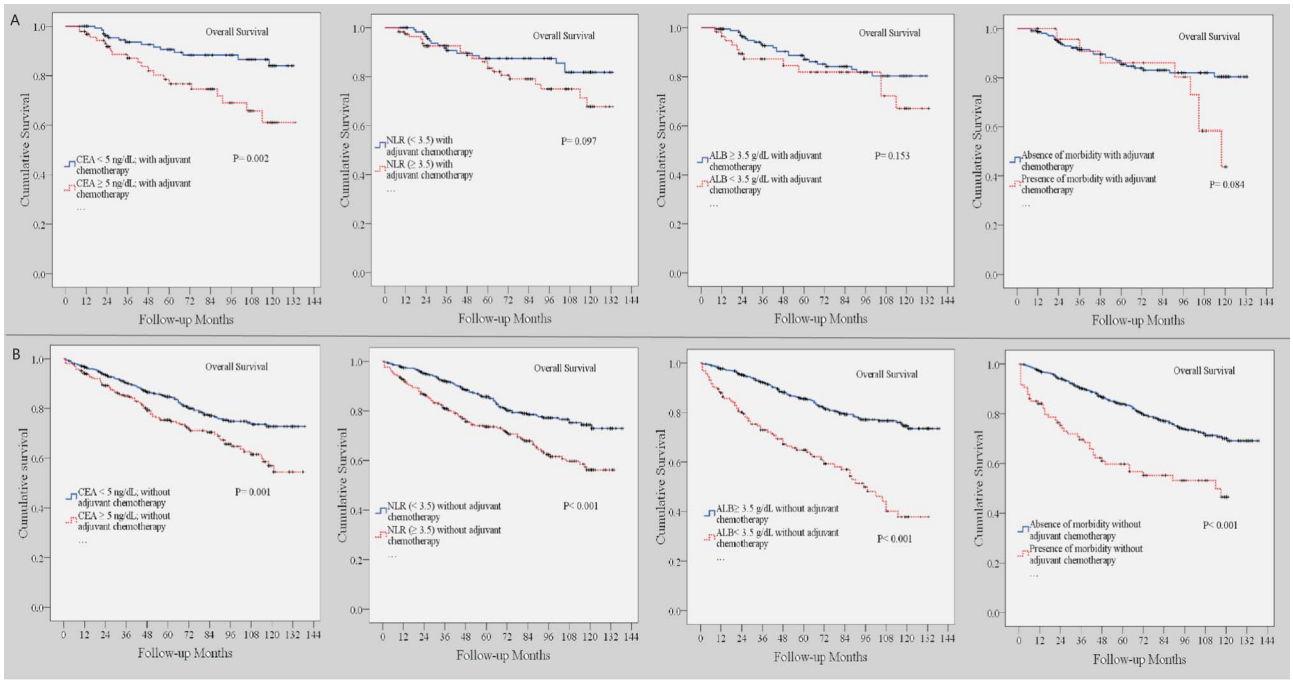

Fig. 1. Independent factors were analyzed using the Kaplan-Meier method for overall survival in patients with stage II colon cancer who received (A) and did not receive (B) adjuvant chemotherapy.

was observed between the adjuvant chemotherapy and observation subgroups (Fig. 2). However, the overall survival did not differ between the 2 subgroups in patients with low NLRs (Fig. 3).

Therefore, we analyzed the effect of adjuvant chemotherapy on the 5-year overall survival of 4 subgroups of our patients, who were stratified by considering the aforementioned independent factors: group A did not exhibit the independent risk factors and had received adjuvant chemotherapy; group B exhibited at least one independent risk factor and had received adjuvant chemotherapy; group C exhibited at least one independent risk factor and had not received adjuvant chemotherapy; and group D did not exhibit independent risk factors and had not received adjuvant chemotherapy. The 5-year overall survival did not differ between groups A and D (p = .654); never-

