Original Article

Using Simple Blood Test and Pathological Risk Factors in Combination to Predict Stage-II Colorectal Cancer Recurrence Risk

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Key Words
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Background and Objectives. Current guidelines recommend adjuvant chemotherapy for high-risk stage-II colorectal cancer, but to date, its therapeutic benefit has been minor. Therefore, identifying other indicators to help select appropriate patients for adjuvant treatment is necessary. We aimed to identify all the possible high-risk factors in stage-II colorectal cancer patients.
Methods. Between January 2004 and December 2011, we evaluated 1563 patients with well-documented clinicopathological characteristics who underwent curative resection for stage-II primary colorectal adenocarcinoma at a single institution.
Results. After a median follow-up of 5.9 years, the overall recurrence rate was 14.3%. Independent predictors, such as rectal cancer, T4-stage tumor, bowel obstruction, perineural invasion, and carcinoembryonic antigen (CEA) and albumin levels were significantly related to a high tumor recurrence risk. Patients with combined neutrophil and monocyte-to-lymphocyte count ratio (NM-L ratio) of > 4.3 had a relatively high rate of recurrence (> 4.3 vs. ≤ 4.3, 21.3% vs. 11.6%, $p < 0.001$); this was confirmed by multivariate analysis (hazard ratio, 1.653; $p = 0.004$). The median disease-free and overall survival rates of the high NM-L ratio group were both inferior to those of the low NM-L ratio group. Combining the aforementioned pathological and blood test-related risk factors, the overall risk of recurrence increased to 24.7% (odds ratio, 3.5).
Conclusion. In addition to the well-known clinicopathological characteristics, some simple blood tests can determine a patient's CEA and albumin levels and NM-L ratio. These data can be used to generate a prognostic prediction. Further research on the effects of adjuvant chemotherapy on patients with stage-II colorectal cancer is warranted.
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Colorectal cancer (CRC) is a common and fatal disease worldwide. In Taiwan, it is the most commonly diagnosed cancer annually and the third leading cause of cancer death. According to the national cancer registry, approximately 5600 patients in Taiwan die of CRC each year. Its prognosis and therapeutic strategies depend on TNM staging.[1] Adjuvant chemotherapy has become a standard treatment for stage-III CRC because it reduces disease recurrence and mortality.[2-5] The benefits of adjuvant chemother-

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apy for stage-II patients are controversial because adjuvant chemotherapy does not improve the survival rate of stage-II patients by > 5%.[6,7]

Stage-II CRC is defined by a more advanced T stage (T3-T4) without locoregional lymph node metastasis.[1] Most guidelines divide patients with stage-II CRC into low- and high-risk groups. High-risk patients have relatively poor oncological outcomes and high recurrence risk that do low-risk patients. Some high-risk patients with stage-II CRC have benefited from chemotherapy, but no data set has correlated the risk factors and chemotherapy selection.[8-14] According to the current guidelines, adjuvant chemotherapy should be considered for patients who present with one of the several risk factors, such as CRC at the T4 stage, poor prognostic features (e.g., poorly differentiated histology, lymphatic and vascular invasion, bowel obstruction, localized perforation, and perineural invasion), or analysis of < 12 lymph nodes after surgery.[15-17] Although these risk factors are associated with a relatively high disease recurrence rate, no strong evidence that adjuvant chemotherapy can improve cancer-specific survival in patients with stage-II CRC with poor prognostic features has been reported.[8-14] Therefore, other indicators must be used to select appropriate patients to receive adjuvant treatment.

All risk factors in the current guidelines depend on pathology reports not completed until 1 week after surgery. Some preoperative examinations, such as CT, PET, and MRI, are associated with the prognostic status, but they are not as precise as a pathological report. In addition to pathological reports and imaging data, simple preoperative blood tests for carcinoembryonic antigen (CEA),[18,19] platelet count,[21] nutrition status, CRP, and neutrophil-to-lymphocyte ratio[22,23] as well as nomography[20] may yield pertinent information regarding recurrence risk. The main analysis of high-risk factors in a simple blood test usually includes the assessment of the patient's immune status, namely nutritional status and inflammatory response.

