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Utility of Immature Granulocyte Percentage in Pediatric Appendicitis

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Abstract

Background—Acute appendicitis is the most common cause of abdominal surgery in children. Adjuncts are utilized to help clinicians predict acute or perforated appendicitis, which may affect treatment decisions. Automated hematologic analyzers can perform more accurate automated differentials including immature granulocyte percentages (IG%). Elevated IG% has demonstrated improved accuracy for predicting sepsis in the neonatal population than traditional immature to total neutrophil count (I/T) ratios. We intended to assess the additional discriminatory ability of IG% to traditionally assessed parameters in the differentiation between acute and perforated appendicitis.

Materials and Methods—We identified all patients with appendicitis from July 2012 to June 2013 by ICD-9 code. Charts were reviewed for relevant demographic, clinical, and outcome data, which were compared between acute and perforated appendicitis groups using Fischer's exact and t-test for categorical and continuous variables, respectively. We utilized an adjusted logistic regression model utilizing clinical lab values to predict the odds of perforated appendicitis.

Results—251 patients were included in the analysis. Those with perforated appendicitis had a higher white blood cell (WBC) count ($p=0.0063$), C-reactive protein (CRP) ($p<0.0001$), and IG%

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($p=0.0299$). In the adjusted model, only elevated CRP (OR 3.46, 95% CI 1.40-8.54) and presence of left shift (OR 2.66, 95% CI 1.09-6.46) were significant predictors of perforated appendicitis. The c-statistic of the final model was 0.70, suggesting fair discriminatory ability in predicting perforated appendicitis.

Conclusions—IG% did not provide any additional benefit to elevated CRP and presence of left shift in the differentiation between acute and perforated appendicitis.

Keywords

appendicitis; pediatric; immature granulocyte percentage

Introduction

Appendicitis is the most common reason for abdominal surgery in children in the United States [1]. Over 80,000 appendectomies are performed each year for pediatric appendicitis [2]. Children have higher rates of perforated appendicitis as compared to adults, ranging from 22% to 52% depending on age and other variables [3]. Distinguishing acute from perforated appendicitis preoperatively may have a significant effect on the treatment plan. For acute appendicitis, treatment includes urgent appendectomy; however for complicated perforated appendicitis, many centers will administer intravenous antibiotics for a defined period followed by interval appendectomy [4]. Prior studies have shown that interval appendectomies assist in decreased hospitalization, complications, and cost when compared to the traditional emergency approach [5, 6].

Many papers have focused on preoperative laboratory parameters, which may improve diagnostic accuracy in distinguishing acute from perforated appendicitis in conjunction with imaging modalities. White blood cell (WBC) counts with a differential and C-reactive protein (CRP) levels are commonly obtained in children with suspected appendicitis. CRP has been shown to increase markedly after appendiceal perforation or abscess formation, making it a potential indicator of perforated appendicitis; however, WBC count is an early marker of appendiceal inflammation but cannot reliably distinguish acute from perforated appendicitis [7]. Recent literature has demonstrated that utilizing automated hematologic analyzer counts can more accurately determine immature granulocyte percentage (IG%) in comparison to manually derived “band” counts or differentials, which underestimate IG% at low counts [8]. Lack of immature granulocytes has been shown to have a high negative predictive value, particularly in neonatal sepsis [9]. The purpose of this study was to determine if IG% would add additional discriminatory ability, in conjunction with traditionally utilized laboratory values, in differentiation of acute and perforated appendicitis in a pediatric population.

Materials and Methods

After IRB approval (Protocol #: X130611004), pediatric patients (< 16 years of age) with appendicitis from July 2012 to June 2013 were identified by ICD-9 code, and a retrospective review was conducted. The following ICD-9 codes were included: appendicitis (541), appendicitis with perforation, peritonitis, or rupture (540.0), and acute appendicitis (540.9).

Hospital records were further reviewed to select patients with acute or perforated appendicitis. We excluded patients with other diagnosed inflammatory conditions or significant co-morbidities that might alter inflammatory markers. All operations were performed at Children's of Alabama. Perforated appendicitis was defined, based on previous studies, as the surgeon's interpretation based on operative findings, including a hole in the appendix, an intraabdominal fecalith, or an intraabdominal abscess [10]. Other variables were collected including demographic data (age, race, and gender) and laboratory values (white blood cell count, C-reactive protein, and presence of a left shift). IG% was determined by the Sysmex XE 2100 automated hematologic analyzer. The immature granulocyte measurement includes promyelocytes, myelocytes, and metamyelocytes, but not bands or blasts. This definition is consistent with previous studies [8, 9]. Detection of immature granulocytes by Sysmex XE-2100 has shown a sensitivity, specificity, and efficiency of 92%, 81%, and 83%, respectively [11]. Left shift, or neutrophilia, was considered present if neutrophils were greater than 75% of the white blood cell count, as described by a previous study [12]. Demographic and clinical characteristics were compared between acute and perforated appendicitis groups using Fischer's exact and t-test for categorical and continuous variables, respectively. Clinical laboratory variables were put into an adjusted logistic model to predict odds of perforated appendicitis.

