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Neutrophil to Lymphocyte Count Ratio Has a Close Association With Severe Acute Colonic Diverticulitis in Patients Undergoing Surgical Treatment

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Objective: To investigate the diagnostic potential of neutrophil-to-lymphocyte count ratio (NLCR) for acute diverticulitis.

Summary of Background Data: We evaluated NLCR in patients with acute colonic diverticulitis who were treated with conservative and surgical treatments.

Methods: A total of 205 patients who underwent surgical treatment or conservative management of acute diverticulitis between 2012 and 2016 were reviewed. Patients' age; sex; hospital days; co-morbidity; complication; period of use of antibiotics; treatment method; body temperature; and initial laboratory results such as neutrophil count, lymphocyte count, NLCR, and serum levels of C-reactive protein (CRP) were assessed.

Results: The median ages of the conservative and surgical treatment groups were 46 and 68 years, respectively. Median CRP and glucose levels were high in acute colonic diverticulitis patients who underwent surgical treatment ($P < 0.001$, $P < 0.001$). Albumin level was low in the surgical treatment group ($P < 0.001$). NLCR was significantly different in both groups (conservative management vs surgical treatment, 4.1 mg/L versus 8.5 mg/L; $P < 0.001$). Median white blood cells was 11.36×10^9/L in the conservative management group and 14.0×10^9/L in the surgical treatment group, with no significance ($P = 0.071$). Multivariate analysis revealed that NLCR >10.21 [odds ratio (OR) = 5.613, $P = 0.022$]; CRP >17.23 mg/L (OR = 4.241, $P = 0.006$); and albumin ≤3.5 (OR = 4.192, $P = 0.036$) were significant for acute colonic diverticulitis patients.

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Conclusion: NLCR, CRP, and albumin levels were significantly associated with acute colonic diverticulitis in the surgical treatment group, and NLCR was the most powerful predictive marker of severe acute colonic diverticulitis.

Key words: Diverticulitis – Neutrophils – Lymphocytes – Ratio – Severity

A colonic diverticulum is an abnormally herniated sac in the colonic wall. Diverticulosis is a clinical condition in which the diverticula in the colon are not inflamed, causing no infection or bleeding. Diverticular disease or diverticulitis is a condition that occurs when the diverticula (pouches) get infected or inflamed. In Western countries, in 25% of patients with colonic diverticulosis, the condition aggravates to diverticular disease, and 75% of this group are diagnosed with diverticulitis and 25% are diagnosed with diverticular bleeding.[1] The symptoms associated with colonic diverticulitis are various (mild abdominal pain and fever), and in 15% to 20% of patients, the condition can proceed to abscess, fistula, ischemia, and perforation. Since diverticular perforation is fatal in 12% to 36% of patients, diagnosis needs to be both early and accurate.[2] Most patients who visit the emergency department are diagnosed via abdominal computed tomography (CT), and receive either outpatient or inpatient care. Since the incidence and admission rates of acute colonic diverticulitis are rising, the burden on health care systems is increasing.[3,4] According to a recent prospective case-control study conducted in Europe, the quality of life and treatment failure rate of the inpatient group were similar to those of the outpatient group. Since the cost of medical care was 3 times higher in the inpatient group than that in the outpatient group, colonic diverticulitis patients without any complications should opt for outpatient care for reasons of safety and cost-effectiveness.[5] The treatment decision should be based on the patient's clinical physiologic state; therefore, biochemical and hematologic markers can help us detect systemic inflammation. A CT scan is useful to diagnose acute abdominal conditions; however, it is expensive and radiation exposure is an important concern. This study uses the neutrophil-to-lymphocyte count ratio (NLCR) as a serologic marker to assess the severity of acute colonic diverticulitis. NLCR has been shown to be a simple, promising method to evaluate systemic inflammation in critically ill patients. In a retrospective study, NLCR was found to be a better predictor of bacteremia than routine parameters, such as C-reactive protein (CRP) level, white blood cell (WBC) count, and neutrophil count.[6] Furthermore, in a study on appendicitis, NLCR was a more accurate prognostic marker for predicting the severity and outcome of diseases than traditional infection markers.[7] However, no study has examined the relationship between acute colonic diverticulitis and NLCR. In the present study, we assessed the potential use of NLCR in patients with acute colonic diverticulitis who were treated with conservative and surgical treatments.