The present study identified all possible high-risk factors in both the pathological report and blood tests in patients with stage-II CRC. Thereafter, we evaluated whether these subgroups of risk factors benefited from adjuvant chemotherapy.

Materials and Methods

Patients and variables

Detailed information regarding clinicopathological variables was retrieved from the Colorectal Section Tumor Registry at Chang Gung Memorial Hospital. This study was approved by the Institutional Review Board of the hospital. The patient-related variables included age, sex, body weight and height, body mass index (BMI), and illness status. Health information for each patient, such as incidence of hypertension, coronary artery disease, cerebrovascular disease, asthma, diabetes mellitus, peptic ulcer disease, hepatitis B or C, and liver cirrhosis, was also collected. The tumor-related variables included tumor location (right and left colon and rectum), tumor size (< 4 and ≥ 4 cm), histological grade (good, moderate, and poor differentiation), histological subtype, tumor obstruction, tumor invasion depth, sampled lymph node number, lymphovascular invasion, and perineural invasion. Blood analysis, including CEA (> 5 and ≤ 5 ng/mL), hemoglobin (≤ 10 and > 10 g/dL), albumin (> 3 and ≤ 3 g/dL), and blood cell counts, was performed before surgery. Because the neutrophil-to-lymphocyte and monocyte-to-lymphocyte ratios are both regarded as potential prognostic factors for CRC,[24-26] we used the ratio from combining neutrophil and monocyte counts and dividing them by the lymphocyte count (i.e., (N+M)/L) and regarded it as NM-L ratio in further evaluation.

Between January 2004 and December 2011, a total of 1744 patients underwent curative resection for stage-II primary colorectal adenocarcinoma. Of them, 25 were excluded from further analysis because of undergoing R1 or R2 resection; moreover, 156 patients with rectal cancer were excluded because they received neoadjuvant chemoradiation. The remaining 1563 patients were enrolled in this study.

Follow-up and end points

All physicians in the same department at this hospital adopt similar follow-up routines and adjuvant treatment protocols. All patients were treated as sub-

jects of weekly multidisciplinary team meetings that aimed to clarify the actual stage of the disease according to clinical information and the pathology report. However, the final decision to proceed to adjuvant chemotherapy depended on each physician's opinion and patient's choice. All patients participated in a follow-up program that included outpatient visits for physical examination and CEA testing every 3-6 months postoperatively and chest X-ray, abdominal sonography or abdominal computed tomography, and colonoscopy examination every 1-3 years postoperatively. The endpoint was an event of recurrence. Disease recurrence was confirmed using the histology of biopsy specimens, reoperation, or radiological studies. The time to recurrence was defined as the duration between the dates of initial surgery and recurrence confirmation. Prognosis was evaluated on the basis of disease-free and overall survival. The overall survival was defined as the duration between the dates of initial surgery and death.

Statistics

All analyses were performed using IBM SPSS Statistics (version 24.0; IBM Corp., Armonk, NY, USA). Clinicopathological characteristics were compared using the chi-square test. The cutoff value for the NM-L ratio was determined using a receiver operating characteristic (ROC) curve analysis. Disease-free survival and time-to-event probabilities were computed using univariate analysis employing the Kaplan-Meier method. Differences were estimated using the log-rank test. To control for confounding and interaction, the time-dependent Cox proportional hazards model was fitted with computed hazard ratios (HRs) and *p* values. Multivariate analysis was performed on the variables with a p value of < 0.1 in the univariate analysis. Statistical significance was set at $p < 0.05$.

Results

We enrolled and analyzed the data of 1563 patients from the Colorectal Section Tumor Registry at Chang Gung Memorial Hospital between January 2004 and December 2011. The mean patient age was 67.0 years. After a median follow-up of 5.9 years, tumors recurred in 223 patients (overall recurrence rate, 14.3%).