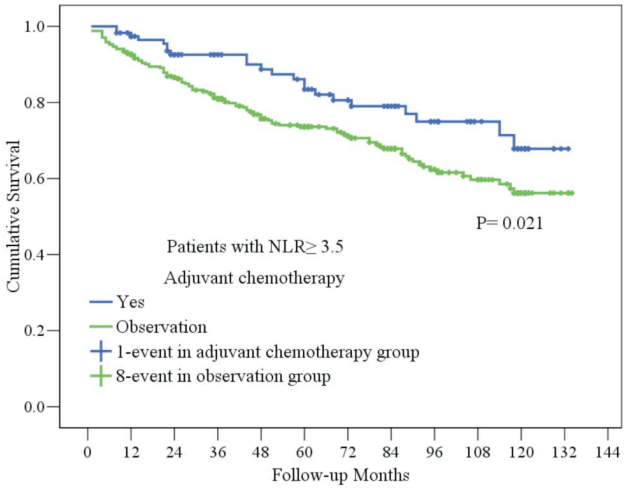

Fig. 2. Effect of adjuvant chemotherapy on the overall survival of patients with high NLRs (≥ 3.5).

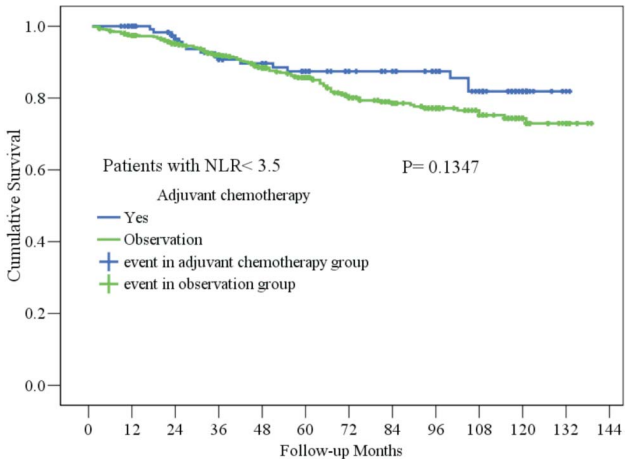

Fig. 3. Effect of adjuvant chemotherapy on the overall survival of patients with low NLRs (< 3.5).

theless, the 5-year overall survival differed significantly between groups B and C (p = .024; Fig. 4).

Discussion

The NLR is part of the routine workup before cancer surgery; it is easily available almost worldwide and entails no additional expense. The results of this study revealed a significant correlation between high NLR and stage II colon cancer characteristics. A high NLR (≥ 3.5) in the preoperative blood routine analysis objectively predicted several clinical stage II colon cancer situations, including advanced T stage cancer, high CEA level, hypoalbuminemia, anemia, poor pathology grade, emergency surgery requirement, and high postoperative morbidity rate. Similar results were reported in a systemic review, which indicated that a high NLR was associated with advanced tumor stage and aggressive tumor behavior, such as increased tumor size, lymphovascular invasion, lymph node metastasis, and high CEA level.[20] Studies have reported poor survival in patients with colon cancer and high CEA level (≥ 5 ng/mL),[21,22] poor nutrition index or hypoalbuminemia,[23-25] advanced T stage cancer,[21,26,27] and anemia.[28] Our study obtained similar results related to overall survival in multivariate analysis. Pretreatment hypoalbuminemia, high NLR (≥ 3.5), high CEA level (≥ 5 ng/mL), and postoperative morbidity were independent predictors of poor overall survival in patients with stage II colon cancer. High postoperative morbidity and mortality rates have been noted after emergency colon cancer resection. Emergency surgery requirement for colon cancer is independently associated with poor overall survival.[29,30]

The NLR is typically associated with emergency surgery for cancer-related obstruction or perforation. Patients develop leukocytosis and high NLRs in cases of acute abdominal conditions or other gastrointestinal conditions caused by colon cancer; these associations can be extremely significant when a high NLR cutoff is used in evaluations. Although the NLR cutoff is critical in clinical practice, its reported values have been inconsistent, and this wide variation remains an obstacle in clinical application. In studies on colorectal cancer, an NLR cutoff of 3 to 5 has been commonly reported.[16-18,31] In our study population, when we used NLR cutoffs of 3.5 and 5, the percentage of patients who had undergone emergency surgery for colon cancer increased from 22.6% to 32.4% (data not shown). In our results, the NLR cutoff of 3.5 might predict the actual survival outcome of stage II colon cancer in elective colon cancer surgery; however, the NLR cutoff of 5 is probably more suitable for patients who require emergency surgery because leukocytosis with a high percentage of neutrophils is common before emergency surgery.