Materials and Methods

We retrospectively analyzed patients treated with conservative or surgical methods for acute diverticulitis diagnosed at Seoul Medical Center between March 2012 and December 2016. The routine algorithm of treatment for acute diverticulitis is shown in Figure 1. A total of 205 patients were enrolled in this study. The patients' age, sex, comorbidity, body temperature, BMI, hospital days, complications, and treatment (surgical or conservative) were reviewed. Initial results of laboratory tests performed at the emergency medicine department or outpatient department were collected; these included WBC count; neutrophil count; lymphocyte count; NLCR; and serum levels of CRP, glucose, albumin, and total bilirubin. NLCR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. In addition, data on duration of hospital stay, radiologic findings, and histopathology reports were collected.

This study was approved by the Institutional Review Board of our hospital, and data collection and analysis were performed in compliance with its requirements. Written and informed consent was provided by all patients or the patients' family. Seoul Medical Center Institutional Review Board, Approval number: 2016-080.

Results

Statistical analysis was performed using commercial software (SPSS 20, IBM Corp, Armonk, New York).

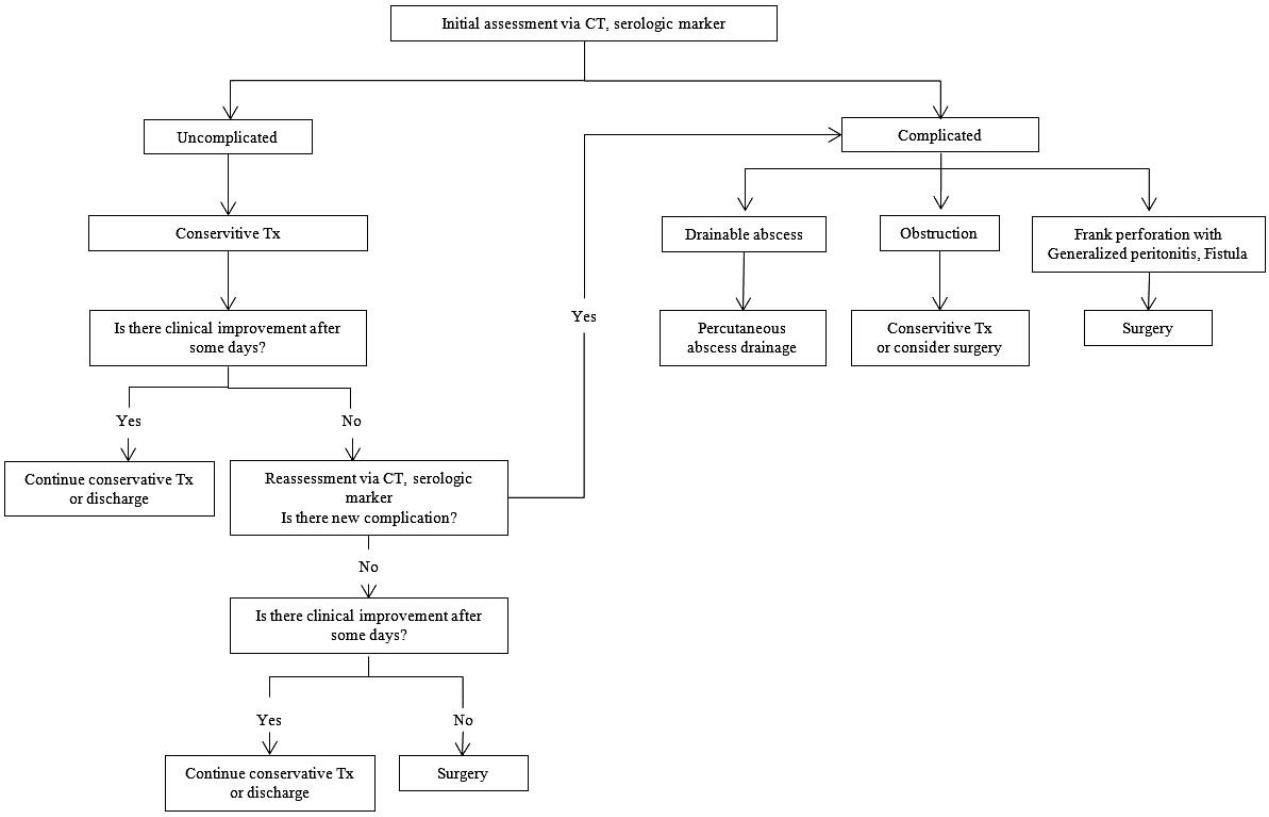

Fig. 1 The routine algorithm of treatment for acute diverticulitis

Fisher's exact test and the Mann-Whitney U test were used to compare variables between patients who received conservative management and surgical treatment. A receiver operator characteristic (ROC) curve was generated to present the best cutoff value, and Youden's index was calculated. A value of $P < 0.05$ was considered to be statistically significant. The variables were classified according to the cutoff value determined in the ROC curve analysis and the univariate analysis was repeated. Statistically significant factors in the univariate analysis ($P < 0.10$) were included in the multivariate logistic regression model.