Risk factors for recurrence

Multiple variables were analyzed and paired to compare recurrence rates; these are presented in Table 1. Patients who had perforated tumors and underwent emergency operations had a higher recurrence rate than those who did not (33.3% vs. 13.7%, $p < 0.001$); patients with bowel obstruction also had a higher recurrence rate than those who did not (20.3% vs. 13.3%, $p = 0.006$). Patients with rectal cancer had a significantly higher recurrence rate than patients with colon cancer (right colon vs. left colon vs. rectum, 12.4% vs. 12.2% vs. 18.8%; $p = 0.004$). Patients with advanced T-stage cancer (T4 vs. T3, 33.3% vs. 13.7%; $p < 0.001$), lymphovascular invasion (22.9% vs. 13.4%, $p = 0.006$), perineural invasion (22.7% vs. 12.0%, $p < 0.001$), and < 12 sampled lymph nodes (23.7% vs. 13.6%, $p = 0.007$), all had significantly high recurrence rates according to the univariate analysis. Abnormal laboratory results, such as hypoalbuminemia (≤ 3 g/dL) and elevated CEA levels (> 5 ng/mL) before surgery, were significantly associated with high rates of recurrence (albumin ≤ 3.0 vs. > 3.0 g/dL, 24.3% vs. 13.5%; $p = 0.005$; CEA > 5.0 vs. ≤ 5.0 ng/mL, 19.2% vs. 11.5%; $p < 0.001$). No statistical difference in recurrence rate was evident when sex, advanced age (> 70 years), BMI, presence of comorbidities, tumor size (≥ 4 cm), histological grade, presence of mucinous adenocarcinoma, or hemoglobin levels (≤ 10.0 g/dL) of patients with stage-II CRC were considered.

All the variables associated with tumor recurrence in patients with stage-II CRC in the univariate analyses were entered into a multiple logistic regression analysis (Table 2). Independent predictors of high recurrence were rectal cancer (HR = 1.77, $p < 0.001$), T4-stage tumor (HR = 1.97, $p < 0.001$), bowel obstruction (HR = 1.71, $p = 0.004$), an inadequate number of sampled lymph nodes from surgery (HR = 1.65, $p = 0.057$), perineural invasion (HR = 1.92, $p < 0.001$), preoperative serum albumin level < 3.0 g/dL (HR = 1.78, $p = 0.015$), and high CEA level (HR = 1.55, $p =$

Table 1. Univariate analysis of risk factors for recurrence of stage II CRC

	Number (%)	Recurrence rate (%)	*p* value
Gender			0.463
Male	904 (57.8)	135 (14.9)	
Female	659 (42.2)	88 (13.4)	
Age			0.390
≤ 70	931 (59.6)	135 (14.5)	
> 70	632 (40.4)	88 (13.9)	
BMI			0.942
< 18.5	96 (6.3)	14 (14.6)	
18.5~27	1164 (76.1)	164 (14.1)	
> 27	269 (17.6)	36 (13.4)	
Comorbidities			
Hypertension			0.589
Yes	579 (37.0)	79 (13.6)	
No	984 (63.0)	144 (14.6)	
Coronary artery disease			0.820
Yes	134 (8.6)	20 (14.9)	
No	1429 (91.4)	203 (14.2)	
Cerebral vascular disease			0.318
Yes	93 (6.0)	10 (10.8)	
No	1470 (94.0)	213 (14.5)	
Asthma			0.722
Yes	50 (3.2)	8 (16)	
No	1513 (96.8)	215 (14.2)	
Diabetes mellitus			0.162
Yes	276 (17.7)	32 (11.6)	
No	1287 (82.3)	191 (14.8)	
Peptic ulcer disease			0.431
Yes	146 (9.3)	24 (16.4)	
No	1417 (90.7)	199 (14.0)	
Hepatitis B or C			
Yes	74 (4.7)	11 (14.9)	0.880
No	1489 (95.3)	212 (14.2)	
Liver cirrhosis			0.886
Yes	23 (1.5)	3 (13.0)	
No	1540 (98.5)	220 (14.3)	
Maximal tumor length			0.504
≥ 4 cm	1165 (74.7)	161 (13.8)	
< 4 cm	394 (25.3)	60 (15.2)	
T stage			0.000
T4	224 (14.3)	51 (22.8)	
T3	1339 (85.7)	172 (12.8)	
Tumor perforation			0.000
Yes	48 (3.1)	16 (33.3)	
No	1515 (96.9)	207 (13.7)	
Bowel obstruction			0.006
Yes	222 (14.2)	45 (20.3)	
No	1341 (85.8)	178 (13.3)	
Tumor location			0.004
Left side colon	483 (31.0)	60 (12.4)	
Right side colon	629 (40.3)	77 (12.2)	
Rectum	447 (28.7)	84 (18.8)	

