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A Pre-Operative Clinical Scoring System to Distinguish Perforation Risk With Pediatric Appendicitis

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Short title: Distinguishing Perforated Appendicitis

Abbreviations: CT - computerized tomography scan; ED - emergency department; ANC - absolute neutrophil count; ROC curve - receiver operating characteristic curve; CBC –complete blood count; WBC - white blood cell

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Abstract
Importance: Appendicitis is a common, potentially serious pediatric disease. An important factor in determining management strategy [whether/when to perform appendectomy, duration of antibiotic therapy/hospitalization, etc.] and predicting outcome is distinguishing whether perforation is present.
Objective: The objective was to determine efficacy of commonly assessed pre-operative variables in stratifying perforation risk in children with appendicitis.
Design: A retrospective analysis of consecutive cases was performed.
Setting: The setting was a large urban hospital pediatric emergency department.
Participants: 448 consecutive cases of CT [computerized tomography]-confirmed pediatric appendicitis during a 6-year period in an urban pediatric ED [emergency department]: 162 with perforation and 286 non-perforated.
Main Outcome(s) and Measure(s): To determine efficacy of clinical and laboratory variables with distinguishing perforation outcome in children with appendicitis.
Results: Regression analysis identified 3 independently significant variables associated with perforation outcome - and determined their ideal threshold values: *duration of symptoms >1 day; ED-measured fever [body temperature >38.0oC]; CBC WBC absolute neutrophil count >13,000/mm3*. The resulting multivariate ROC [receiver operating characteristic] curve after applying these threshold values gave an AUC [area under curve] of 89% for perforation outcome [p <0.001]. Risk for perforation was additive with each additional predictive variable exceeding its threshold value, linearly increasing from 7% with no variable present to 85% when all 3 variables are present.
Conclusions: A pre-operative scoring system comprised of 3 commonly assessed clinical/laboratory variables is useful in stratifying perforation risk in children with appendicitis. Physicians can utilize these factors to gauge pre-operative risk for perforation in children with appendicitis, which can potentially aid in planning subsequent management strategy.

Keywords

pediatric appendicitis; perforated appendicitis

Introduction

Appendicitis is a common pediatric disease. An important factor in determining management strategy [whether/when to perform appendectomy, duration of antibiotic therapy/hospitalization, etc.] and predicting outcome is distinguishing whether appendiceal perforation is present. Physical findings can generically correlate with presence of peritoneal irritation, yet lack specificity for perforation.[1] Radiographic imaging, particularly abdominal CT scan, can accurately aid in stratifying risk; yet is not universally sensitive, nor routinely performed often due to concern for exposing children to ionizing radiation.

Pre-operative assessment for appendicitis perforation risk is multi-factorial; integrating aspects of the history, physical examination, laboratory data, and diagnostic imaging. Prior studies[2-19] examined aspects of the clinical assessment to determine predictive value for distinguishing presence vs absence of appendicitis in children - with variable success. There is a lack of published studies specifically assessing efficacy of variables in distinguishing the presence vs absence of perforation in children with appendicitis.

The purpose of this study is to determine efficacy of commonly assessed pre-operative variables in stratifying perforation risk in children with appendicitis.

Methods

A review was performed of consecutive children <18 years of age with acute appendicitis evaluated in the Pediatric Emergency Department of Maimonides Medical Center presenting between 2010-2015. Studied were those who fulfilled radiographic criteria for CT-diagnosed appendicitis [Figure 1] [20].

Data analyzed included patient age; gender; days of pre-ED symptoms; ED-measured body temperature [fever defined as any ED temperature measured $\geq 38^{o}C$] and other vital signs; ED-performed CBC WBC/differential cell counts, and abdominal CT scan results. CBC [complete blood count] absolute neutrophil count [ANC] and absolute band count [ABC] were calculated. Presence of appendicitis, appendicolith and appendiceal perforation status were determined as per tissue visual inspection per attending-level surgeon/pathologist reports in cases resulting in appendectomy; and per attending-level radiologist interpretation of CT scans in cases which were solely managed medically. In each instance in which laparoscopy was performed, the surgeons' operative report was the ultimate arbiter used to diagnose the presence of appendicitis and perforation status. In cases solely managed medically, admission CT results and surgeons' admitting/discharge diagnoses were used to determine the presence of appendicitis and distinguish perforation status. All CT scans were performed after the administration of oral and intravenous contrast material; patients drank a weight-based amount of a 2% diatrizoate meglumine solution approximately 1-2 hours before the scan. Standard dose of 2 mL/kg Omnipaque 200 was administered intravenously.

