COMPARISON OF MANUAL AND AUTOMATED BLOOD CELL COUNTS IN THE DIAGNOSIS OF PEDIATRIC APPENDICITIS

by

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STATEMENT OF THESIS APPROVAL

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ABSTRACT

Children with appendicitis present with nonspecific symptoms such as abdominal pain, fever, and vomiting. Clinicians utilize clinical findings, and laboratory and imaging tests to determine the likelihood of appendicitis. A complete blood count (CBC) with manual differential is ordered to determine if the patient has an increased number of white blood cells (WBCs) or immature WBCs present in the peripheral blood (known as a left shift). Leukocytosis (WBC count >10,000/uL), left shifted differential, elevated band count, and neutrophilia >75% are used to risk-stratify patients with suspected appendicitis. Immature granulocyte percentage (IG%) is an alternative measurement of left shift. The IG% can be obtained from an automated differential, which is faster, more reproducible, and less subject to sampling error.

A cohort definition was used to compile data including patients who presented with a chief complaint of abdominal pain, and patients who received an ultrasound of the appendix in the Primary Children's Hospital emergency department (ED). Data collected included patient age, WBC count and differential, IG%, and pathology report. A diagnosis of acute appendicitis was determined by the pathology reports. The sensitivity, specificity, and area under receiver operating characteristic curves (AUC) were determined for total WBC count (>10,000/μL), band count, IG%, and neutrophil percentage (>75%).

The total WBC count (>10,000/μL) showed the best predictive value with a sensitivity of 85.3%, specificity of 63.4%, and AUC of 80.1%. A neutrophil percentage >75% was also predictive of appendicitis with a sensitivity of 70.5%, specificity of 66.6%, and AUC of 73.4%. Band count showed no predictive value with an AUC of 57.7%. IG% was slightly more useful with a sensitivity of 68.5, specificity of 59.7%, and AUC of 66.7%.

The parameters obtained from a CBC with automated differential count: WBC count, neutrophil percentage, and IG%; were each more successful in correctly identifying pediatric patients with appendicitis than band count, which was not a reliable indicator and showed no added benefit in diagnosis. Eliminating the band count, and hence the need for a manual differential, could improve turn-around-time for patients presenting with abdominal pain without reducing the utility of the CBC.

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CHAPTER 1

INTRODUCTION

With over 60,000 cases per year in the United States and Canada, appendicitis is the most common reason for abdominal surgery in children[1–8]. Children with appendicitis are difficult to diagnose, as they present with nonspecific symptoms such as fever, abdominal pain, nausea, and vomiting[4,5,8,9]. Abdominal pain is a common complaint among children, and possible causes range from mild and transient to potentially life threatening[4,5,8]. The current practice of evaluating a patient with abdominal pain is lengthy and time consuming[5]. Suspected cases of appendicitis are evaluated using clinical findings, laboratory tests, ultrasound, and/or computed tomography (CT), which in some cases may be harmful to the patient[1,3–5,7,10].

Complications of Appendicitis

Delayed diagnosis of appendicitis can lead to perforation and peritonitis[2–5,11,12]. Appendiceal perforation occurs in as many as 30% of pediatric cases[5]. A delay of 36 hours or more increases perforation rates to as high as 65%[4]. There is a need for rapid and accurate diagnostic modalities that can be used to risk-stratify patients with acute abdominal pain.

Laboratory Utilization

Clinicians rely on laboratory tests, including white blood cell (WBC) count and differential, to rule out infection in patients presenting with acute abdominal pain[1–4,6,9,10,13–15]. In response to an infection, such as appendicitis, large numbers of segmented neutrophils and their more immature precursor cells (band neutrophils, metamyelocytes, and myelocytes) are mobilized[10]. Therefore, increased numbers of immature granulocytes in the peripheral blood, known as a "left shift", can be an indicator of possible infection[9,15].

Laboratory tests commonly ordered for pediatric abdominal pain patients can delay patient assessment and be unreliable for the diagnosis of appendicitis. Optimization of these laboratory assays could potentially reduce the number of complications as well as reduce the time and resources utilized in investigation of acute abdominal pain.

CHAPTER 2

PEDIATRIC APPENDICITIS: PRESENTATION AND DIAGNOSIS

Anatomic and Physiologic Significance

The vermiform appendix is a diverticulum of the cecum just beyond the junction of the small and large intestine[16,17]. It contains abundant lymphoid tissue that plays a role in mucosal immunity[16,18]. Appendicitis occurs when the appendix becomes obstructed by a fecalith (a firm fragment of undigested food), a foreign body, or tumor[17]. Inflammation begins in the mucosa and spreads into the wall of the appendix and causes edema, vasocongestion, inflammation, necrosis, and potential perforation[16].

Presentation and Differential Diagnosis

Patients with appendicitis present to the emergency department (ED) complaining of acute abdominal pain. Acute abdominal pain is not typically life-threatening and is most commonly caused by viral gastroenteritis or constipation[4,5,8]. However, some cases require emergent intervention, such as appendicitis or intestinal obstruction[4,8].

A clinician evaluating a patient with acute abdominal pain will obtain a medical history and perform a physical examination[2,4,8,9]. The medical history will include a description of the onset, progression, and location of symptoms[4,8]. Characteristic signs of appendicitis include periumbilical pain, that then localizes to the right lower quadrant (RLQ); anorexia; nausea; vomiting; and fever[2,4,5,8,9,17]. Cramping pain suggests intestinal

obstruction and diarrhea raises the question of gastroenteritis[4,8]. Diffuse pain may suggest gastroenteritis or mesenteric adenitis and lower abdominal pain is seen with constipation[4,8]. An abdominal examination is performed to determine the degree of tenderness, location of pain, and presence or absence of rebound tenderness[2,4,5,9].