Table 1. Continued

	Number (%)	Recurrence rate (%)	*p* value
Histology grade			0.778
Poorly differentiated	119 (7.6)	18 (15.1)	
Well or moderately differentiated	1438 (92.4)	204 (14.2)	
Sampled lymph nodes			0.007
No. of lymph nodes < 12	93 (6.0)	22 (23.7)	
No. ≥ 12	1468 (94.0)	200 (13.6)	
Lymphovascular invasion			0.006
Yes	109 (7.1)	25 (22.9)	
No	1429 (92.9)	191 (13.4)	
Perineural invasion			0.000
Yes	291 (18.9)	66 (22.7)	
No	1246 (81.1)	150 (12.0)	
Mucinous adenocarcinoma			0.292
Yes	120 (7.7)	21 (17.5)	
No	1443 (92.3)	202 (14.0)	
Albumin level (g/dl)			0.005
≤ 3.0	103 (6.8)	25 (24.3)	
> 3.0	1404 (93.2)	189 (13.5)	
Hemoglobin level (g/dl)			0.930
≤ 10.0	332 (21.3)	48 (14.5)	
> 10.0	1229 (78.7)	175 (14.2)	
CEA level (ng/ml)			0.000
> 5.0	563 (36)	108 (19.2)	
≤ 5.0	999 (64)	115 (11.5)	
NM-L ratio			0.000
> 4.3	338 (25.2)	72 (21.3)	
≤ 4.3	1004 (74.8)	116 (11.6)	

CEA, carcinoembryonic antigen; NM-L ratio, (Neutrophil + Monocyte)/Lymphocyte.

Table 2. Multivariate Cox regression analysis

	HR	95% CI	*p* value
Rectal cancer	1.765	1.282-2.430	0.000
T4 tumor	1.969	1.372-2.826	0.000
Tumor perforation	1.436	0.707-2.917	0.317
Bowel obstruction	1.708	1.183-2.465	0.004
Inadequately sampled lymph nodes (No. of lymph nodes < 12)	1.653	0.986-2.772	0.057
Lymphovascular invasion	1.228	0.748-2.019	0.417
Perineural invasion	1.919	1.377-2.675	0.000
Albumin level < 3.0 g/dl	1.778	1.118-2.828	0.015
CEA level > 5.0 ng/ml	1.545	1.142-2.091	0.005
NM-L ratio	1.653	1.180-2.317	0.004

All variables with a *p* value of < 0.1 in the univariate analysis were entered into the multivariate analysis.
CEA, carcinoembryonic antigen; NM-L ratio, (Neutrophil + Monocyte)/Lymphocyte.

0.005). The presence of neither tumor perforation nor lymphovascular tumor invasion yielded significant differences in recurrence rates in the multiple logistic regression analysis.

NM-L ratio analysis

The ROC curve analysis of the NM-L ratio is presented in Fig. 1. The cutoff value for these patients

was 4.3 with the largest area under the ROC curve (0.556). Patients with a preoperative NM-L ratio of > 4.3 had a higher recurrence rate (> 4.3 vs. ≤ 4.3, 21.3% vs. 11.6%; $p < 0.001$; Table 1). The multivariate analysis also indicated that a higher NM-L ratio (> 4.3) was significantly related to tumor recurrence (HR, 1.653; 95% confidence interval, 1.180-2.317; $p = 0.004$; Table 2).

The median disease-free survival time was 71 and 55 months in the low and high NM-L ratio groups, respectively (Fig. 2). The result of the log-rank test that compared the long-term survival curves stratified by NM-L ratio was statistically significant ($p < 0.001$). The median overall survival time of the low NM-L ratio group was also significantly higher than the high NM-L ratio group (> 4.3 vs. ≤ 4.3, 72 vs. 60 months, $p < 0.001$; Fig. 3).