Each study co-investigator received a comprehensive tutorial regarding guidelines to standardize data gathering prior to reviewing cases. All symptoms listed in the templated medical record were surveyed to determine pre-ED symptom onset [in days]; specifically noting the presence of abdominal pain, nausea, vomiting, fever [temperature $\geq 38^{o}C$], anorexia. Also gathered from each case was information from the dictated operative report [surgeon] and histologic report [pathologist], specifically noting whether there was visual evidence of appendiceal perforation.

Our previously published appendicitis study[21] assessed inter-rater agreement in data gathering, randomly selecting 20% of total appendicitis cases which were re-examined by 3 investigators [9 variables identical to those in the present study]. Continuous variables were compared using intra-class correlations while categorical variables were compared using kappa coefficients. The median coefficient of agreement was 1.0 [range 0.8 - 1.0], indicating excellent agreement.

Appendicitis perforation status on abdominal CT scan was determined by criteria seen in Figure 1. Abdominal CT scan results were classified as *appendicitis without perforation* when criteria for appendicitis was not associated with any of the following findings: intra-abdominal abscess, phlegmon, extra-luminal air, extra-luminal appendicolith, or focal defect in enhancing appendiceal wall. [20]

The study was approved by our Investigational Review Board.

<u>Statistical analysis</u>

Normally distributed data are described in terms of mean [±SD] while categorical data are described in terms of frequency [percent].

Receiver Operator Characteristic (ROC) curves were generated to compare the strength of association between each predictor and perforation status. The statistical significance of the association was determined using a non-parametric technique similar to the Mann-Whitney test. Multivariate logistic regression with backwards selection was then used to select an optimal set of predictors from the ones which were significant by ROC analysis. Relative sensitivity and specificity at each value of a continuous predictor were examined to establish the ideal threshold or cutoff for that continuous variable. These were then retested using multivariate logistic regression to determine if they remained significant.

All tests were carried out using p <0.05 as the significance level and were calculated using IBM SPSS Statistics for Windows, version 20 [IBM Corp, Armonk, NY].

Results

During the study period, there were 448 children with CT-diagnosed appendicitis which represented >95% of all patients with appendicitis. In 14 cases, a CBC was performed without a differential count, resulting in 434 complete medical records. Of these, 162 had appendiceal perforation [105 underwent laparoscopic appendectomy and 57 had medical management only] and 286 patients had appendicitis without perforation [all underwent laparoscopic appendectomy]. All patients with appendicitis solely managed medically had both CT evidence of perforation [intra-abdominal abscess or phlegmon] and surgeon admitting/discharge diagnoses of perforated appendicitis.

All patients received broad spectrum parenteral antibiotics initiated in the ED. No patient had hypotension requiring pressor therapy, respiratory insufficiency requiring mechanical ventilation, or admission to the pediatric intensive care unit. There were no deaths.

Demographically, rates of gender distribution, mean patient age, ED-measured fever, and presence of appendicolith were not significantly different between those with and without perforation [p = NS].

Univariate ROC curve analysis was performed, regressing perforation outcome onto each of the 10 candidate predictors [Figure 2]. Of these, 7 showed statistically significant associations with perforation [Table 1]: patient age; days of symptoms; ED-measured body temperature