The clinician may also perform imaging studies. Ultrasound and CT scan are commonly used to investigate the cause of abdominal pain[1,3–5,7,8,11]. While both methods offer advantages, they are costly and time consuming[1,4,5,8]. A CT scan also exposes the patient to potentially harmful ionizing radiation[1,4,5,7] and has been shown to have limited utility in children due to the absence of periappendiceal fat that facilitates visualization[1]. Ultrasound has fewer risks, but is known to be less accurate and operator dependent[1,4,7].

Laboratory Evaluation

The clinician will typically order a complete blood count (CBC) with differential, urinalysis, and chemistry tests to evaluate abdominal pain[2–4,7–9,11,13–15]. CBC and differential findings suggestive of appendicitis include leukocytosis, left shifted differential, and neutrophilia greater than 75%[2,6,11,14]. Urinalysis is necessary to rule out urinary tract infection or other urogenital complications[13]. Chemistry tests are used to assess fluid and electrolyte imbalances. C-reactive protein may also be ordered to assess inflammatory status[13].

Diagnostic Scoring Systems

Physicians may also use comprehensive diagnostic scoring systems such as the Alvarado score and pediatric appendicitis score (PAS)[3–5,7,12,13,19,20]. These scoring systems have some utility in diagnosing appendicitis, but both have been found to be

unreliable in some cases[3,7,12,13].

The Alvarado Score

The Alvarado score was published by Alfredo Alvarado in 1986[19]. It was based on a retrospective analysis of 305 patients who were hospitalized for abdominal pain[19]. Patient age ranged from 4 to 80 with a mean age of 25. Alvarado determined the sensitivity, specificity, joint probability (diagnostic effectiveness), and predictive value for the symptoms, signs, and findings commonly seen in appendicitis. He found correlation between a final diagnosis of appendicitis and the following observations:

- Symptoms:
    - Migration of pain, anorexia, and nausea/vomiting
- Physical signs:
    - Tenderness, rebound pain, and fever
- Laboratory findings:
    - Leukocytosis and left shift

Left shift was defined by Alvarado as a neutrophil percentage greater than 75% with no specification as to cell maturity[19]. This observation is more appropriately termed neutrophilia. Alvarado did not document findings of elevated band counts or other descriptions of granulocyte differentiation.

The findings that had good predictive value were assigned a diagnostic weight. Tenderness and leukocytosis were given a value of two, as they had the highest diagnostic weight[19]. A value of one was assigned to the remaining elements to reach a possible total score of ten[19]. In Alvarado's study, all patients with confirmed appendicitis had a mean score greater than seven, while the mean score for patients without

appendicitis was 5.24[19]. Therefore, a score of six was determined to be the diagnostic threshold[4,19]. A score less than six indicated that the patient should be re-evaluated after a period of observation[19].

The Pediatric Appendicitis Score

The pediatric appendicitis score (PAS) was a modification to the Alvarado score that was published in 2002[4,12]. It was developed by Madan Samuel from a prospective analysis of 1,170 children who were hospitalized for abdominal pain[12]. Patient age ranged from 4 to 15 with a mean age of 10[12].

As with the Alvarado score, clinical data as well as laboratory findings were evaluated for specificity, sensitivity, predictive value, and joint probability[12]. A diagnostic weight was determined to form a scoring system. A threshold score of six proved to be the most useful in maximizing the number of correct diagnoses and minimizing the rate of unnecessary operations[12].

The PAS focused more on symptoms and physical signs than the Alvarado score. Laboratory data used in the PAS included WBC count and left shift; however, physical findings were weighted more heavily than laboratory data[12]. The PAS did not use rebound pain in its evaluation because it caused pain to the patient and can be difficult to assess in children[4,12]. Percussion tenderness was substituted and found to have a higher diagnostic weight[12].

Limitations

The Alvarado score and PAS have major limitations in that neither system gives 100% diagnostic certainty[12,19]. Leukocytosis, fever, nausea, and abdominal pain are well

known to be present in a number of conditions[2,3,6,13–15]. Samuel claimed that the PAS was 100% sensitive and 92% specific with a positive predictive value of 96% and a negative predictive value of 99%[12]. The Alvarado score did not delineate its results in the same way, but did claim that with score >6 there was a 5.8% risk of potential perforations and with a score <6 there was a 8.7% risk of unnecessary surgeries[19].

A false positive diagnosis can result in unnecessary surgery and harm to the patient[1–4,12,13]. A false negative can delay diagnosis and escalate to perforation and peritonitis. Both false positives and false negatives can lead to a lengthened hospital stay, increase in cost to the patient, and prolonged recovery time[12].

CHAPTER 3

LABORATORY ROLE IN APPENDICITIS

Complete Blood Count and White Blood Cell Differential

A complete blood count (CBC) is a test that provides information about the quantity and type of cells present in the blood. A CBC includes WBC count, red blood cell (RBC) count, hemoglobin, hematocrit, RBC indices, and platelet count.

The WBC differential can measure the percentage of the various types of WBCs present in the blood including neutrophils, lymphocytes, monocytes, eosinophils, and basophils. The differential is also used to assess the morphology of WBCs, RBCs, and platelets.

Neutrophil Differentiation

Neutrophils are the cells of most interest to a physician evaluating a patient for suspected appendicitis. Neutrophils are cells of the innate immune system that are responsible for phagocytosis and activation of bactericidal mechanisms including inflammation[15,18]. During an infection, such as appendicitis, neutrophils increase in number and undergo a left shift[10,14,15]. A left shift can be determined from a manual differential or automated differential. A manual differential demonstrates a left shift by enumerating immature neutrophil forms, particularly bands, in the peripheral blood. An automated differential identifies left shift from the immature granulocyte percentage

(IG%) parameter.

