Kaohsiung Journal of Medical Sciences (2015) 31, 591—596

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ORIGINAL ARTICLE

Predictive role of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios for diagnosis of acute appendicitis during pregnancy

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Received 27 July 2015; accepted 29 September 2015
Available online 18 November 2015

KEYWORDS
Acute appendicitis;
Alvarado scores;
Neutrophil-to-lymphocyte ratio;
Platelet-to-lymphocyte ratio;
Pregnancy

Abstract Acute appendicitis (AA) is not uncommon during pregnancy but can be difficult to diagnose. This study evaluated the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in addition to conventional diagnostic indicators of the disease to diagnose AA during pregnancy. Age, gestational age, white blood cell (WBC) count, Alvarado scores, C-reactive protein (CRP), lymphocyte count, NLR and PLR were compared among 28 pregnant women who underwent surgery for AA, 35 pregnant women wrongly suspected as having AA, 29 healthy pregnant women, and 30 nonpregnant healthy women. Mean WBC counts and CRP levels were higher in women with proven AA than in those of control groups (all $p < 0.05$). Among all the groups, the median NLR and PLR were significantly different in women with proven AA (all $p < 0.05$). Receiver operating characteristic analysis was used to determine cut-off values for WBC count, CRP, lymphocyte count, NLR and PLR, and multiple logistic regression analysis showed that NLR and PLR used with routine methods could diagnose AA with 90.5% accuracy. Used in addition to routine diagnostic methods, NLR and PLR increased the accuracy of the diagnosis of AA in pregnant women.

Conflicts of interest: All authors declare no conflicts of interest.
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http://dx.doi.org/10.1016/j.kjms.2015.10.005
1607-551X/

Introduction

Acute appendicitis (AA) is the most common general surgery emergency. It is also the most common nonobstetric/non-gynecological surgical emergency in pregnant women with a reported incidence ranging from 1 in 766 to 1 in 1440 pregnancies [1]. Although reports vary, the incidence of AA appears to increase in the second trimester [2,3]. Diagnosis of AA in pregnancy is challenging because symptoms of nausea, vomiting, and abdominal pain can be difficult to distinguish from pregnancy-related symptoms. In addition, the use of imaging modalities is limited during pregnancy. Importantly, delays in diagnosis because of these difficulties may place both the mother and fetus at risk, potentially leading to abortion or preterm delivery [4].

Although there is no specific laboratory parameter for AA, the white blood cell (WBC) count and C-reactive protein (CRP) level are commonly used in the diagnosis of AA [5]. However, physiological leukocytosis occurs in pregnancy, and the WBC count increases with gestational week to reach a peak during labor. Therefore, an increased WBC count is not a specific parameter for the diagnosis of AA in pregnancy [5,6]. The level of CRP, an acute phase reactant, increases in many inflammatory conditions and can be used in the diagnosis of AA [7]; however, the CRP level may also be increased in healthy pregnant women [8]. Ultrasonography is the most frequently used imaging modality to diagnose AA, but the appendix may be difficult to visualize in pregnancy because of anatomical changes [6]. Magnetic resonance imaging (MRI) and computed tomography (CT) are of limited use in pregnancy because MRI is not widely available and CT involves exposure to ionizing radiation [6,9]. The Alvarado scoring system, first described in 1986 [10] and based on clinical and laboratory data, is recommended for use in the diagnosis of AA. However, the findings of a recent prospective study indicated that the Alvarado scoring system alone is not sufficient to accurately diagnose AA [11].

Neutrophils are the most abundant WBCs and are important cells in the immune defense system. They also regulate other cells, including mast cells, epithelial cells and macrophages, and play an active role in inflammatory events. Changes in the neutrophil-to-lymphocyte ratio (NLR) can be an early sign of bacterial and viral infections. Another parameter that has been used in the diagnosis of infection is the platelet-to-lymphocyte ratio (PLR) [12]. Platelets are cells that help in modulating various inflammatory conditions; therefore, changes in PLR may be a useful indicator of acute infection, including AA.