Of the 205 patients evaluated in this study, 178 received conservative management and 27 received surgical treatment. The median age of the conservative and surgical treatment groups was 46 (range 15–93) and 68 (range 23–88) years, respectively. The male-to-female ratio was 0.88, and 75 patients (36.6%) had comorbidities as follows: hypertension in 45 patients, diabetes in 28 patients, COPD in 3 patients, CRF in 1 patient, malignancy in 4 patients, and previous surgery in 5 patients. Patients' sex and BMI did not present significant differences in the conservative and surgical treatment groups ($P = 0.522$, $P = 0.658$). Median duration of hospital stay was 5.9 days (range: 2–71) in the conservative management group and 18.3 days (range: 2–71) in the surgical treatment group, showing a significant difference. The patient and laboratory test details are presented in Table 1.

There were significant differences between both groups in CRP (conservative management versus surgical treatment, 3.05 mg/L versus 18.25 mg/L, $P < 0.001$). Glucose level was higher in the surgical treatment group than that in the conservative management group (conservative management versus surgical treatment, 103.8 mg/L versus 107.0 mg/L, $P < 0.001$). The albumin level was lower in the surgical treatment group than that in the conservative management group (conservative management versus surgical treatment, 4.28 mg/L versus 3.5 mg/L, $P < 0.001$). Significant differences were observed between both groups in NLCR (conservative management versus surgical treatment, 4.1 mg/L versus 8.5 mg/L, $P < 0.001$). Median WBC was higher in the surgical treatment group than in the conservative management group (conservative management ver-