$\geq$38.0°C; CBC total WBC count, %-band forms, ABC, and ANC [patient gender, presence of appendicolith, and CBC %-PMN's were not significant (p = NS)]. Based on the principle of maintaining equal levels of sensitivity and specificity, logistic regression with backward selection then identified 3 variables [and their threshold values] as the best and non-redundant subset of predictive factors [Table 1]: duration of symptoms *>1 day*; ED-measured fever [body temperature $\geq$*38.0°C*]; CBC WBC ANC *>13,000/mm*^{3}. Figure 3 shows the combined multivariate ROC curve resulting from including these 3 predictors in a multivariate logistic regression model [all in their original continuous forms] after applying threshold values to each predictor. The AUC for the multivariate categorical model was 0.89 ($p < 0.001$). As a sensitivity analysis, the overall sample was randomly divided into two sub-samples ($n_1 = 218$, $n_2 = 230$) and the 3 factors were then applied to predict perforation in each sub-sample. The resulting AUCs for the two sub-samples were 0.85 and 0.90, respectively (both $p < 0.001$). There was no statistically significant difference between the AUCs of these two models.

Figure 4 shows the average probability for perforation using each combination of positive significant variables [exceeding threshold values] which a patient can present with anywhere from 0 positive variables to 3 positive variables. For example, the graph presents the average probability when a] any one of the 3 variables is present; b] for the 3 combinations that a patient can have when there are 2 positive variables present [variables 1 and 2, or variables 2 and 3, or variables 1 and 3]; or c] all 3 positive variables are present. Figure 4 illustrates that a patient with no positive variables has about a 7% chance of having perforation, while a patient with 2 variables has a 59% chance of perforation. When all 3 variables exceed the threshold value, the chances increase to 85%.

Discussion

Multiple prior studies[1-19] have evaluated the accuracy of clinical variables in distinguishing between appendicitis vs no appendicitis in children. Few comprehensively analyzed variables have been used to distinguish perforated vs non-perforated appendicitis. Usually, individually-significant variables are reported, including the presence of fever[22,23], duration of symptoms[24], serum C-reactive protein concentration and CBC differential count[25], serum D-lactate level[26], and serum bilirubin concentration.[27-32]

A prior prospective study[33] of pediatric appendicitis devised a pre-operative scoring system to distinguish perforation status which included history, physical exam, laboratory, and radiographic imaging results. The sample with perforation that was analyzed had approximately one-fourth the number with perforation in our study. Although their scoring system factored abdominal US and CT scan results [criteria for diagnosing perforation were not specified], the reported specificity for distinguishing perforation was relatively lower [83%].

A recent retrospective analysis[34] of pediatric appendicitis calculated the odds ratios for perforation outcome using clinical and laboratory variable cutoff values. Symptom duration >24 hours, hyponatremia, patient age <5 years, and CBC leukocytosis were found to independently predict complicated appendicitis. A deficit in this analysis is a lack of utilizing pre-operative ED imaging results to accurately assign perforation status pre-operatively, potentiating the possibility that some patients with perforation at laparoscopy, who were actually non-perforated at the time of presentation, *developed* in-hospital perforation, which several recent studies[35,36] have shown can occur as a function of in-hospital delay to appendectomy in nearly one-fourth of patients, potentially causing misclassification.

Our study encompasses the largest group of pediatric patients examining this issue to date. All had CT-confirmed appendicitis with perforation status determined utilizing validated radiologic criteria. Those who underwent laparoscopy also had surgeon and/or pathologist-visualized evidence of perforation status. The groups that were compared had equivalent baseline demographics. Although we utilized abdominal CT scan results to determine perforation status assignment, we did not include radiographic findings as a predictive variable in the model analyzed as we preferred to devise a purely clinical scoring system that also had utility in determining the need for advanced imaging.[37]

The initial 10 factors initially examined are relatively objective variables routinely assessed pre-operatively in appendicitis cases, and they include aspects of history, physical findings, and laboratory assessment. Of these, regression analysis identified the 3 most accurate predictors. We excluded analysis of certain physical findings [abdominal tenderness, guarding, rebound tenderness, abdominal pain migration, pain with coughing/hopping] utilized in prior scoring systems to distinguish appendicitis vs non-appendicitis[18,19]. Since peritoneal inflammation commonly can accompany both perforated and non-perforated processes, we anticipated they would lack discriminatory value to distinguish perforation status. Consistent with this, a prior prospective study[33] of pediatric appendicitis documented the surgeon finding of diffuse abdominal tenderness was present only 62% in patients with perforation. Also, the rate of focal right lower quadrant abdominal tenderness were nearly identical in those with appendiceal perforation compared to those with abdominal pain/no appendicitis.