Manual Differential

A manual WBC differential is performed using a Wright's stained peripheral blood smear. A trained medical laboratory scientist reviews the smear under a microscope on 1000 x magnification and classifies 100 WBCs[10,14,15,21,22]. Each cell encountered must be identified as a certain type of neutrophil, lymphocyte, monocyte, eosinophil, basophil, or blast. A manual differential provides additional information about granulocyte maturity. Neutrophils are subdivided into subtypes including segmented neutrophils, band neutrophils, metamyelocytes, myelocytes, and promyelocytes. A comparison of granulocyte subtypes observed during a left shift is given in Figure 3.1.

Segmented Neutrophil

The segmented neutrophil is 9-15 µm with a nucleus to cytoplasm (N:C) ratio of 1:4[23]. It can be identified by a segmented nucleus that has 2-5 distinct lobes connected by a thin filament of nuclear material[10,23,24]. The segmented neutrophil has a pink cytoplasm containing many small granules[23,24]. Segmented neutrophils are normally found in the peripheral blood and comprise 35-80% of leukocytes[23].

Band Neutrophil

The band neutrophil is 10-15 µm and has an N:C ratio of 1:2[10,23]. Bands have a well-defined nuclear indentation and a horseshoe shaped nucleus without segmentation[10,23]. The cytoplasm is pale pink and contains small primary and secondary granules[10,23]. Bands are fully functional and can normally be found in the peripheral

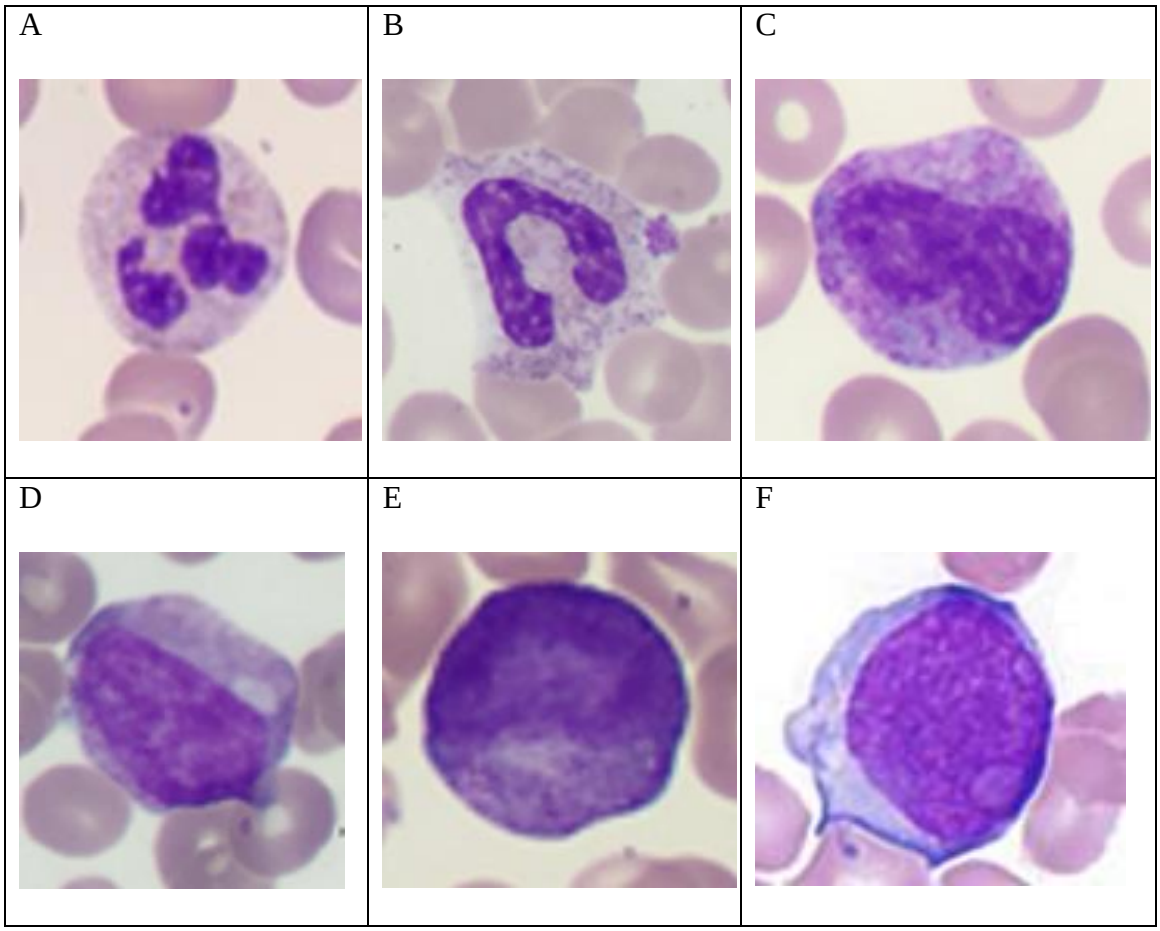

Figure 3.1 Granulocytes observed during left shift (Wright Stain) A) Segmented neutrophil, B) Band neutrophil, C) Metamyelocyte, D) Myelocyte, E) Promyelocyte, F) Blast

blood at a concentration of 0-5% of WBCs[10,23].

An elevated band neutrophil count (bandemia) has historically been used by clinicians in the ED as an indicator of when to perform appendectomy on suspected appendicitis patients[6,10,11,13,14]. Kogut et al. recommend appendectomy in appendicitis patients with a band count >15%[11].