Table 1 Demographics and characteristics of acute diverticulitis

Characteristics	All (n = 205)	Conservative Tx (n = 178)	Surgical Tx (n = 27)	*P* value
Age, y	46.0 (15-93)	44.2 (15-93)	68.0 (23-88)	< 0.001
Sex				
Male, n (%)	96 (46.8)	83 (46.6)	13 (48.1)	0.522
Female, n (%)	109 (53.2)	95 (53.4)	14 (51.9)	
Comorbidity				
Yes, n (%)	75 (36.6)	106 (59.6)	24 (88.9)	0.002
No, n (%)	130 (63.4)	72 (40.4)	3 (11.1)	
Site				
Right, n (%)	175 (85.4)	158 (88.7)	17 (63.0)	0.002
Left, n (%)	30 (14.6)	20 (11.2)	10 (37.0)	
Complication				
Yes, n (%)	59 (28.8)	38 (21.3)	20 (11.2)	<0.001
No, n (%)	146 (71.2)	140 (78.7)	6 (22.2)	
Body temperature, ℃ (range)	36.5 (36–38.3)	36.5 (36.0–38.1)	36.7 (36.0–38.3)	0.023
WBC, 10^9/L (range)	11.40 (3.70–80.10)	11.36 (4.20–29.00)	14.00 (3.70–80.10)	0.071
Neutrophil, % (range)	73.1 (46.2–94.8)	72.3 (46.2–94.8)	81.0 (50.2–92.3)	0.001
Lymphocyte, % (range)	17.4 (1.9–45.6)	17.9 (1.9–45.6)	10.1 (2.5–38.5)	<0.001
NLCR	4.2 (1.03–49.89)	4.1 (1.0–49.9)	8.5 (1.3–35.6)	<0.001
CRP, mg/L (range)	7.05 (0.01–30.67)	3.05 (0.01–24.50)	18.25 (1.06–50.67)	<0.001
Total bilirubin, mg/dL (range)	0.7 (0.2–6.1)	0.7 (0.2–6.1)	0.7 (0.2–2.2)	0.334
Glucose, mg/dL (range)	107.0 (77.0–596.0)	103.8 (77.0–314.0)	107.0 (77.0–596.0)	<0.001
Hospital stay, d (range)	7.0 (2.0–71.0)	5.9 (2.0–70.0)	18.3 (2.0–71.0)	<0.001
Albumin, g/dL (range)	4.2 (2.1–5.0)	4.28 (2.1–5.0)	3.5 (2.3–4.7)	<0.001
Platelet, # (range)	243.0 (3.4–570.0)	237.4 (3.4–441.0)	259.0 (72.0–570.0)	0.309
BMI, kg/m^2 (range)	23.7 (15.2–35.0)	23.8 (36.0–38.1)	36.7 (36.0–38.3)	0.658

sus surgical treatment, 11.36 × 10^9/L versus 14.0 × 10^9/L) but no statistical significance was observed (P = 0.071). As observed in these results, CRP levels, NLCR, glucose levels, albumin levels, and hospital days significantly differed between the groups ($P <$ 0.001).

To determine the cutoff values for CRP, NLCR, glucose level, albumin level, neutrophils, and lymphocytes, an ROC curve was generated and Youden's index was calculated. The area under the curve (AUC) value of CRP was 0.720 [95% confidence interval (CI) = 0.653–0.781, $P < 0.001$], and the cutoff value was 7.23 mg/L (sensitivity 65.38% and specificity 78.53%). For NLCR, the AUC value was 0.705 (95% CI = 0.637–0.766, $P < 0.001$), and the cutoff value was 10.21 (sensitivity 46.15% and specificity 94.41%). For albumin, the AUC value was 0.762 (95% CI = 0.698–0.819, $P < 0.001$) and the cutoff value was 0.432 (sensitivity 53.85% and specificity 89.39%). For glucose, the AUC value was 0.744 (95% CI = 0.679–0.802, $P < 0.001$), and the cutoff value was 108 (sensitivity 80.77% and specificity 56.42%). For neutrophil, the AUC value was 0.686 (95% CI = 0.618–0.749, $P = 0.0028$), and the cutoff value was 80.9 (sensitivity 50.00% and specificity 86.03%). For lymphocyte, the AUC value was 0.700 (95% CI = 0.632–0.762; $P = 0.0015$), and the cutoff value was 11.5 (sensitivity 57.69% and specificity 83.80%). The ROC curves are presented in Figure 2. Univariate analysis using the logistic regression model revealed that WBC, neutrophil, lymphocyte, NLCR, CRP level, albumin level, and glucose level were associated with the severity of acute colonic diverticulitis. In addition, the values observed in the ROC curve, including NLCR >10.21 (odds ratio [OR] = 13.091, $P < 0.001$); CRP >17.23 mg/L (OR = 7.962, $P < 0.001$); glucose >108 mg/dL (OR = 3.515, $P = 0.007$); and albumin ≤3.5 mg/dL (OR = 9.825, $P < 0.001$) were significantly associated with severe acute diverticulitis in patients (Table 2). The results of other variables analyzed are presented in Table 2. Table 3 presents the significant factors associated with surgical treatment for acute diverticulitis patients as follows: age (OR 0.911, $P = 0.626$); comorbidity (OR 3.041, $P = 0.145$); WBC ≤10.58 × 10^9/L (OR 0.983, $P = 0.573$); NLCR >10.21 (OR 5.613, $P = 0.022$); CRP level > 17.23 mg/L (OR = 5.219, $P =$ 0.0246); and albumin level ≤3.5 (OR 4.192, $P =$ 0.036).