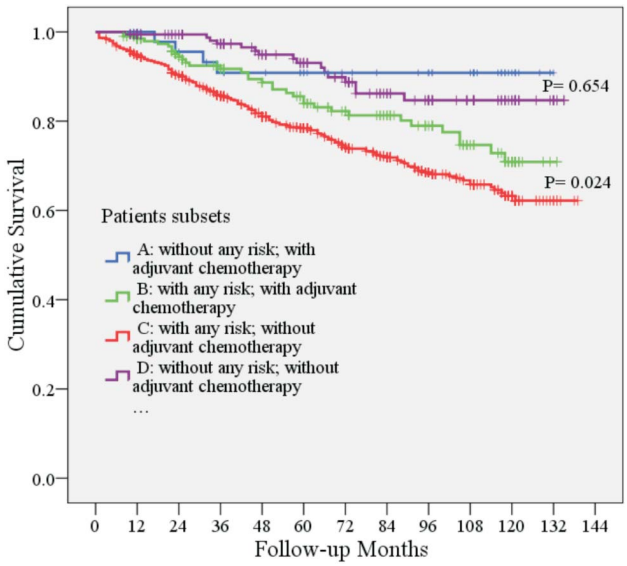

Fig. 4. Overall survival of the 4 subgroups compared using the Kaplan-Meier method. Adjuvant chemotherapy significantly affected the overall survival of patients with adverse factors, such as high preoperative CEA level, preoperative hypoalbuminemia, and high preoperative NLR (≥ 3.5). Nevertheless, a negative effect was observed in patients without the risk factors (p = .110).

The NLR represents not only tumor behavior but possibly also the host immune response. Human lymphocytes represent cell-mediated immunity and are regulatory factors in a cancer environment. T-cell type (including CD3+ and CD8+) and location or density exhibit prognostic correlations in colorectal cancer.[32-34] A high level of infiltration of T cells, comprising large numbers of cytotoxic and helper T cells at the tumor site, is associated with favorable survival in certain cancers, including colon cancer.[35] Cytotoxic T cells

produce cancer-specific antigens and IFN-γ, which may induce cancer cell cycle arrest, apoptosis, angiostasis, and tumor-associated macrophage activity. Neutrophilia typically accompanies acute inflammation or infection, and neutrophils can promote tumor growth by increasing the production of inflammatory cytokines, proteases, or growth factors.[8] A high NLR indicates neutrophilia and lymphocytopenia, which represent a reduction in cell-mediated immune activity and an increase in the levels of tumor-promoting agents. The tumor microenvironment might clarify the prognostic effect of the circulating NLR in our retrospective observation.

In the present study, adjuvant chemotherapy was an independent prognostic factor. Kishi et al.[36] demonstrated that the effect on survival of adverse factors, such as a high NLR, can be normalized after patients receive chemotherapy for their metastatic colorectal cancer. The authors suggested that a high NLR indicates chemotherapy and predicts response. In addition, if a high NLR is normalized after the first cycle of first-line chemotherapy for nonresectable metastatic colorectal cancer, a considerably improved outcome is expected. To our knowledge, most studies on the association between the NLR and chemotherapy have focused on patients with advanced colorectal cancer,[36,37] and patients who have received adjuvant chemotherapy have been excluded from most of the other colon cancer studies.[38-40] In a small cohort study, patients who had and had not received adjuvant chemotherapy were enrolled, and the effects of the NLR and local inflammatory cells on survival were analyzed. The results of the study demonstrated that the patients with poor clinicopathological features and high NLRs (≥ 5) exhibited the poorest outcome, and adjuvant chemotherapy was conclusively recommended for these patients.[41] In the present study, the findings were similar. The patients who had received adjuvant chemotherapy after emergent colectomy for stage II colon cancer had a lower mortality risk. The patients with risk factors who had not received adjuvant chemotherapy exhibited lower survival than the patients with independent adverse factors who had received adjuvant chemotherapy. The patients with independent risk factors who had not received adjuvant chemotherapy exhibited poorest outcomes. Therefore, relatively high preoperative NLR (≥ 3.5), preoperative hypoalbuminemia (< 3.5 g/dL), and postoperative morbidity might facilitate the identification of patients who should receive adjuvant chemotherapy.