Although AA is the most common infection requiring emergency surgery, accurate and timely diagnosis is potentially challenging. Unnecessary or delayed surgery is of particular concern in patients suspected as having AA. The situation becomes even more challenging and complex in pregnant women presenting with AA symptoms. Therefore, the aim of this study was to assess the use of NLR and PLR in combination with conventional methods to facilitate accurate and timely diagnosis of AA in pregnant women.

Materials and methods

This retrospective study included 78 pregnant women admitted to our clinic between January 2005 and January 2015 suspected as having AA. Of these, 36 women with confirmed AA underwent surgery (the appendectomy group). Forty-two patients were found not to have AA and did not proceed to surgery (the expectant group). The study controls included 29 pregnant women who presented to our clinic for routine examinations during the same period (the healthy pregnant control group) and 30 nonpregnant women who presented to our polyclinic with breast pain during the same period but had no pathology on examination (the healthy women control group).

Exclusion criteria included the following: hematological disorders; chronic liver or kidney disease; chronic obstructive pulmonary disease; asthma; any viral, bacterial or parasitic infection; cancer or autoimmune disease; and history of smoking and/or alcohol consumption. Patients with incomplete records were also excluded. Based on these criteria, eight of the 36 patients in the appendectomy group were excluded: four had systemic diseases (hypertension in two patients, chronic obstructive pulmonary disease in one patient and diabetes mellitus in one patient), one patient had incomplete records and three patients had no histology results to confirm the diagnosis of AA. The remaining 28 patients in the appendectomy group were included in the analysis. Seven of the 42 patients in the expectant group were excluded: two had diabetes mellitus, one had asthma, two were smokers, one had hypertension, and one had tonsillopharyngitis. The remaining 35 patients in the expectant group were included in the analysis. Age, gestational age, WBC count, lymphocyte count, Alvarado score, CRP levels, NLR, and PLR were recorded for patients in the appendectomy and expectant groups. All parameters except the Alvarado score and CRP were recorded for patients in the healthy pregnant and healthy women control groups. The scientific research ethics committee of the Kahramanmaraş Sütçü İmam University Medical Faculty approved the study protocol.

All statistical analysis was performed using SPSS 22.0 software (IBM Corporation, Armonk, NY, USA). The Shapiro–Wilk test was used to determine the compliance of the data to a normal distribution, and the Levene test was used to determine the homogeneity of variances among the groups. The independent samples *t* test with bootstrap results was used to compare two independent groups, whereas the Mann–Whitney *U* test was used with the Monte Carlo simulation technique. One-way analysis of variance (robust test: Brown–Forsythe) was used together with bootstrap results to compare more than two groups with other groups. The Kruskal–Wallis *H* test, least-significant differences and Games–Howell tests were used for *post hoc* analysis. Correlation between classification of the patient groups separated by cut-off values was calculated according to the variables, and real classification was expressed by examination of sensitivity and specificity using receiver operating characteristic (ROC) curve analysis. A logistic regression test was used to define the cause–effect relationship of the categorical response variable with explanatory variables in binomial and multinomial categories. Quantitative data are expressed as mean $\pm$ standard deviation, median $\pm$ interquartile range, or median and range (maximum–minimum). Categorical data are expressed as *n* (number) or percentage (%). Data were analyzed at a 95% confidence interval, and statistical significance was set at $p < 0.05$.

Results

Results of the comparisons among the four groups are shown in Table 1. There was no significant difference among the four groups for mean age ($p = 0.128$) or mean gestational age ($p = 0.295$), and there was no significant difference between the appendectomy and expectant groups for mean Alvarado score ($p = 0.562$). However, the median CRP level was significantly higher in the appendectomy group compared with the expectant group ($p < 0.001$). The mean WBC count was significantly higher in the appendectomy group compared with the other three groups combined ($p < 0.001$), and compared with the expectant, healthy pregnant control and healthy women control groups (all $p < 0.05$). The mean WBC count in the expectant group was significantly higher compared with the healthy pregnant control and healthy women control groups (both $p < 0.05$), and the mean WBC count was significantly higher in the healthy pregnant control group compared with the healthy women control group ($p < 0.05$).