Discussion

Accurate and early diagnosis of diverticulitis, as well as the presence of comorbidities, can largely

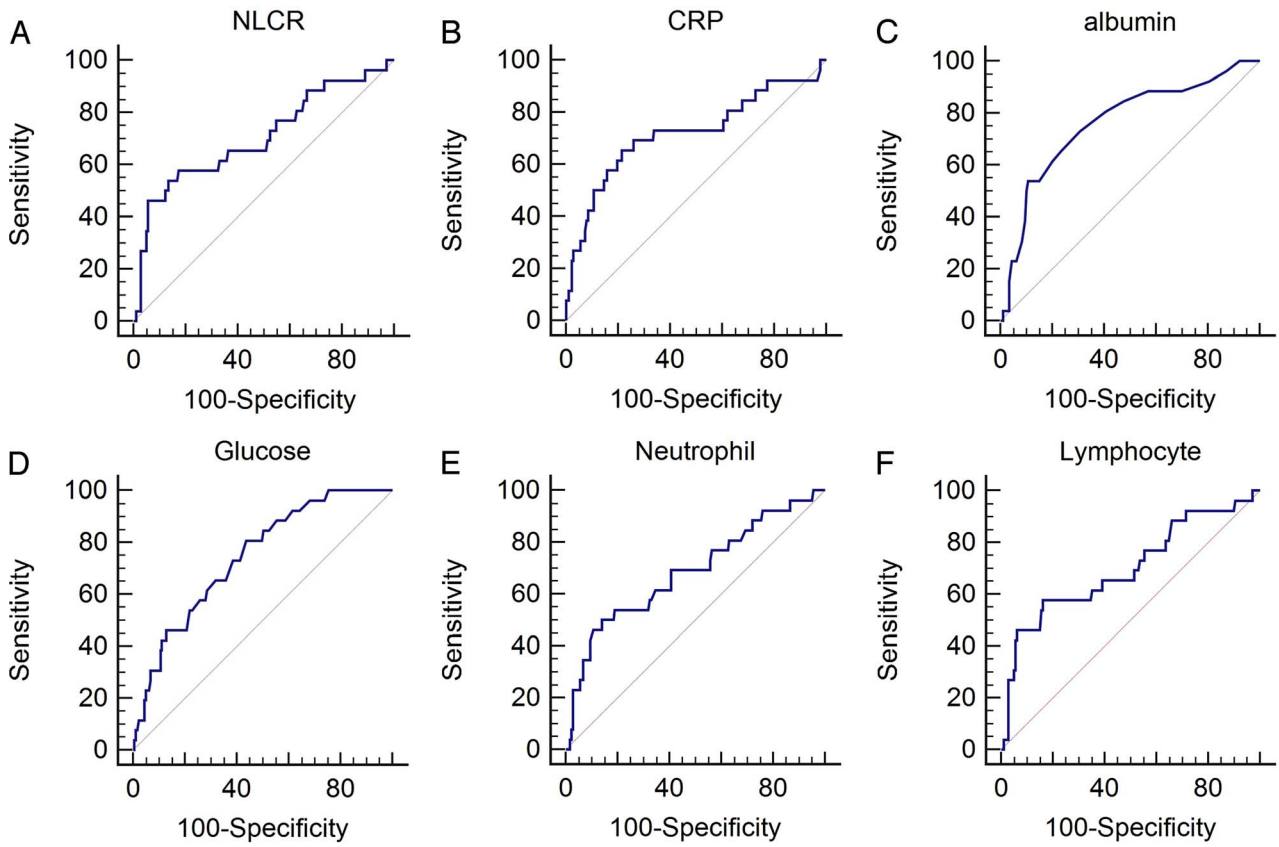

Fig. 2 ROC curves for severity of acute colonic diverticulitis. (A) The AUC of the NLCR was 0.705. (B) The AUC of CRP was 0.720. (C) The AUC of albumin was 0.762. (D) The AUC of glucose was 0.744. (E) The AUC of neutrophil was 0.686. (F) The AUC of lymphocyte was 0.700.