Band counts have very poor reproducibility due both to sampling error on a peripheral blood smear and interobserver variation[10,14,15,21,22,24,25]. Nuclear filaments and indentations are not always clearly visible due to folding or twisting of nuclei, making

accurate identification of bands more challenging[24]. Studies have demonstrated that the variation between trained laboratory staff can be as high as 15.7% in band identification[10,15,21]. There is no standard reference range for bands[10,14]. Published reports have proposed ranges from 1% to 11%[10]. It has also been reported that normal ranges are dependent on gender, age, and race, making a standardized range very difficult to establish[10].

Metamyelocyte, Myelocyte, and Promyelocyte

The metamyelocyte, myelocyte, and promyelocyte are larger in size than the band and segmented neutrophil[23]. The N:C ratio decreases with cell maturity, and is thus higher in these immature granulocytes[23]. These cells also contain larger granules that help to differentiate them from their more mature subtypes[23]. Nuclear indentation occurs as the cell differentiates. A small indentation can be seen in the metamyelocytes, giving a kidney bean shape, but the nucleus is characteristically round or oval in myelocytes and promyelocytes[23].

Automated Differential

An automated WBC differential is performed using an automated hematology analyzer. At Primary Children's Hospital in Salt Lake City, Utah, CBCs and automated differentials are performed on the Sysmex XE-5000 (XE) (Kobe, Japan). The XE combines flow cytometry and direct current/radio frequency to report a six part automated differential including neutrophils, lymphocytes, monocytes, eosinophils, and basophils[26]. The Sysmex XE-5000 also offers the immature granulocyte percentage (IG%) as part of its six-part automated differential[25,26]. The IG% is based on the

population of metamyelocytes, myelocytes, and promyelocytes[25,26]. IG% is a direct measure of left shift.

Direct Current/Radio Frequency

Direct current/radio frequency is used to detect the IG%[26]. Immature myeloid cells (metamyelocytes, myelocytes, promyelocytes, and myeloblasts) are isolated from the remaining cells based on the lipid content of their cell membrane[25,26]. Because these cells have a higher amino acid content in their cell membrane, they are preserved while all other cell types are lysed[26]. Direct current is used to generate an electrical signal based on the size of a particle passing through an aperture[26]. Radio frequency waves are used to measure the internal complexity of the cell nucleus[26]. The signal generates a histogram, like the one provided in Figure 3.2, to demonstrate the presence of immature granulocytic cells[26].

Advantages and Disadvantages

Manual and automated differentials both have advantages and disadvantages. One disadvantage of manual differentials is that only 100 cells are examined, whereas automated analyzers analyze 7,000 to 10,000 cells[10,14,15,21,22,25]. The precision of a differential count is proportional to the number of cells counted[25].

Manual differentials delay result reporting due to the additional time required for slide preparation, staining, and review by a scientist[14,15,25]. A benchmark study performed at Primary Children's Hospital (D. Yamane, personal communication, October 2015) demonstrated that a CBC with automated differential can take as little as 2-5 minutes, while a manual differential can add an additional 20-60 minutes to the turn-

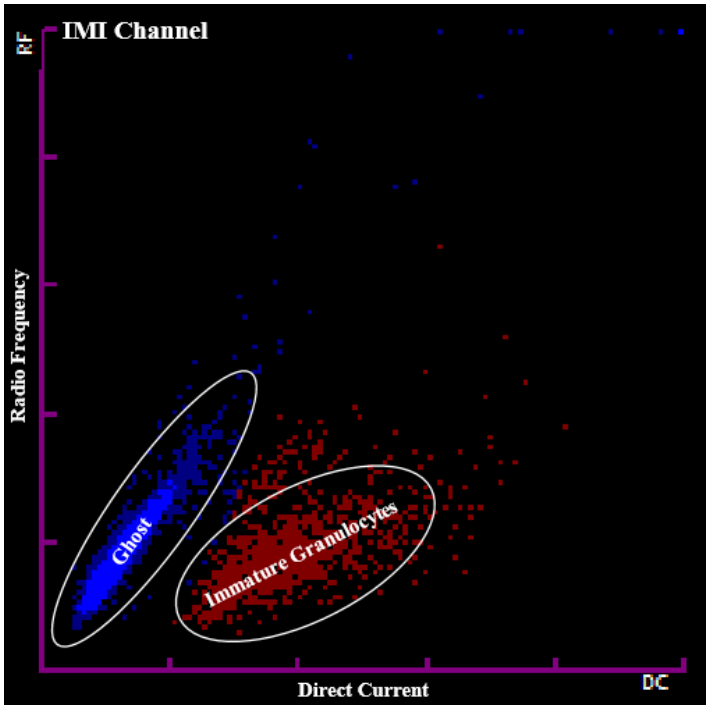

Figure 3.2 IMI histogram depicting the presence of immature granulocytes.

around time.

A disadvantage to automated analyzers is that they are not able to specifically characterize the different stages of granulocyte maturity. An automated differential provides a neutrophil count comprised of segmented neutrophils and bands and an immature granulocyte percentage for the remaining stages of immature granulocytes. A scientist performing a manual differential can differentiate segmented neutrophils, band neutrophils, metamyelocytes, myelocytes, as well as early myeloid cells. However, granulocyte maturation is a continuous process and differentiating discrete stages has a high degree of interobserver discordance[10,14,15,21,22,24,25].