In our approach, high CEA level was a strong prognostic factor for poor overall survival, even in patients who had received adjuvant chemotherapy. High preoperative CEA level can predict patient prognosis in colon cancer.[21] The results of the present study suggest that patients with stage II colon cancer and independent risk factors – such as high NLR, high CEA level, postoperative morbidity, and hypoalbuminemia – may benefit from adjuvant chemotherapy; however, studies supporting this opinion are scant. A prospective clinical trial is thus warranted for examining the effects of adjuvant chemotherapy on the survival of patients with stage II colon cancer with the aforementioned independent risk factors.

Conclusion

In this study, we identified postoperative morbidity and preoperative objective serum data, including a high NLR (≥ 3.5), hypoalbuminemia, or high CEA level, as independent prognostic factors for the overall survival of patients with stage II colon cancer; we also revealed their prognostic role in the survival of patients, which possibly could be normalized after adjuvant chemotherapy. Prospective clinical trials are warranted to verify our small-scale observation.

Author Contributions

Kuo YH, Ho KC and Huang CY designed the report, performed most of the study and this manuscript; Ho KC and Huang CY contribute equally and they were co-first author of this manuscript. Chin CC and Kuo YH analyzed patient data; Huang CY, Chen CJ, Huang WS, and You JF collected and provided clinical stage II colon cancer data.

References

1. André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004;350: 2343-51.
2. Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. *N Engl J Med* 2005;352:476-87.
3. Quasar Collaborative Group, Gray R, Barnwell J, McConkey C, Hills RK, Williams NS, Kerr DJ. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet* 2007;370:2020-9.
4. Benson AB 3rd, Schrag D, Somerfield MR, Cohen AM, Figueredo AT, Flynn PJ, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. *J Clin Oncol* 2004;22:3408-19.
5. O'Connor ES, Greenblatt DY, LoConte NK, Gangnon RE, Liou JI, Heise CP, Smith MA. Adjuvant chemotherapy for stage II colon cancer with poor prognostic features. *J Clin Oncol* 2011;29:3381-8.
6. Poplin EA, Benedetti JK, Estes NC, Haller DG, Mayer RJ, Goldberg RM, et al. Phase III Southwest Oncology Group 9415/Intergroup 0153 randomized trial of fluorouracil, leucovorin, and levamisole versus fluorouracil continuous infusion and levamisole for adjuvant treatment of stage III and high-risk stage II colon cancer. *J Clin Oncol* 2005;23:1819-25.
7. Peng SL, Thomas M, Ruszkiewicz A, Hunter A, Lawrence M, Moore J. Conventional adverse features do not predict response to adjuvant chemotherapy in stage II colon cancer. *ANZ J Surg* 2014;84:837-41.
8. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cancer* 2010;140:883-99
9. Galizia G, Orditura M, Romano C, Lieto E, Castellano P, Pelosio L, et al. Prognostic significance of circulating IL-10 and IL-6 serum levels in colon cancer patients undergoing surgery. *Clin Immunol* 2002;102:169-78.
10. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. *Cancer Treat Rev* 2013;39:534-40.
11. Mei Z, Liu Y, Liu C, Cui A, Liang Z, Wang G, et al. Tumour-infiltrating inflammation and prognosis in colorectal cancer: systematic review and meta-analysis. *Br J Cancer* 2014;110: 1595-605.
12. Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. *J Surg Oncol* 2005;91:181-4.
13. Halazun KJ, Aldoori A, Malik HZ, Al-Mukhtar A, Prasad KR, Toogood GJ, Lodge JP. Elevated preoperative neutrophil to lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases. *Eur J Surg Oncol* 2008; 34:55-60.
14. Absenger G1, Szkandera J, Stotz M, Postlmayr U, Pichler M, Ress AL, et al. Preoperative neutrophil-to-lymphocyte ratio predicts clinical outcome in patients with stage II and III colon cancer. *Anticancer Res* 2013;33:4591-4.
15. Paramanathan A, Saxena A, Morris DL. A systematic review and meta-analysis on the impact of pre-operative neutrophil lymphocyte ratio on long term outcomes after curative intent resection of solid tumours. *Surg Oncol* 2014;23:31-9.
16. Guthrie GJ, Roxburgh CS, Farhan-Alanie OM, Horgan PG, McMillan DC. Comparison of the prognostic value of longitudinal measurements of systemic inflammation in patients undergoing curative resection of colorectal cancer. *Br J Cancer* 2013;109:24-8.
17. Chiang SF, Hung HY, Tang R, Changchien CR, Chen JS, You YT, et al. Can neutrophil-to-lymphocyte ratio predict the survival of colorectal cancer patients who have received curative surgery electively? *Int J Colorectal Dis* 2012;27:1347-57.
18. Ding PR, An X, Zhang RX, Fang YJ, Li LR, Chen G, et al. Elevated preoperative neutrophil to lymphocyte ratio predicts risk of recurrence following curative resection for stage IIA colon cancer. *Int J Colorectal Dis* 2010;25:1427-33.
19. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009;250: 187-96.
20. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. *Crit Rev Oncol Hematol* 2013;88:218-30.
21. Lin HH, Yang HL, Lin JK, Lin CC, Wang HS, Yang SH, et al. The number of risk factors determines the outcome of stage II colorectal cancer patients. *Hepatogastroenterology* 2014;61: 1024-7.
22. Thirunavukarasu P, Talati C, Munjal S, Attwood K, Edge SB, Francescutti V. Effect of incorporation of pretreatment serum carcinoembryonic antigen levels into AJCC staging for colon cancer on 5-year survival. *JAMA Surg* 2015;150:747-55.
23. Tokunaga R, Sakamoto Y, Nakagawa S, Miyamoto Y, Yoshida N, Oki E, et al. Prognostic nutritional index predicts severe complications, recurrence, and poor prognosis in patients with colorectal cancer undergoing primary tumor resection. *Diseases of the Colon & Rectum* 2015;58:1048-57.
24. Lai CC, You JF, Yeh CY, Chen JS, Tang R, Wang JY, Chin CC. Low preoperative serum albumin in colon cancer: a risk factor for poor outcome. *Int J Colorectal Dis* 2011;26:473-81.
25. McMillan DC. An inflammation-based prognostic score and its role in the nutrition-based management of patients with cancer. *Proc Nutr Soc* 2008;67:257-62.
26. Snaebjornsson P, Coupe VM, Jonasson L, Meijer GA, van Grieken NC, Jonasson JG. pT4 stage II and III colon cancers carry the worst prognosis in a nationwide survival analysis. Shepherd's local peritoneal involvement revisited. *Int J Cancer* 2014;135:467-78.
27. Kim MJ, Jeong SY, Choi SJ, Ryoo SB, Park JW, Park KJ, et al. Survival paradox between stage IIB/C (T4N0) and stage