The mean lymphocyte count was significantly lower in the appendectomy group compared with the other three groups combined ($p < 0.001$) and compared with the expectant, healthy pregnant control and healthy women control groups (all $p < 0.05$). The mean lymphocyte count in the expectant group was significantly lower compared with the healthy pregnant control and healthy women control groups (both $p < 0.05$). There was no significant difference between the healthy pregnant control group and the healthy women control group ($p > 0.05$). There was no difference in platelet count among the four groups ($p = 0.366$).

The median NLR was significantly higher in the appendectomy group compared with each of the other three groups (all $p < 0.05$). In addition, the median NLR in the healthy women control group was significantly lower compared with the expectant and healthy pregnant control groups (both $p < 0.05$). The median PLR was significantly higher in the appendectomy group compared with each of the other three groups (all $p < 0.05$). In addition, the median PLR in the healthy women control group was significantly lower compared with the expectant and healthy pregnant control groups (both $p < 0.05$).

Cut-off values calculated using ROC analysis are shown in Table 2. For the diagnosis of AA, a WBC count >13,880 cells/μL had 57.1% sensitivity and 82.9% specificity, a CRP level >10.1 mg/L had 85.7% sensitivity and 88.6% specificity, and a lymphocyte count <1540 cells/μL had 75% sensitivity and 68.6% specificity. An NLR >6.84 had 78.6% sensitivity and 80% specificity for the diagnosis of AA, and a PLR >121.78 had 100% sensitivity and 42.9% specificity.

The results of the multiple logistic regression analysis are shown in Table 3. The WBC count, CRP level, and lymphocyte count were significant independent predictors of a diagnosis of AA. The model had an explanatory power of 75.5%, and using the cut-off values of these five parameters, a diagnosis of AA could be established with 90.5% accuracy.

Discussion

In pregnant women, appendectomy is the most common surgical procedure after gynecological/obstetric procedures [1–4]. Unnecessary laparotomies are performed in 8–10% of cases because of atypical presentations during

Table 1 Comparison of age, gestation, C-reactive protein level, Alvarado scores, white blood cell count, lymphocyte count, platelet count, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio among the four study groups.

	Appendectomy group (*n* = 28)	Expectant group (*n* = 35)	Healthy pregnant control group (*n* = 29)	Healthy women control group (*n* = 30)	*p*
Age (y)*	26.93 ± 5.86	28.80 ± 6.70	29.62 ± 6.51	30.93 ± 6.84	0.128
Gestation (wk)*	22.43 ± 8.32	24.46 ± 7.98	21.45 ± 7.19		0.295
CRP (mg/L)**	26.65 (178–3.3)	3.46 (183–2.21)			<0.001
Alvarado score**	7 (9–5)	7 (8–6)			0.562
WBC (K/μL)*	13,768.57 ± 3.443.76 [a–c]	12,352.29 ± 3467.90[b,c]	10,762.76 ± 1513.96[c]	7850.33 ± 1626.96	<0.001
Lymphocyte count (K/μL)*	1.30 ± 0.38[a–c]	1.69 ± 0.49[b,c]	1.96 ± 0.51	2.25 ± 0.63	<0.001
Platelet (K/μL)*	234.43 ± 24.64	250.80 ± 61.06	253.93 ± 78.81	232.83 ± 53.55	0.366
NLR**	8.99 (26.28–2.98)[a–c]	4.86 (8.94–1.30)	3.89 (7.82–1.80)	2.12 (5.79–0.93)[a,b]	<0.001
PLR**	172.08 (917.86–122.75)[a–c]	138.16 (881.82–82.94)	132.35 (262.63–58.23)	92.78 (282.79–58.90)[a,b]	<0.001

Mann–Whitney *U* test (Monte Carlo)—one-way ANOVA (Brown–Forsythe)—(Bootstrap).
Post hoc test: LSD (Least Significant Difference)-Games Howell.
Kruskal–Wallis test.
Post hoc test (Monte Carlo): nonparametric *post hoc* test (Miller, 1966).
* Mean ± standard deviation.
** Median (range, maximum–minimum).
CRP = C-reactive protein; WBC = white blood cells.
[a] $p < 0.05$, compared with the expectant group.
[b] $p < 0.05$, compared with the healthy pregnant group.
[c] $p < 0.05$, compared with the healthy patients group.