Combination of blood test-related and pathological risk factors

To best render our study results applicable to daily practice, we divided the risk factors into two groups: pathological (T4, bowel obstruction, and perineural invasion) and blood test related (low albumin level and high CEA level and NM-L ratio). The Venn diagram in Fig. 4 illustrates the recurrence rates and odds ratios (ORs) of the pathological risk group, blood test risk group, combination of the pathological and blood test groups, and no high-risk group. The relationship between the pathological and blood test risk groups entailed overlapping and independent events. Patients who had a pathological and blood test risk had 20.4% (OR, 2.8), and 18.4% (OR, 2.4) recurrence rates, respectively. If a patient had overlapping risk factors in both groups, the recurrence rate was as high as 24.7% (OR, 3.5). In patients with no risks factors, the recurrence rate was only 8.5%.

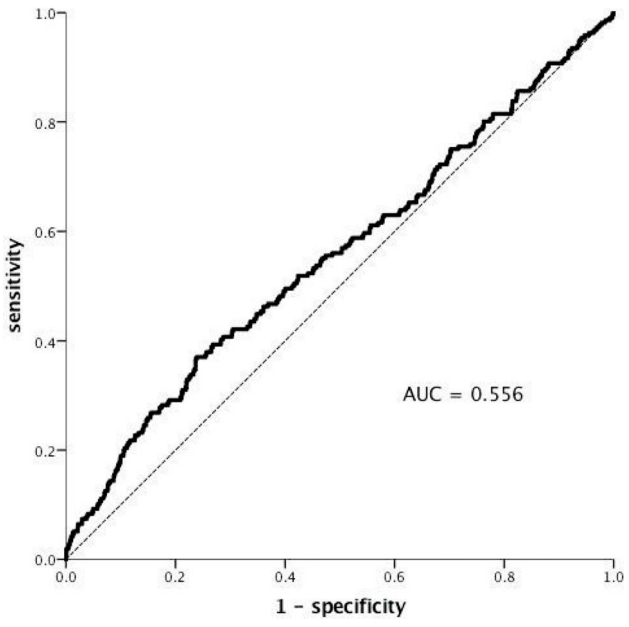

Fig. 1. ROC curve of the NM-L ratio.

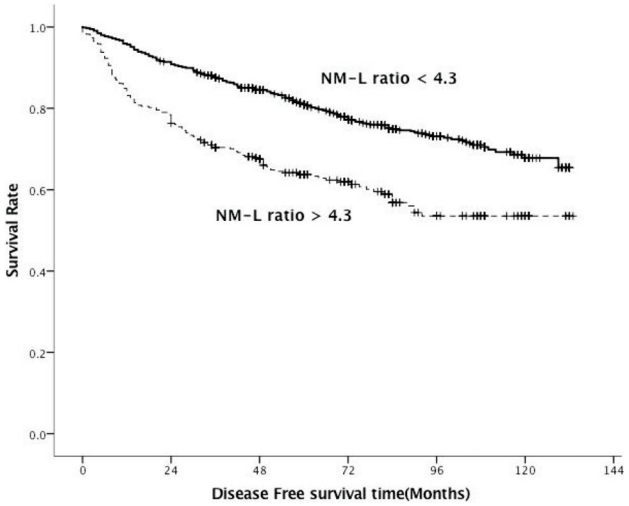

Fig. 2. NM-L ratio and disease free survival. $p < 0.001$ (log rank test).

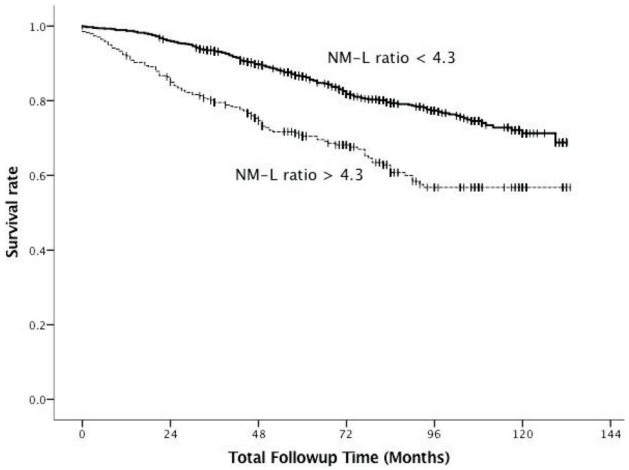

Fig. 3. NM-L ratio and overall survival. $p < 0.001$ (log rank test).

