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Original Contribution

Is the neutrophil-to-lymphocyte ratio a potential diagnostic marker for peptic ulcer perforation? A retrospective cohort study

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ABSTRACT

Objectives: Peptic ulcer perforation (PUP) accounts for 5% of all abdominal emergencies and is recognized as a gastrointestinal emergency requiring rapid and efficient clinical evaluation and treatment. The mortality rate ranges from 10% to 40% among patients with perforation. In the present retrospective study, we examined the potential utility of the neutrophil-to-lymphocyte ratio (NLR) in early diagnosis of PUP; we asked whether this ratio allowed PUP and peptic ulcer disease to be distinguished.
Methods: We enrolled the following patients: 58 with PUP, 62 with noncomplicated peptic ulcer diseases (NCPU), and 62 controls, between May 2010 and 2015. Patients who underwent surgical repair to treat PUP were included in the study group. Another group consisted of NCPU patients who had a noncomplicated peptic ulcer. The control group consisted of patients presenting with nonspecific abdominal pain to the emergency department.
Results: The mortality rate was 5.2% in the PUP group. The white blood cell count, C-reactive protein, and NLRs were higher in the PUP compared to the other groups ($P < .001$ for all). The white blood cell count and NLR did not differ between the NCPU and control groups. The sensitivities, specificities, positive predictive values, and negative predictive values of the NLRs were 68.0%, 88.0%, 82.9%, and 72.9%, respectively.
Conclusions: We suggest that preoperative NLR aids in the diagnosis of PUP and can be used to distinguish this condition from peptic ulcer disease. Thus, the NLR should be calculated in addition to the clinical examination.

1. Introduction

Peptic ulcer disease (PUD), one of the most common gastrointestinal disorders, affects 4 million people annually worldwide [1]. Despite our advanced understanding of the multifactorial etiology of PUD, life-threatening complications, including hemorrhage or perforation, occur in a significant proportion of patients [2]. Peptic ulcer perforation (PUP) is the most serious complication associated with PUD, accounting for 5% of all abdominal emergencies [3]. The mortality rate ranges from 10% to 40% among patients with perforation, which is 10-fold higher compared to other abdominal emergencies such as acute appendicitis and acute cholecystitis [4,5].

Currently, there is no criterion standard for the diagnosis of PUP, and patient history is the most important contributor to determining this diagnosis. Indeed, diagnosing the condition is very difficult in patients with no previous history of PUD. However, the sudden onset of severe abdominal pain, vomiting, shock, and classical signs of peritonitis, such as the presence of defense and rebound in a patient with a previous history of PUD, suggests a diagnosis of perforation [6].

The optimal treatment of PUP is surgery. Delay in diagnosis and surgical treatment is associated with high morbidity and mortality, and early recognition accompanied by aggressive resuscitation and early surgical intervention will clearly help to maintain low morbidity and mortality [6,7].

Gastric colonization with *Helicobacter pylori* results in peptic ulcers, and the outcome of infection is dependent on reciprocal interactions between bacterial pathogenic factors and the host response [8]. Several studies have indicated a positive association between coronary heart disease and *H pylori* and have demonstrated that the mechanisms of this relationship are an induction of dyslipidemic alterations; fibrinogen elevation; induction of inflammatory parameters, such as C-reactive protein (CRP), and white blood cells (WBCs); and an induction of hypercoagulability [9,10]. In addition, an acute inflammatory response and consequent mucosal damage occur in many cases of perforation [11,12].

To predict the prognosis of inflammatory diseases, several inflammation-based scoring systems have been suggested, including the platelet-to-lymphocyte ratio, prognostic nutritional index, and neutrophil-to-lymphocyte ratio (NLR) [13]. The NLR, derived from

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counts of circulating neutrophils and lymphocytes, has received great interest because it can be measured noninvasively, is easily detected in peripheral blood, and does not require additional cost.

Recent studies have focused on such materials because early and accurate detection of inflammation is essential to optimizing the treatment and prognosis of patients with medical emergencies [14]. Several biomarkers, such as CRP, procalcitonin, and mean platelet volume (MPV), have been used as indicators of inflammation. Neutrophilia develops during inflammation and is triggered by the release of arachidonic acid metabolites and platelet activation. Such stress induces relative lymphopenia. Thus, NLR accurately reflects underlying inflammatory processes. Although several studies have explored the utility of the NLR in the diagnosis and prognosis of inflammatory and malignant diseases, there has been no study to date that applies the NLR to diagnose peptic ulcer [15,16]. In the present study, we evaluated the diagnostic utility of the NLR compared to traditional parameters in patients with peptic ulcer perforation.

2. Methods

2.1. Study groups and study design

This was a retrospective, cross-sectional study approved by our local ethics committee. We enrolled 58 patients with PUP, 62 patients with noncomplicated peptic ulcer diseases (NCPU), and 62 control patients. All patients were enrolled between 1 May 2010 and 30 April 2015. Archived and electronically stored records were accessed. Prestudy power analysis showed that the chosen sample size afforded a power of 0.9 for achievement of a 95% confidence interval.

Patients were divided into 3 groups: PUP, NCPU, and controls.