Results

A total of 281 patients were initially identified based on ICD-9 codes. 30 patients were excluded from the analysis: 14 for appendectomy for reasons other than appendicitis, 13 for incomplete data, and 3 for other inflammatory diagnoses that might affect laboratory parameters. A total of 251 patients were included in the analysis: 168 with acute appendicitis (67%) and 83 with perforated appendicitis (33%). All patients included in the analysis underwent either immediate or interval appendectomy. Patient demographics are shown in Table 1. Collectively, the mean age was 11.1 years, and 62% were male. The majority of patients were Caucasian (52%). There were no significant differences in age, race, or sex between perforated and non-perforated groups.

Those with perforated appendicitis had higher mean WBC count ($p=0.0063$), CRP ($p<0.0001$), absolute neutrophil count (ANC) ($p=0.005$), and IG% ($p=0.0299$), as seen in Table 2. Additionally, those with perforated appendicitis were more likely to have a left shift present ($p=0.0146$). Clinical laboratory variables were put into an adjusted logistic model predicting odds of perforated appendicitis (Table 3). In the adjusted model, only elevated CRP (OR 3.46, 95% CI 1.40-8.54) and presence of left shift (OR 2.66, 95% CI 1.09-6.46) were significant predictors of perforated appendicitis. The c-statistic of the final model was 0.70, suggesting fair discriminatory ability of this model to predict perforated appendicitis.

Discussion

Appendicitis is the most common reason for abdominal surgery in children in the United States. Despite being such a common condition, the best biochemical markers to aid in the diagnosis of appendicitis are still under debate, especially when distinguishing acute and perforated appendicitis. Laboratory data reported to be associated with ruptured appendicitis

include elevated C-reactive protein, increased bands, elevated erythrocyte sedimentation rate, and increased total white blood cell count [13-16]. The reported sensitivities and specificities for these markers are highly variable and cannot be independently relied upon to accurately exclude, confirm, or differentiate between acute and perforated appendicitis [16-20]. The use of laboratory adjuncts alone is limited and should only be used as a guide, with the combination of the clinical history, physical exam, and imaging findings to form a complete clinical picture. We intended to evaluate the laboratory values that aided us the most in distinguishing acute versus perforated appendicitis in our pediatric patients and assessed whether IG% would add additional diagnostic benefit in this population.

Laboratory adjuncts most studied for diagnosis of appendicitis include white blood cell count, CRP, band count, and ANC. Most of these studies addressed utilization of laboratory values in differentiation of appendicitis from other common diagnoses leading to abdominal pain in children. Their results showed that values of CRP and white blood cell count were significantly higher in patients with definitive appendicitis. A CRP greater than 3 mg/dL in combination with white blood cell count above 12,000 cells/mm³ may distinguish appendicitis from other urgent pediatric diagnoses [21]. Additional studies support the prior study that CRP may be a useful addition to clinical and other laboratory data in diagnosing appendicitis [22, 23]. Although WBC counts are frequently ordered in children with suspected appendicitis, results are nonspecific and insensitive. One study found that leukocytosis (WBC >15,000 cells/mm³ if <10 years and >13,000 cells/mm³ if ≥ 10 years) was 18% sensitive for acute appendicitis in patients with symptoms present less than 24 hours, but 90% sensitive for those with symptoms present for more than 48 hours [24]. Some studies suggested that a combination of CRP with WBC or ANC may be useful in diagnosing appendicitis [25-28]. Other investigators have suggested that a normal WBC and CRP can exclude the diagnosis of acute appendicitis [7, 26].

Fewer studies have attempted to address the question of which laboratory values may help in differentiating acute versus perforated appendicitis in addition to the information obtained from clinical history and imaging. Beltran et al. assessed the predictive value of WBC count and CRP in children with appendicitis. They found that not only CRP levels, but also WBC count could aid in discrimination between acute and perforated appendicitis. While the specificity of WBC counts in distinguishing perforated appendicitis remained relatively constant from symptom onset to diagnosis, the sensitivity of WBC increased from symptom onset to diagnosis. However, the diagnostic accuracy declined from its peak (90%) at 12 hours as time from onset of symptoms increased. CRP level and its sensitivity also increased from the time of the onset of symptoms to diagnosis, and the specificity remained high (90%) at 12, 24, and 48 hours from onset of symptoms to diagnosis. However, as with WBC count, the diagnostic accuracy of CRP peaked at 12 hours but decreased significantly thereafter [16]. Willams et al. examined a pediatric population with abdominal pain that included those with abdominal pain that was not appendicitis, acute appendicitis, and perforated appendicitis. They developed a scoring system to potentially improve the accuracy of delineating perforated appendicitis preoperatively. The only laboratory value that generated points in their scoring system was a WBC >19,400. Although they did not examine CRP in their study, they did not find percentage of bands to be helpful in distinguishing these three diagnoses from one another [4]. In contrast, our data suggested