affect the treatment plan for diverticulitis, which can involve conservative management or medical treatment using antibiotics or surgical treatment.[8] Approximately 75% of patients are known to develop uncomplicated colonic diverticulitis[9]; their typical symptoms include lower quadrant pain, fever, and leukocytosis, and are diagnosed via abdominal CT scans. Inpatients with abdominal tenderness in the absence of abdominal pain are able to drink water, and they can be discharged if they do not experience aggravating abdominal pain after meals. Uncomplicated diverticulitis patients can gradually start eating meals 2 to 3 days after their symptoms begin to alleviate. If the patients' clinical symptoms do not improve, further radiologic examinations and general surgery consultations are necessary to explore the presence of complications such as perforation.[10] Approximately 25% of patients undergo surgery, since their diverticulitis symptoms are not alleviated.[11] Approximately 33% of patients experience recurring diverticulitis; previously, patients with second episodes were recommended to undergo elective surgery to prevent further episodes, since recurring diverticulitis was believed to have severe outcomes.[12] However, this belief has been recently challenged. Elective surgery should be performed on a case-by-case basis, depending on the number of attacks, severity of attacks, the patient's age, and accompanying diseases.[13] If elective surgery is indeed selected, laparoscopy is recommended due to several clinical advantages: 90% of the cases can go through primary anastomosis, and according to a randomized-clinical trial, patients experienced pain relief, short hospitalization periods, elevated quality of life, and decreased morbidity rate (15.4%). Morbidity rate was decreased to 27% six months after the elective surgery.[14,15] Patients with diffuse peritonitis, resulting from colon perforation, and those for whom conservative management is unsuccessful may require an emergency or elective colectomy.

Table 2 Univariate analysis of severe acute diverticulitis patients performed by surgical treatment

Characteristics	Odds ratio	95% CI	*P* value
Age	1.039	1.017–1.062	0.001
Sex			
Male	1.233	0.537–2.832	0.621
Body temperature	3.918	1.592–9.641	0.003
BMI	1.054	0.935–1.188	0.392
Comorbidity	5.159	1.493–17.821	0.009
WBC (10^9/L)	1.058	0.666–1.121	0.053
Neutrophil, %	1.072	1.024–1.121	0.003
Neutrophil, %			
≤80.9 (ref)	5.885	2.456–14.102	<0.001
>80.9			
Lymphocyte, %	0.911	0.860–0.966	0.002
Lymphocyte, %			
>11.5 (ref)	7.053	2.944–16.898	<0.001
≤11.5			
NLCR	1.082	1.029–1.137	0.002
NLCR			
≤10.21 (ref)	13.091	4.898–34.991	<0.001
>10.21			
CRP	1.137	1.075–1.202	<0.001
CRP			
≤17.23 (ref)	7.962	3.219–29.690	<0.001
>17.23			
Glucose	1.009	1.001–1.016	0.020
Glucose			
≤108 (ref)	3.515	1.407–8.780	0.007
>108			
Albumin (g/dL)	0.242	0.126–0.463	<0.001
Albumin (g/dL)			
>3.5 (ref)	9.825	3.971–24.308	<0.001
≤3.5			
Total bilirubin (mg/dL)	0.683	0.277–1.684	0.128

Table 3 Multivariate logistic regression analysis of severe acute diverticulitis patients performed by surgical treatment

Variable	Odds ratio	95% CI	*P* value
Age	0.991	0.956–1.027	0.626
Comorbidity	3.041	0.681–13.576	0.145
WBC (10^9/L)	0.983	0.925–1.044	0.573
NLCR			
≤10.21 vs. >10.21	5.613	1.282–24.577	0.022
CRP			
≤17.23 vs. >17.23	5.219	1.292–19.060	0.024
Albumin (g/dL)			
>3.5 vs. ≤3.5	4.192	1.095–16.044	0.036
Total bilirubin, mg/dL	0.596	0.184–1.931	0.388