C-Reactive Protein

C-reactive protein (CRP) is an acute-phase reactant that is used as a marker of nonspecific inflammation[13,27,28]. CRP can be elevated in the presence of inflammation, infection or tissue injury[13,27,28]. Normal individuals have CRP values below 0.8 mg/dL. CRP is one of the first acute phase reactants to become elevated following an inflammatory event[28,23]. CRP levels may rise above 20 mg/dL in as little as eight hours[13,27,23]. CRP is typically measured by immunoassay. At Primary Children's Hospital, an automated latex agglutination assay is used. A reaction occurs between the CRP in the sample and latex particles coated with anti-CRP antibody[27,28]. This reaction results in agglutination which causes a change in absorbance that is proportional to the amount of CRP in the sample[27].

CRP has been used as an inflammatory marker in the evaluation of appendicitis[1,3,4,6,13]. Like WBC count, CRP levels are not specific for appendicitis[3,13]. Moreover, recent physical exercise and lifestyle habits like smoking, alcohol, and obesity can increase CRP levels. A person who takes anti-inflammatory medication may have a falsely decreased CRP level. These factors limit the utility of CRP in the diagnosis of inflammatory conditions.

CHAPTER 4

STUDY DESIGN

Hypothesis

Our hypothesis was that the immature granulocyte percentage would be more predictive of acute appendicitis than leukocytosis or band count. Numerous publications in the literature have addressed the utility of leukocytosis, neutrophilia, and CRP. One paper addressed the utility of IG% in the differentiation of perforated from acute appendicitis and found no significant correlation. We found no publications addressing IG% in the diagnosis of acute appendicitis, making our study unique.

Enterprise Data Warehouse

Data for the study were collected at Primary Children's Hospital (Intermountain Healthcare) using the Enterprise Data Warehouse (EDW). The EDW is a database repository, containing over 100 billion records. The EDW integrates data from the laboratory information system, hospital information system, medical records, pharmacy and several other databases across the Intermountain Healthcare enterprise.

Cohort Definition

The EDW inclusion criteria for case detection included patients who presented to the Primary Children's Hospital ED with a chief complaint of abdominal pain and patients who received an ultrasound of the appendix in the ED between January 2014 and

December 2014. Additional inclusion criteria required a CBC be performed and an ED physician clinical note that contained the word 'appendicitis'. Patients were excluded if they had a prior appendectomy or if they were missing laboratory data. Patients who had incidental appendectomy (i.e., removal of appendix during surgery for an unrelated diagnosis) were also excluded. A flowchart of the cohort definition strategy is provided in Figure 4.1.

The following data was collected on each patient meeting inclusion/exclusion criteria:

- Chief complaint
- Demographics including gender and age
- WBC count
- Differential (both manual and automated)
- IG%
- CRP
- Pathology report
- Number of days between initial visit and surgery

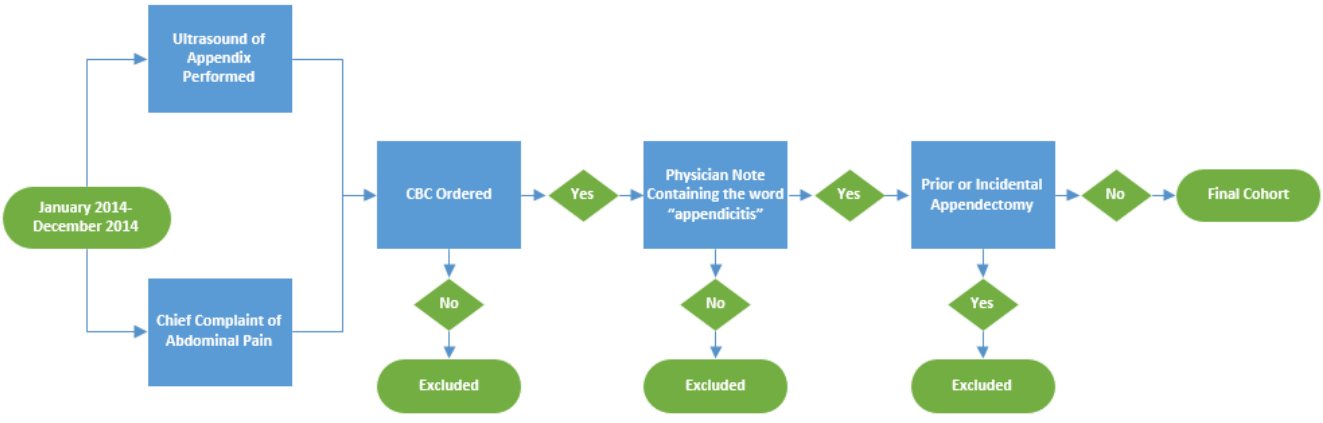

Figure 4.1 Flowchart of cohort definition

Significance of Collected Data

The pathology report was used as the gold standard to determine a "true appendicitis" diagnosis. A histopathological diagnosis of acute appendicitis is made if an infiltration of neutrophils is present in the mucosa and wall of the appendix[16]. Neutrophils limited to the lumen, luminal dilation without mucosal inflammation or mucosal or mural necrosis, or isolated serosal inflammation (periappendicitis) were not acceptable for a diagnosis of appendicitis. A comparison of normal and inflamed appendices is provided in Figure 4.2.

Laboratory parameters were evaluated above and below the cutoff value listed below:

- WBC count (>10,000/µL)
- Neutrophil percentage (>75%)
- Band count (>10%)
- IG% (>0.25%)
- CRP (>1.0 mg/dL)

The cutoff value used for WBC count and neutrophil percentage was the same as the cutoffs used in the Alvarado score and PAS. Cutoffs for band count, IG%, and CRP were based on other diagnostic thresholds[6,10,11,13,14,23,27].