Table 2 Sensitivity and specificity of white blood cell count, C-reactive protein level, lymphocyte count, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio cut-off values to diagnose acute appendicitis in pregnant women, based on the area under the receiver operating characteristic curve.

Parameters (cut-off)	Expectant group (n = 35)	Appendectomy group (n = 28)	Accuracy rate	AUC ± SE	p
WBC (K/μL) ≤ 138,800	29 (82.9)[a]	12 (42.9)		0.661 ± 0.074	0.030
WBC (K/μL) > 138,800	6 (17.1)	16 (57.1)[b]	71.4%		
CRP (mg/L) ≤ 10.1	31 (88.6)[a]	4 (14.3)		0.876 ± 0.048	<0.001
CRP (mg/L) > 10.1	4 (11.4)	24 (85.7)[b]	87.3%		
Lymphocyte count (K/μL) > 1.54	24 (68.6)[a]	7 (25)		0.743 ± 0.062	<0.001
Lymphocyte count (K/μL) ≤ 1.54	11 (31.4)	21 (75)[b]	71.4%		
NLR ≤ 6.84	28 (80)[a]	6 (21.4)		0.852 ± 0.049	<0.001
NLR > 6.84	7 (20)	22 (78.6)[b]	79.4%		
PLR ≤ 121.78	15 (42.9)[a]	0 (0)		0.712 ± 0.065	0.001
PLR > 121.78	20 (57.1)	28 (100)[b]	68.3%		

ROC curve analysis (Youden index J — Honley and McNell).
AUC = area under the receiver operating characteristic curve; CRP = C-reactive protein; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio; SE = standard error; WBC = white blood cells.
[a] Specificity.
[b] Sensitivity.

pregnancy and because even in nonpregnant women, many diseases can cause pain in the right lower quadrant similar to that experienced in AA [9,11]. Erekson et al. [3] reported that the most common nonobstetric surgical procedure among 1969 pregnant women was appendectomy (44%), and major complications occurred in 5.8% and mortality in 0.25% of cases [3]. In their study of 3313 pregnant women with AA, McGory et al. [13] found a fetal loss rate of 20% in women with perforation. They also found an increased risk of fetal loss in women who underwent negative laparotomy (10% risk) compared with 4% for those who underwent uncomplicated appendectomy [13].

The accurate diagnosis of AA in pregnant women is particularly challenging because of the physiological, anatomical, and hormonal changes associated with pregnancy. Ultrasound scans can be difficult to interpret because of the displacement of the appendix and cecum secondary to enlargement of the uterus [4]. Furthermore, MRI is not always readily available in the emergency setting, and CT involves exposure to ionizing radiation [6,9]. Another factor that can complicate the diagnosis of AA is the physiological leukocytosis of pregnancy, which increases with gestational age [5,6]. Although the small sample size of the present study limits the strength of the findings, there was a significant difference in the WBC count between the healthy pregnant control and healthy women control groups. The WBC count was also higher in the expectant group than in the two control groups but was significantly lower compared with that in the appendectomy group.

The level of CRP, an acute phase reactant that is synthesized in the liver and released into the circulation, is a useful parameter to diagnose and monitor acute and chronic inflammatory conditions [1]. However, a high CRP is not specific for AA in pregnant women but can be useful to support the diagnosis when AA is suspected [1]. In the present study, CRP levels were significantly higher in the appendectomy group compared with those in the expectant group. An Alvarado score of 7 or higher is suggestive of a diagnosis of AA [10]. In a study comparing Alvarado score, CT findings and pathology outcomes in 143 patients suspected as having AA, the condition was confirmed by CT in 51 of 55 patients with an Alvarado score of 8—10, and AA was histopathologically verified in 50 of those 51 patients.

Table 3 Results of the multiple logistic regression analysis of white blood cell count, C-reactive protein level, lymphocyte count, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio to determine independent predictors of acute appendicitis in pregnant women.