IIIA (T1-2N1) colon cancer. *Ann Surg Oncol* 2015;22:505-12.
28. Zhen L, Zhe S, Zhenning W, Zhifeng M, Zhidong L, Xiaoxia L, et al. Iron-deficiency anemia: a predictor of diminished disease-free survival of T3N0M0 stage colon cancer. *J Surg Oncol* 2012;105:371-5.
29. Bakker IS, Snijders HS, Grossmann I, Karsten TM, Havenga K, Wiggers T. High mortality rates after non-elective colon cancer resection: results of a national audit. *Colorectal Dis* 2016 Jan 8. doi: 10.1111/codi.13262
30. Teloken PE, Spilsbury K, Levitt M, Makin G, Salama P, Tan P, et al. Outcomes in patients undergoing urgent colorectal surgery. *ANZ J Surg* 2014;84:960-4.
31. He W, Yin C, Guo G, Jiang C, Wang F, Qiu H, et al. Initial neutrophil lymphocyte ratio is superior to platelet lymphocyte ratio as an adverse prognostic and predictive factor in metastatic colorectal cancer. *Med Oncol* 2013;30:439.
32. Chiba T, Ohtani H, Mizoi T, Naito Y, Sato E, Nagura H, et al. Intraepithelial CD8+ T-cell-count becomes a prognostic factor after a longer follow-up period in human colorectal carcinoma: possible association with suppression of micrometastasis. *Br J Cancer* 2004;91:1711-7.
33. Deschoolmeester V, Baay M, Van Marck E, Weyler J, Vermeulen P, Lardon F, Vermorken JB. Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients. *BMC Immunol* 2010;11:19.
34. Chew A, Salama P, Robbshaw A, Klopcic B, Zeps N, Platell C, Lawrance IC. SPARC, FOXP3, CD8 and CD45 correlation with disease recurrence and long-term disease-free survival in colorectal cancer. *PLoS One* 2011;6:e22047
35. Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pagès C, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. *Science* 2006;313:1960-4.
36. Kishi Y, Kopetz S, Chun YS, Palavecino M, Abdalla EK, Vauthey JN. Blood neutrophil-to-lymphocyte ratio predicts survival in patients with colorectal liver metastases treated with systemic chemotherapy. *Ann Surg Oncol* 2009;16:614-22.
37. Chua W, Charles KA, Baracos VE, Clarke SJ. Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. *Br J Cancer* 2011;104:1288-95.
38. Galizia G, Lieto E, Zamboli A, De Vita F, Castellano P, Romano C, et al. Neutrophil to lymphocyte ratio is a strong predictor of tumor recurrence in early colon cancers: a propensity score-matched analysis. *Surgery* 2015;158:112-20.
39. Malietzis G, Giacometti M, Askari A, Nachiappan S, Kennedy RH, Faiz OD, et al. A preoperative neutrophil to lymphocyte ratio of 3 predicts disease-free survival after curative elective colorectal cancer surgery. *Ann Surg* 2014;260:287-92.
40. Hung HY, Chen JS, Yeh CY, Changchien CR, Tang R, Hsieh PS, et al. Effect of preoperative neutrophil-lymphocyte ratio on the surgical outcomes of stage II colon cancer patients who do not receive adjuvant chemotherapy. *Int J Colorectal Dis* 2011;26:1059-65.
41. Turner N, Wong HL, Templeton A, Tripathy S, Whiti Rogers T, Croxford M, et al. Analysis of local chronic inflammatory cell infiltrate combined with systemic inflammation improves prognostication in stage II colon cancer independent of standard clinicopathologic criteria. *Int J Cancer* 2016;138:671-8.