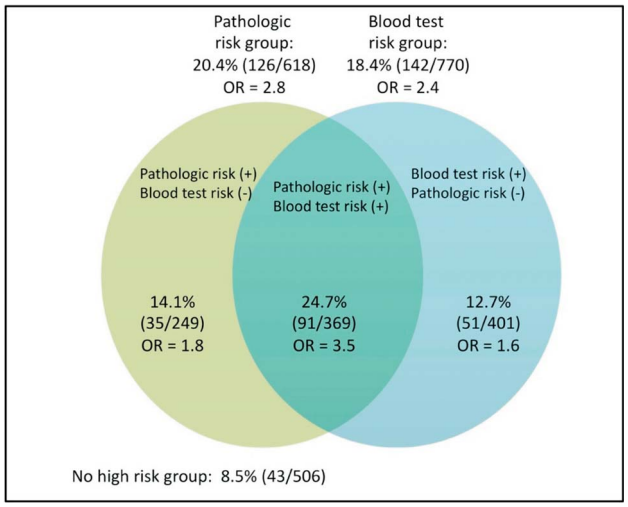

Fig. 4. Recurrence rates and ORs of the pathological risk group, blood test risk group, combination of pathological and blood test group, and no high-risk group.

Discussion

According to current guidelines, several factors occurring postoperatively and related to pathology militate for treating patients with stage-II CRC using adjuvant chemotherapy after surgery to lower the recurrence rate and cure the disease. Because these factors are revealed only after surgery, doctors are unable to make a precise prognosis before an operation. Moreover, despite recognizing the condition of these patients and appreciating the merit of administering further adjuvant chemotherapy, chemotherapy did not guarantee lower incidence of recurrence. The biased selection of high-risk patients may account for unfavorable results from treatment with adjuvant chemotherapy. Therefore, we searched for more clinical features potentially associated with prognosis to achieve greater precision with respect to predicting a patient's prognosis.

CEA has long been used as a recurrence surveillance marker during the posttreatment period.[27] However, its role as a prognostic predictor is now being recognized. Some studies have advocated for incorporating CEA into the TNM staging system as the biochemical aspect of the disease.[28] In our study, a high preoperative CEA level (> 5 ng/mL) was a strong predictor of tumor recurrence in patients with stage-II CRC, a finding which is consistent with other studies.[18,20,28] Although classified as having stage-II CRC, these patients may exhibit lymph-node or distant metastasis in the future. The CEA level is primarily viewed as a tumor marker, but it may also be elevated as a result of several other conditions such as liver cirrhosis, chronic obstructive pulmonary diseases, and cardiometabolic diseases. However, according to the results of our study, a high preoperative CEA level may be a poor prognostic factor for patients with stage-II CRC. Among our study population, the threshold for an abnormal CEA level seemed to be the same as the globally accepted value.

Patients with hypoalbuminemia, particularly those with advanced cancer, are typically malnourished. Stage-II cancers might not present with lymph node metastasis, but a large primary tumor may create a significant metabolic burden and cause malnutrition. The recurrence rate is high in these patients,[29] not only because of a high likelihood of tumor metastasis but also because the tumor acts as a biological stressor, which weakens host immunity, thus compromising the ability of the patients' immune system to effectively combat the tumor.