Independent variables	B ± SE	p	Odds ratio (95% CI)
WBC	0.138 ± 1.147	0.904	1.15 (0.12—10.86)
CRP	3.573 ± 1.074	0.001	35.61 (4.34—291.98)
Lymphocyte count	0.094 ± 0.971	0.923	1.10 (0.16—7.37)
NLR	0.772 ± 1.147	0.501	2.16 (0.23—20.48)
Constant	−2.774 ± 1.164	0.017	0.06
Dependent variable: groups	Nagelkerke R^2 = 0.755	Predicted (%): 90.5	$p < 0.001$

Multiple logistic regression (method = enter).
B = the set of coefficients estimated for the model; CI = confidence interval; CRP = C-reactive protein; NLR = neutrophil-to-lymphocyte ratio; SE = standard error; WBC = white blood cells.

However, five patients with Alvarado scores greater than 8 had normal pathology [14]. Although use of the Alvarado score alone can result in false-negative and false-positive diagnoses of AA, it provides valuable information for surgeons who have to work with limited facilities or imaging resources [14]. The present study was the first to assess the use of the Alvarado score in pregnant women. There was no significant difference between the appendectomy and expectant groups, which may reflect the physiological changes of pregnancy. Many of the parameters used to generate the Alvarado score could be affected by the enlargement of the uterus with the progression of gestational age, limiting the use of this score to diagnose AA in pregnant women with abdominal pain.

Neutrophils are very important cells in the immune defense system, are potent regulators of mast cells, epithelial cells and macrophages, and play an active role in inflammatory events. Changes in NLR are observed early in the course of bacterial and viral infections. PLR has also been used to investigate acute infection [12]. Given that platelets are helper cells in the modulation of various inflammatory conditions, changes in PLR might also be useful for the diagnosis of AA. Therefore, the main aim of the present study was to investigate the use of NLR and PLR as safe and readily available tests for the early diagnosis of AA in pregnant women. The values used were based on recently reported results for studies of NLR and PLR in a number of different inflammatory conditions [15—18].

In a study of patients with pulmonary embolism, the red cell distribution width and NLR and PLR were increased relative to controls [15]. However, the authors concluded that the diagnostic value of these parameters alone was low and recommended using them combined with imaging studies and other laboratory tests [15]. Another study found that patients having tuberculosis had a higher NLR compared with patients having sarcoidosis [17]. Azab et al. [17] reported that NLR with a cut-off value of >4.7 was a simple and effective parameter to evaluate the severity of acute pancreatitis [17]. Conversely, in a study of patients having brucellosis, Olt et al. [18] found no significant difference between affected patients and controls for PLR, but NLR was significantly lower compared with controls.

İlhan et al. [12] reported that NLR with a cut-off value of 4.1030 was a simple and effective parameter to determine the severity of acute pancreatitis in pregnant women. Interestingly, similar to Alvarado scoring system for AA in the present study, the Ranson scoring system for acute pancreatitis was not effective for pregnant women. The authors attributed this to the young age of the pregnant women relative to age >55 years that is one of the criteria in the Ranson scoring system [12]. The criteria used in the Alvarado scoring system such as nausea and vomiting and localization of pain between the epigastric area and the right lower quadrant could be modified for pregnant women. Further large-scale studies are needed to determine modifications of the Alvarado scoring system for use along with NLR to diagnose AA during pregnancy. The cut-off values for NLR and PLR calculated in the present study resulted in sensitivity of 78.6% and 100%, respectively and specificity of 80% and 42.9%, respectively. When NLR and PLR were combined with the WBC count, CRP level and lymphocyte count, an accurate diagnosis of AA could be established with 90.5% accuracy.

Limitations of the present study include the retrospective design and the small sample size, because of the relatively low incidence of AA in pregnancy.

In conclusion, to the best of our knowledge, this is the first study to evaluate the use of NLR and PLR to diagnose AA during pregnancy. It is also the first study to investigate the use of the Alvarado score to diagnose AA in pregnant women and to demonstrate that its use is limited during pregnancy. To protect the lives of both mothers and newborns it is essential to establish an early and accurate diagnosis of AA to ensure timely surgery and to avoid unnecessary laparotomy. Although NLR and PLR alone are not sufficiently specific for AA during pregnancy, they are valuable parameters when used in combination with the physical examination, laboratory analysis, imaging modalities, and scoring systems such as the Alvarado score.

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