ROC Curve

Different laboratory parameters were analyzed using ROC (receiver operating characteristic) curves. A ROC curve is a plot of the sensitivity of a test against 1-specificity of the test. Accuracy of the test is measured by the area under the curve, or AUC. The AUC measures a tests ability to correctly classify those with and without the

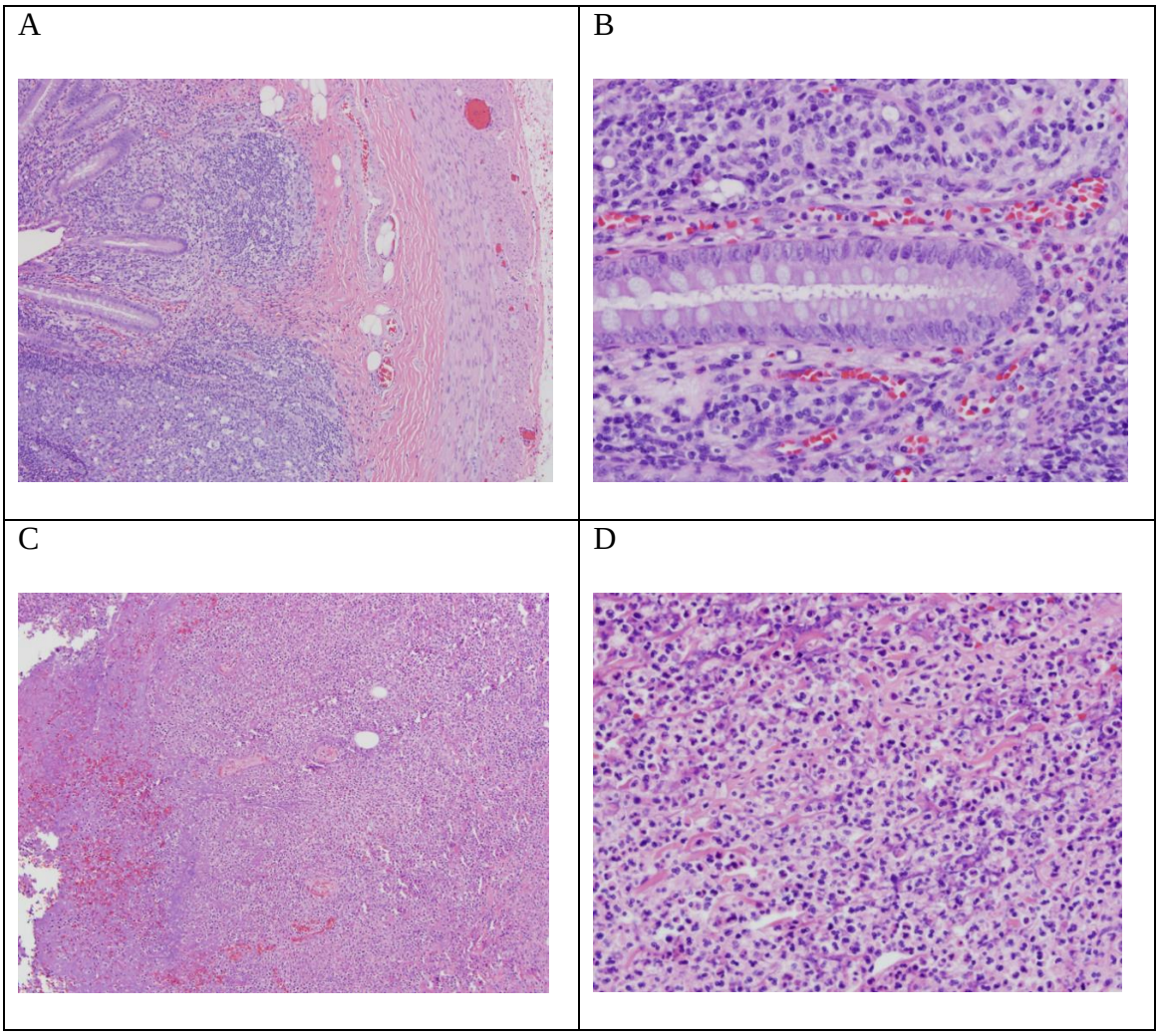

Figure 4.2 Comparison of a normal appendix and appendicitis (Hematoxylin & Eosin Stain). A) Normal appendix, 100x magnification. Mucosa with crypts and lymphoid follicles, extending into the submucosa and no acute inflammation. B) Normal appendix, 400x magnification. Many lymphoid cells with only a rare neutrophil. C) Acute appendicitis, 100x magnification. Necrotic and hemorrhagic mucosa with inflammation spreading through appendiceal wall. D) Acute appendicitis, 400x magnification. Transmural infiltrate of neutrophils throughout the appendiceal wall.

condition in question. An AUC of one represents a test that will correctly predict the outcome 100% of the time and an area of 0.5 represents a test that is only correct 50% of the time.

To construct a ROC curve, a table of data is constructed including numeric test results, such as WBC count, and whether or not each patient was positive or negative for the specified diagnosis, in this case a diagnosis of appendicitis according to histopathology. The number of true and false positives and true and false negatives for different cutoff values of the test can be tabulated to calculate the respective sensitivities and specificities.

Other Statistics

In addition to ROC curve analysis, data were analyzed by calculating the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Sensitivity is a measure of a tests ability to correctly identify disease positive individuals and is calculated by dividing the number of true positives by the number of total positives (true positives + false negatives). Specificity is defined as a test's ability to correctly identify disease negative individuals and is calculated by dividing the number of true negatives by the number of total negatives (true negatives + false positives). Predictive value combines the sensitivity and specificity with the prevalence of the disease. PPV is defined as the probability that the disease of interest is present in an individual with a positive test result. NPV is defined as the probability that the disease of interest is absent in an individual with a negative test result.