Our analysis has generated an easily-determined, practical 3-variable pre-operative predictive model that accurately distinguishes perforated vs non-perforated appendicitis. Perforation was more likely with longer duration of symptoms, presence of fever, and CBC left-shift in the differential profile. Ideal threshold values were identified which gave the best predictive model. Certainly, all children medically evaluated for abdominal pain would be expected to receive performance of a history of present illness [defining symptom duration] and vital sign measurements [quantitating body temperature]. One would anticipate the majority suspected of having an abdominal surgical condition would also have a CBC. As such, these evaluative measures can be expected to widely apply to the majority of children evaluated for possible appendicitis.

Physicians can utilize these variables to gauge pre-operative risk for perforation in children with appendicitis. It can potentially aid in planning subsequent management strategy, including the need for advanced imaging. For surgeons who discriminate whether to perform immediate appendectomy based on perforation status, a child with appendicitis and 0-1 variables could be considered at relatively low risk for associated perforation. However a child with 2, and certainly 3 positive variables might exceed the threshold for perforation suspicion, warranting performance of advanced imaging to delineate the intra-abdominal milieu or potentially influencing whether to institute medical management alone and whether to consider the option of performing an interval appendectomy.

Limitations

As with any retrospective analysis, there are limitations on what can be competently analyzed through a review of charts. We limited our analysis of variables to those that were assessed in each case.

References

1. Bundy D, Byerly J, Liles A, et al: Does this child have appendicitis? JAMA 2007;298:438-451

2. Keskek M, Tez M, Yoldas O, et al: Receiver operating characteristic analysis of leukocyte counts in operations for suspected appendicitis. Am J Emerg Med 2008;26:769-772
3. Wang L, Prentiss K, Simon J, et al: The use of white blood cell count and left shift in the diagnosis of appendicitis in children. Pediatr Emerg Care 2007;23:69-76
4. Kwan K, Nager A: Diagnosing pediatric appendicitis: Usefulness of laboratory markers. Am J Emerg Med 2010;28:1009-1015
5. Yu C, Juan L, Wu M, et al: Systematic review and meta-analysis of the diagnostic accuracy of procalcitonin, C-reactive protein and white blood cell count for suspected acute appendicitis. Br J Surg 2013;100:322-329
6. Okamoto T, Sano K, Ogasahara K: Receiver-operating characteristic analysis of leukocyte counts and serum C-reactive protein levels in children with advanced appendicitis. Surg Today 2006;36:515-518
7. Stefanutti G, Ghirardo V, Gamba P: Inflammatory markers for acute appendicitis in children: Are they helpful? J Pediatr Surg 2007;42:773–776
8. Gronroos J, Gronroos P: Leucocyte count and C-reactive protein in the diagnosis of acute appendicitis. Br J Surg 1999;86:501-504
9. Sack U, Biereder B, Elouahidi T, et al: Diagnostic value of blood inflammatory markers for detection of acute appendicitis in children. BMC Surgery 2006;15:3-8
10. Anandalwar S, Callahan M, Bachur R: Use of white blood cell count and PMN leukocyte differential to improve the predictive value of ultrasound for suspected appendicitis in children J Am Coll Surg 2015;220:1010-1017.
11. Gronroos P, Huhtinen H, and Gronroos J: Normal leukocyte count and C-reactive protein value do not effectively exclude acute appendicitis in children. Dis Colon Rectum 2009;52:1028-1029
12. Bates M, Khander A, Steigman S, et al: Use of white blood cell count and negative appendectomy rate. Pediatrics 2014;133:39-44
13. Beltran M, Almonacid J, Vicencio A, et al. Predictive value of white blood cell count and C-reactive protein in children with appendicitis. J Pediatr Surg 2007;42:1208-1214.
14. Mekhail P, Naguib N, Yanni F, et al: Appendicitis in pediatric age group: correlation between preoperative inflammatory markers and postoperative histological diagnosis. Afr J Paediatr Surg 2011;8:309-312
15. Siddique K, Baruah P, Bhandari S, et al: Diagnostic accuracy of white cell count and Creactive protein for assessing the severity of pediatric appendicitis. JRSM Short Rep 2011;2:59
16. Korner H, Soreide J, Sondena: Diagnostic accuracy of inflammatory markers in patients operated on for suspected acute appendicitis: a receiver operating characteristic curve analysis. Eur J Surg 1999;165:679-685
17. Samuel M: Pediatric appendicitis score. J Pediatr Surg 2002;37:877-881 18. Alvarado A: A practical score for the early diagnosis of acute appendicitis. 1986;15:557-564
19. Horrow M, White D, Horrow J: Differentiation of perforated from non-perforated appendicitis at CT. Radiology 2003;227:46-51
20. Bonadio WA, Brazg J, Telt N, et al: Impact of In-Hospital Timing to Appendectomy on Perforation Rates in Children With Appendicitis. J Emerg Med 2015;49:597-604
21. Obinwa O, Peirce C, Cassidy M, et al: A model predicting perforation and complications in pediatric appendicectomy. Int J Colorectal Dis 2015;30:559-565
22. Peng Y, Lee H, Yeung C, et al: Clinical criterial for diagnosing perforated appendicitis in pediatric patients. Pediatr Emerg Care 2006;22:475-479