1. PUP group: Patients who underwent surgical repair to treat PUP were included in this group. Diagnosis of patients with suspected peptic ulcer perforation according to the clinical (presence of defense and rebound), radiologic (presence of subdiaphragmatic free air), and laboratory evaluation (presence of high inflammatory parameters) were confirmed using abdominal tomography. Intraoperative assessment was performed for a definitive diagnosis. Intraoperatively, patients without PUP were excluded from the study.
2. NCPU group: Patients who had a noncomplicated peptic ulcer were included in this group. These patients were recruited from the gastroenterology clinic. Endoscopic evaluation was performed in all patients. Patients who were diagnosed for peptic ulcer in endoscopic evaluation and histopathologically confirmed were included in this study.
3. Control group: This group consisted of patients presenting with abdominal pain to the emergency department. These patients had only nonspecific and colicky abdominal pain, and the laboratory and radiologic findings of patients in this group were normal. In addition, these patients did not have additional comorbid disease.

2.2. Complete blood count and biochemical analysis

All biochemical tests and complete blood counts (CBCs) (on venous blood) were automated. Complete blood count data obtained from all 3 hospitals were similar to the recognized international norms. White blood cell counts, MPVs, and red cell distribution widths (RDWs) were evaluated. Neutrophil-to-lymphocyte ratios were calculated. The normal values of all parameters were the reference figures accepted by hematology laboratories nationwide.

2.3. Statistical analysis

All statistical analyses were performed using SPSS version 19.0 software (SPSS, Inc, Chicago, IL). The data distribution was evaluated using the Kolmogorov-Smirnov test. Continuous variables are expressed as the mean ± SDs, and categorical variables are expressed as frequencies (percentages). The significance of each difference between continuous variables was examined using the independent-samples *t* test or the Mann-Whitney *U* test. The significance of each difference between categorical variables was compared using Pearson χ^2 test. Receiver operating characteristic (ROC) curve analysis was used to define the optimal cutoffs of the NLR and RDW, for which specificities, sensitivities, positive and negative predictive values, and overall accuracies were calculated. Youden index was used to optimize the accuracies of all calculations. $P < .05$ was considered to reflect statistical significance.

3. Results

We enrolled 58 PUP, 62 NCPU, and 62 control patients. The mean patient age did not differ significantly among groups, which were 48.06, 52.04, and 55.28 years, respectively. Of the PUP patients, 13 (26.0%) were female and 37 (74.0%) were male; 28 (56.0%) NCPU patients were female and 22 (44.0%) were male; and 32 (64.0%) control patients were female and 18 (36%) were male. The mortality rate was 5.17% (3 patients) in the PUP group.

The WBC counts, CRP levels, RDWs, MPVs, and NLRs are shown in Table 1. The WBC count, CRP level, and NLRs were significantly higher in the PUP compared to other groups ($P < .001$ for all). Although the WBC and NLR did not differ between the NCPU and the control groups, the CRP in the NCPU was significantly higher in the control group ($P = .022$).

The sensitivities and specificities of the CRP levels and CBC data used to distinguish control and PUP patients and ROC data on WBC counts, CRP, and NLRs are shown in Table 2 and Fig. 1. The sensitivities, specificities, positive predictive values (PPVs), and negative predictive values (NPVs) of the NLRs were 68.0%, 88.0%, 82.9%, and 72.9%, respectively. Receiver operating characteristic curve analysis showed that the cutoff values for the WBC count, CRP level, MPV, and NLR yielded the best sensitivities and specificities, which were 11.22 × 109/L (56%-96%), 1.10 mg/dL (66%-98%), 9.10 f. (46%-70%), and 5.45 (68%-88%), respectively. The areas under the curves for the WBC count, CRP, and NLR were 78.8%, 85.1%, and 82.8%, respectively.

The sensitivities and specificities of the CRP levels and CBC data used to distinguish the NCPU and PUP patients and ROC data on WBC counts, CRP, and NLRs are shown in Table 3 and Fig. 2. The sensitivities, specificities, PPVs, and NPVs of the NLRs were 68.0%, 86.0%, 82.9%, and 72.9%, respectively. Receiver operating characteristic curve analysis showed that the cutoff values for the WBC count, CRP level, MPV, and NLR yielded the best sensitivities and specificities, which were 9.03 × 109/L (80%-80%), 3.20 mg/dL (52%-94%), 8.8 f. (52%-70%), and 4.72 (68%-86%), respectively. The areas under the curves for the WBC count, MPV, and NLR, were 81.3%, 75.6%, and 82.2, respectively.

4. Discussion

We found that the NLR was highly sensitive and specific when used to identify patients with PUP. Because delaying the diagnosis and treatment of patients with PUP is life threatening, the differential diagnosis of PUP must be rapid.

Table 1
Laboratory data from all groups

	PUP, n = 58	NCPU, n = 62	Control, n = 62
WBC ($\times 10^9$/L)	12.70 (2.28-28.34)[a]	7.43 (3.68-13.55)	8.12 (4.15-12.20)
CRP (mg/dL)	3.40 (0-32.60)[a]	0.55 (0-4.80)[b]	0.20 (0-2.11)
RDW (%)	13.10 (11.10-45.60)	13.30 (6.70-33.10)	13.20 (11.60-34.60)
MPV (fL)	8.95 ± 1.08	9.39 ± 0.96[c]	8.72 ± 0.96
NLR	8.99 (1.14-43.05)[a]	2.39 (0.87-13.11)	2.75 (1.12-12.28)

[a] $P < .001$ vs noncomplicated peptic ulcer and control.
[b] $P = .022$ vs control.
[c] $P = .001$ vs control.