原　著

術前檢驗資料，包括中性粒細胞-淋巴細胞比值、血清癌胚抗原和血清白蛋白預測 II. 期結腸癌患者術後整體生存率

何寬助[1]　黃政義[1]　陳志榕[1]　郭益宏[1,3]　游正府[2]　靳志堅[1,3]　黃文詩[1,3]

[1]長庚醫院嘉義分院　外科部　大腸直腸外科

[2]長庚醫院　外科部　大腸直腸外科

[3]長庚大學　臨床醫學研究所

背景　全身炎症和免疫反應與第二期結腸癌的常見的風險因子可能存在相關性，對癌症治療至關重要。術前嗜中性粒細胞-淋巴細胞比值 (NLR)、低血漿白蛋白和癌胚抗原增高對第二期結腸癌預後可能可以提供客觀的評估。

方法　在這個觀察性研究中，我們分析了 1180 位第二期結腸癌患者,他們在 1995 年 1 月到 2005 年 12 月間於單一醫學中心進行結腸癌手術。所有患者持續追蹤直到 2009 年 12 月。

結果　高術前嗜中性粒細胞-淋巴細胞比值的患者 (≥ 3.5) 有在結腸癌 TNM 分期中較容易有更深的侵犯深度 (T4)、術前貧血、低血漿白蛋白 (3.5 g/dl) 和 超出標準值的癌胚抗原 (≥ 5 ng/ml)。與其他術前嗜中性粒細胞-淋巴細胞比值 < 3.5 的患者相比，這一類病患也有較高的可能性面臨術後發病率較高的急診手術。多因素分析顯示，高術前嗜中性粒細胞-淋巴細胞比值，高於標準的癌胚抗原，以及存在低血漿白蛋白是所有本研究納入患者和其中接受選擇性結腸癌手術的患者 5 年存活率的獨立風險因素。我們根據獨立風險因素存在與否 (如高術前嗜中性粒細胞-淋巴細胞比值、超標的癌胚抗原水準和存在低血漿白蛋白) 來進一步分層研究的患者。當患者有任一獨立的不利因素時, 接受輔助化療的人的總體生存率明顯高於未進行輔助治療的人 (p = 0.024)。當患者沒有這些因素時，接受與未接受輔助化療的組別之間沒有顯著差異 (p = 0.654)。

結論　高於 3.5 的術前嗜中性粒細胞-淋巴細胞比值、癌胚抗原水準和存在低血漿白蛋白是成本效益高的客觀資料，可用於預測第二期結腸癌患者的整體生存。這些因素的不良影響在施行輔助化療後可產生顯著的改善。

關鍵詞　第二期結腸癌、嗜中性粒細胞-淋巴細胞比值、癌胚抗原、低血漿白蛋白、總體生存。