Limitations

Because the study was performed retrospectively, the type and amount of data was limited to what was available in the EDW. For example, a patient who presented with abdominal pain, but was sent home without a blood draw, would not be selected. In addition, the time course from onset of symptoms to time of surgery was not consistent among patients[3]. Another difficulty was that data obtained were deidentified. This made it impossible to obtain additional details about patient history, presentation, or evaluation. Finally, a major limitation to retrospective analysis is that there is no control group for data comparison, as there would be if enrolling patients in a study prospectively. The lack of a control group in this study may have contributed to bias in the data.

CHAPTER 5

RESULTS AND DATA ANALYSIS

Cohort Details

The patient cohort obtained from the EDW included 942 subjects. Sixty-three subjects were excluded due to age, prior appendectomy, incidental appendectomy, or missing laboratory data. The final cohort contained 879 subjects, 52.1% male, with a mean age of 10.6 years. The age distribution is shown in Figure 5.1.

A pathologic diagnosis of acute appendicitis was determined by review of pathology reports and identified 217 "positive" patients (24.7% of total patient cohort). If the report had one of the diagnoses listed in Table 5.1, the patient was classified as "positive" for appendicitis. If the report did not make the diagnosis of appendicitis or if surgery did not occur then the patient was classified as "negative" for appendicitis.

Results

The sensitivity, specificity, PPV, NPV and area under receiver operating characteristic curves (AUC) were determined for total WBC count (>10,000/μL), band count (>10%), IG% (>0.25%), CRP (>1.0 mg/dL), and neutrophil percentage (>75%). Data are presented in Table 5.2 and ROC curves are presented in Figure 5.2. WBC count had the best correlation with appendicitis with a sensitivity of 85.3%, specificity of 63.4%, PPV of 43.3%, and NPV of 92.9%, and AUC of 80.1% (95% confidence interval:

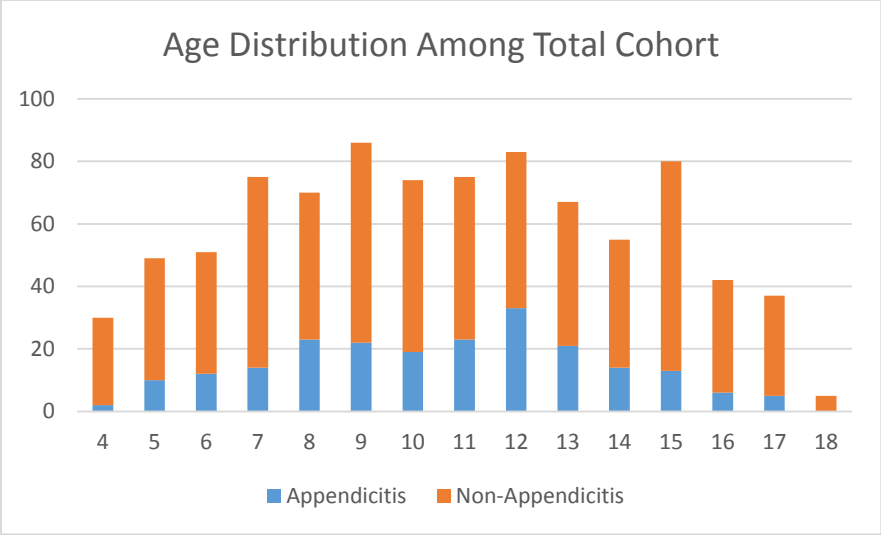

Figure 5.1 Age distribution among patient cohort.

76.8-83.5%). Neutrophilia was also indicative with a sensitivity of 70.5%, specificity of 66.6%, PPV of 40.9%, NPV of 87.3%, and AUC of 73.4% (95% confidence interval: 70.0- 76.8%). CRP (>1.0 mg/dL) also appeared slightly more predictive with a sensitivity of 73.9%, specificity of 56.1%, PPV of 42.5%, NPV of 83.0%, and AUC of 70.3% (95% confidence interval: 65.1-75.5). IG% appeared slightly more promising with a sensitivity of 68.5%, specificity of 60.2%, PPV of 37.8%, NPV of 84.4%, and AUC of 66.7% (95% confidence interval: 61.6- 71.7%). Band count showed no predictive value with a specificity of 54.2%, specificity of 53.6%, PPV of 27.8%, NPV of 78.0%, and AUC of 57.7% (95% confidence interval: 50.7- 64.7).

Table 5.1 List of diagnoses included in the "positive" patient cohort.

Number of cases	Diagnosis
93	Acute suppurative appendicitis
26	Acute appendicitis
23	Acute appendicitis with periappendicitis
13	Acute gangrenous appendicitis
9	Acute appendicitis with periappendicitis and fecalith
8	Early acute appendicitis
7	Acute gangrenous appendicitis with perforation
7	Gangrenous appendicitis
6	Gangrenous appendicitis with rupture
5	Acute appendicitis with fecalith
5	Acute appendicitis with periappendicitis and perforation
3	Acute appendicitis and periappendicitis with fecalith and perforation
3	Acute suppurative appendicitis with fecalith
3	Acute suppurative appendicitis with perforation
1	Acute appendicitis with perforation
1	Acute gangrenous appendicitis with fecalith
1	Acute gangrenous appendicitis with perforation and fecalith
1	Appendicitis with acute and chronic inflammation
1	Benign appendix with rare neutrophilic crypt abscess
1	Rare small focus of acute (neutrophilic) cryptitis