To the best of our knowledge, no other study has described the role of the NM-L ratio with respect to the recurrence of stage-II CRC. The results of this study are the first to demonstrate that the NM-L ratio is a useful marker for predicting stage-II CRC recurrence risk and survival outcome. Serum inflammation markers, namely the neutrophil-to-lymphocyte, lymphocyte-to-monocyte, and platelet-to-lymphocyte ratios, and their roles in CRC prognosis at various stages have been investigated extensively. Each marker, alone or in combination, has been demonstrated to have statistical significance.[24,25,30,31] Neutrophil count is typically high in many advanced cancers. Neutrophils are recruited and deregulated by tumor cells and thus support tumor growth and angiogenesis.[32,33] Circulating monocytes can differentiate into macrophages or dendritic cells. Another study proved that monocytes can contribute to tumor development when conditions are favorable.[34] Additionally, tumor-associated neutrophils and tumor-associated macrophages are both thought to encourage tumor development;

cause tumor proliferation, invasion, and angiogenesis; and inhibit immune surveillance.[35] Lymphocytes, however, represent the host's immune reaction to specific antigens and even tumor cells. Lymphocytic infiltration of a tumor improves the CRC prognosis. In addition, lymphopenia in advanced cancer is typically associated with disease severity and prognosis.[36-38] The NM-L ratio integrates these markers and is a strong prognostic predictor of recurrence and disease-free survival. An NM-L ratio of > 4.3 is associated with a 1.6-fold risk of shortened disease-free and overall survival.

In the present study, the preoperative CEA and albumin levels and NM-L ratio were proven to be prognostic markers of CRC recurrence. Some may argue that other markers, such as defective DNA mismatch repair, BRAF and KRAS mutations, or even genomic signature tools, could act as superior prognostic factors; however, the advantage of the aforementioned prognostic markers is that they are efficient, economical, and most importantly, preoperatively available. Thus, these data can give physicians and patients a preliminary indication of how future therapy might proceed, obviating the need to wait for the final pathological report to determine whether adjuvant chemotherapy should be administered. Furthermore, incorporating these blood test-related risk factors with current pathological risk factors can considerably improve the prediction of recurrence rates, clearly indicating that the blood test-related risk factors are strongly associated with recurrence in the stage-II patients.

The present study has some limitations. First, this was a retrospective study, conducted at a single institute by using prospectively collected data; thus, it is subject to various biases. Second, some data concerning clinicopathological characteristics were missing from this study, which might have influenced the outcome. However, the effect of missing data should have been insignificant because the missing data for each factor constituted less than 5% of the data in this study. Third, microsatellite instability was not measured during the study period, but it is now known to be an essential factor in stage-II CRC.

Conclusion

Multiple factors play essential roles in stage-II CRC recurrence. In addition to well-known clinicopathological characteristics, such as tumor location, T4-stage tumor, tumor obstruction, and perineural invasion, blood tests that determine CEA and albumin levels and NM-L ratio could provide prognostic prediction. A gap remains between having high-risk factors for recurrence and the need to receive adjuvant chemotherapy. Further analysis of these clinicopathological characteristics should be undertaken using large randomized trials not only to better understand their exact roles in the recurrence of stage-II CRC but also to evaluate the effect of adjuvant chemotherapy for these patients with high-risk factors.

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原　著

第二期大腸直腸癌復發之因素分析

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背景　目前國際治療準則建議第二期大腸直腸癌患者若具備較高危險因子，可選擇接受輔助性化學治療。但目前研究證據顯示此類病患接受化療之後的幫助並不顯著。我們認為可能尚有其他臨床危險因子並未被發現，因此影響成效。

方法　挑選本院 2004 年至 2011 年第二期大腸直腸癌接受根除性切除但排除接受放射治療之病患。比較其手術前臨床因子、手術後病理因子及後續復發之關係。

結果　在這群患者之中，整體的復發比率為 14%，中位追蹤年份為 5.9 年。影響較高復發機率的因子有直腸癌患者、T4 腫瘤、腸阻塞、近神經侵犯、較高的癌胚抗原數值以及較低的白蛋白數值。若 (嗜中性白血球 + 單核球)/淋巴球之比值大於 4.3，亦有較高的復發機率 (> 4.3 vs. ≤ 4.3, 21.3% vs. 11.6%, $p < 0.001$)。若將前述的病理因子及臨床因子合併計算，總體復發機率將增加至 24.7% (OR = 3.5)。

結論　結合在本研究中的各項臨床及病理因子，可進一步找出可能復發之大腸直腸癌第二期病患。但仍須探討化學治療是否對此類病患有效。

關鍵詞　癌胚抗原、白蛋白、嗜中性白血球、單核球、淋巴球、大腸直腸癌。