that CRP and presence of a left shift aided the most in discrimination of acute versus perforated appendicitis. Our model did not show that elevated WBC or elevated IG% added an additional benefit to CRP or presence of a left shift.

There are limited data assessing the utility of newer automated hematologic analyzers and the data they generate, such as immature granulocyte count and percentage. The presence of immature granulocytes in the peripheral blood of otherwise healthy individuals indicates substantially increased bone marrow activation as seen in infections and sepsis. Most of the studies examined its utility in predicting sepsis in adult and pediatric populations. In an adult study, Selig et al. found significantly elevated numbers of immature granulocytes in patients with bacterial infections compared with healthy controls [29]. An adult study found that IG% was a stronger correlate of infection and positive blood culture results than WBC count [30]. Although IG% has not been shown to be sensitive enough to be used as a screening tool, significantly increased IG% measurements (>0.3) have a specificity for sepsis greater than 90% [9, 30]. According to our findings, although there was a statistical difference between IG% in acute and perforated appendicitis, IG% was of no additional benefit for predicting perforated appendicitis in conjunction with CRP and presence of a left shift. This suggests that, although IG% has provided acceptable discrimination of those with sepsis in prior literature, it may not be sensitive enough to differentiate between those with variations of disease as in acute versus perforated appendicitis. To our knowledge, this is the first study available on IG% pertaining specifically to pediatric appendicitis.

Limitations of this study include the limited population size, lack of a control group, and retrospective nature. Automated differential information was not reliably recorded until July 2012, which restricted the study's population. Performing a retrospective study also limited the type and amount of information collected. All laboratory values recorded in the study were the earliest values documented in the patients' charts, but the time course from onset of symptoms to drawing of blood specimens was not consistent among patients, limiting our ability to predict sensitivity of these indicators at different time points in the disease process. Additionally, perforation was defined based on operative findings and therefore subject to the interpretations of multiple surgeons.

In conclusion, appendicitis is a common problem in the pediatric population, and rates of perforation are greater than in the adult population. Quick and reliable identification of perforation may decrease morbidity associated with perforated appendicitis; however, there is little evidence concerning the best means of predicting these cases. A combination of useful clinical laboratory markers, clinical history, physical exam, and imaging findings should allow us to accurately differentiate between acute and perforated appendicitis. In this study, we found that elevated CRP and presence of a left shift were reliable predictors of perforated appendicitis. However, IG% did not add any additional benefit in making the diagnosis.

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Table 1

Comparison of demographic characteristics of children with perforated and acute appendicitis

	Perforated (n=83)	Acute (n=168)	p-value*
DEMOGRAPHICS			
Mean age (years)	10.8 ± 3.7	11.3 ± 3.3	0.2273
Race (%)			
Caucasian	55 (66.3)	127 (75.6)	0.3574
African American	17 (20.5)	24 (14.3)	
Hispanic	11 (13.3)	16 (9.5)	
Asian	0 (0.0)	1 (0.6)	
Sex (%)			
Male	51 (61.5)	104 (61.9)	1.0000
Female	32 (38.6)	64 (38.1)	

* Based on Fisher's exact chi-square and t-test for categorical and continuous variables, respectively

Table 2

Comparison of clinical characteristics of children with perforated and acute appendicitis

	Perforated (n=83)	Acute (n=168)	p-value*
CLINICAL			
WBC count	16.7 ± 6.4	14.4 ± 5.2	0.0063
CRP	11.7 ± 10.4	2.8 ± 3.4	<0.0001
Absolute Neutrophil Count	13.4 ± 5.3	11.3 ± 5.4	0.005
IG % (normal <0.3)	0.34 ± 0.14	0.29 ± 0.19	0.0299
Left shift present (%)	59 (78.7)	89 (61.8)	0.0146

* Based on Fisher's exact chi-square and t-test for categorical and continuous variables, respectively

Table 3

Clinical predictors of perforated appendicitis

	OR* (95% CI)
Elevated WBC count	0.80 (0.34-1.84)
Elevated CRP	3.46 (1.40-8.54)
Elevated IG %	1.73 (0.77-3.91)
Left shift present	2.66 (1.09-6.46)

C = 0.70

* Adjusted for other variables in table