Table 5.2 Data summary

Parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (%)	AUC (%) 95% Confidence Interval
WBC Count (>10,000/µL)	85.3	63.4	43.3	92.9	80.1	76.8-83.5
Neutrophilia (>75%)	70.5	66.6	40.9	87.3	73.4	70.0-76.8
CRP (>1.0 mg/dL)	73.9	56.1	42.5	83.0	70.3	65.1-75.5
IG% (>0.25)	68.5	60.2	37.8	84.4	66.7	61.6-71.7
Band Count (>10%)	54.2	53.6	27.8	78.0	57.7	50.7-64.7

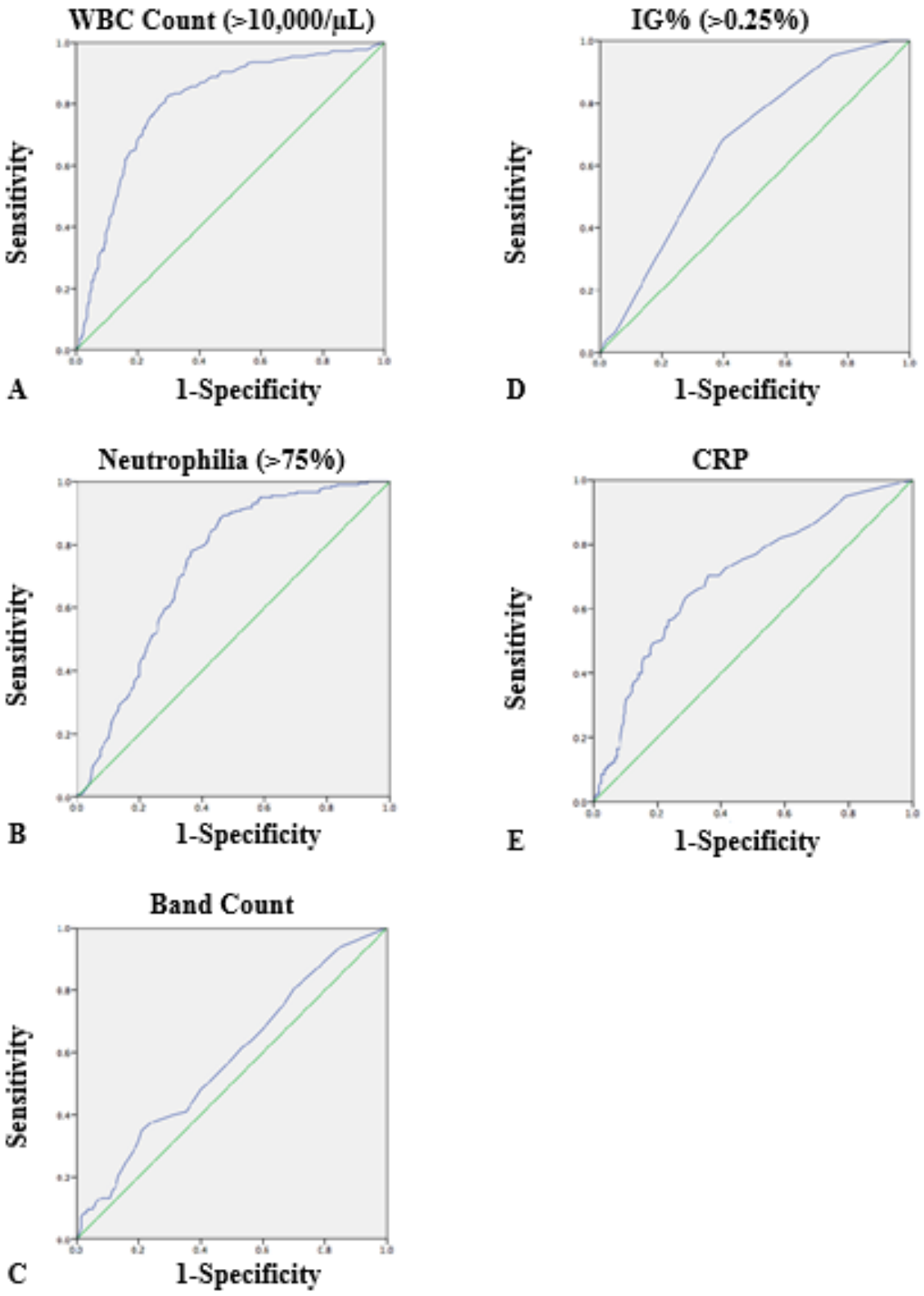

Figure 5.2 ROC curves for each parameter analyzed.

CHAPTER 6

CONCLUSION

WBC count, neutrophil percentage, CRP, and IG% correctly identified children with appendicitis (AUC 80.1, 73.4, 70.3, and 66.7, respectively). Band count showed an AUC of only 57.7. Band count was the least reliable indicator and showed no added benefit in diagnosis.

The hypothesis that IG% is a better indicator of appendicitis than band count in pediatric populations was confirmed. IG% offers a test that is more reproducible than band count, and it is available from an automated differential. Eliminating the band count and, hence, the need for a manual differential would improve turn-around-time for CBCs on patients presenting with acute abdominal pain without reducing the utility of the CBC. Faster turn-around-time may equate to shorter wait times in the ED and quicker diagnosis and surgery, when indicated. Use of IG% may also lessen reliance on imaging methods such as CT scan and ultrasound procedures that might also contribute to higher wait times.

Appendicitis is a condition in which delayed diagnosis may result in morbidity and complications. Providing a faster automated method for diagnosis could decrease the number of perforations due to late diagnosis and related surgical complications. The IG% is an automated parameter that can be reported with the CBC. This test requires no

additional specimen or time for analysis. This method is more accurate and reproducible than the historical methods of band count and manual differential.

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