The present study was conducted to identify the diagnostic factors for acute colonic diverticulitis required for patients to undergo surgical treatment. NLCR, neutrophil count, lymphocyte count, CRP level, glucose level, and albumin level differed between the conservative and surgical treatment groups. Acute diverticulitis patients with NLCR ≤10.21, CRP level ≤17.23 mg/L, and albumin level >3.5 g/dL received conservative management. AUC for NLCR was high, and NLCR >10.21 showed the highest sensitivity and acceptable specificity.

CRP and WBC were reported to be associated with acute colonic diverticulitis. Hogan *et al*[16] reported that CRP is the most accurate parameter in distinguishing the severity of diverticulitis.[16] Serologic markers demonstrated a strict relationship with the degree of histologic damage in acute uncomplicated diverticulitis.[17] However, data on diverticulitis is not adequate. In contrast, a vast amount of data is available on the relationship between acute appendicitis and inflammatory parameters. In addition, McGowan *et al* demonstrated that CRP (>34.6 mg/L) and hyperbilirubinemia (plasma level >1.26 mg/dL) were higher in perforated appendicitis. Furthermore, in the investigation of CRP and bilirubin for predicting perforation by Kaser *et al*, CRP (>50 mg/L) appeared to be superior to bilirubin. The results of the present study correspond well with those observed in the earlier studies, indicating that the CRP level (>17.23 mg/L) was higher in the surgical treatment group than in the conservative management group.

To the best of our knowledge, this is the first report on the relationship between NLCR and acute colonic diverticulitis. The studies by McGowan *et al* and Kaser *et al* did not consider NLCR as a biomarker in the treatment of acute diverticulitis. Since NLCR was introduced by Goodman *et al*.[7] in an investigation of the prediction parameters for acute appendicitis, there has been a great deal of useful research on NLCR as a prognostic marker of oncological, cardiovascular, and infectious diseases.[18,19] However, no reports evaluating NLCR as a diagnostic tools for acute diverticulitis have been published. In our study, NLCR was correlated with the severity of acute colonic diverticulitis, and it was found to be superior to traditional infection markers.

However, the reason for the association of NLCR with severity of acute colonic diverticulitis remains unclear. Neutrophilia is characterized by a high inflammatory response and suppressed immune cells, such as lymphocytes, activated T cells, and natural killer cells.[20] NLCR could represent an inflammatory condition.[21] Because NLCR can be easily calculated on admission to the emergency or surgical outpatient departments, previous studies reported NLCR as being associated with severe infectious diseases. High NLCRs were revealed to

be more strongly associated with bacteremia than other inflammatory markers in the study by de Jager *et al*.[6] In addition, Loonen *et al*[22] suggested that NLCR is useful to rapidly determine bloodstream infections in emergency care units.

Several other conditions, such as metabolic syndrome and hypertension, as well as medication use, could influence the NLCR calculation. Thus, NLCR needs to be carefully interpreted in emergency and surgical departments.[23–25] However, the present study had some limitations because of its small sample size and retrospective nature. In addition, we included patients who were treated for short periods, resulting in selection bias. Despite these limitations, we believe that our findings will help determine the accurate treatment methods for acute colonic diverticulitis patients in emergency and surgical departments. Early diagnosis could ensure prompt surgical interventions for severe acute diverticulitis patients, resulting in better treatment outcomes.

In conclusion, NLCR >10.21, CRP level >17.23 mg/L, and albumin level ≤3.5 mg/dL were significantly associated with acute colonic diverticulitis, considering that NLCR was a powerful predictive marker for the treatment of acute colonic diverticulitis. Thus, NLCR can be easily assessed and included as a diagnostic tool for assessing the severity of acute colonic diverticulitis.

Acknowledgments

Conflict of interest: Drs Kim TH, Moon T, Yoon J, Park SS, Jang YS, Lee KB, Jung JW, Kwon YJ, Lee S, and Cho DH have no conflict of interest or financial ties to disclose.

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