23. Ngim C, Quek K, Dhanoa A, et al: Pediatric appendicitis in a developing country: what are the clinical predictors and outcome of perforation? J Trop Pediatr 2014;60:409-414
24. Mathews E, Griffin R, Mortellaro V, et al: Utility of immature granulocyte percentage in pediatric appendicitis. J Surg Res 2014;190:230-234
25. Unverir P, Karcioglu O: A Review of the predictive role of plasma D-lactate level in acute appendicitis: A myth or truth? ISRN Toxicology 2011;1:1-6
26. Atahan K Uryen O, Asian E, et al: Preoperative diagnostic role of hyperbilirubinemia as a marker of appendix perforation. J Intern Med Res 2011;39:609-618
27. Giordano S, Paakonen M, Salminen P, et al: Elevated serum bilirubin in assessing the likelihood of perforation in acute appendicitis: A diagnostic meta-analysis. Int J Surg 2013;11:795-800
28. Emmanuel A, Murchan P, Wilson I, et al: The value of hyperbilirubinaemia in the diagnosis of acute appendicitis. Ann R Coll Surg 2011;93:213-217
29. Estrada J, Petrosyan M, Barnhart J, et al: Hyperbilirubinemia in appendicitis: A new predictor of perforation. J Gastrointest Surg 2007;11:714-718
30. Burcharth J, Pommergaard H, Rosenberg J, et al: Hyperbilirubinemia as a predictor for appendiceal perforation: A systematic review. Scand J Surg 2013;102:55-60
31. Sand M, Bechara F, Holland-Letz T, et al: Diagnostic value of hyperbilirubinemia as a predictive factor for appendiceal perforation in acute appendicitis. Am J Surg 2009;198:193-198
32. Williams R, Blakely M, Fischer P, et al: Diagnosing ruptured appendicitis preoperatively in pediatric patients. J Am Coll Surg 2009;208:819-828.
34. Pham X, Sullins V, Kim D, et al: Factors predictive of complicated appendicitis in children. J Surg Res 2016;206:62-66
35. Bonadio WA: Discordant rates of surgeon versus pathologist visual diagnosis of perforation with pediatric appendicitis. Pediatr Emerg Care J 2017 [publication pending]
36. Meltzer JA, Kunkov S, Chao JH, et al: Association of delay in appendectomy with perforation in children with appendicitis. Pediatr Emerg Care 2016; Sep 30. [Epub ahead of print]
37. Lin C, Chen J, Tiu C, et al: Can ruptured appendicitis be detected preoperatively in the ED? Am J Emerg Med 2005;23:60-66

Figure 1. CT radiologic criteria for diagnosing appendicitis and distinguishing perforation status*****

CT

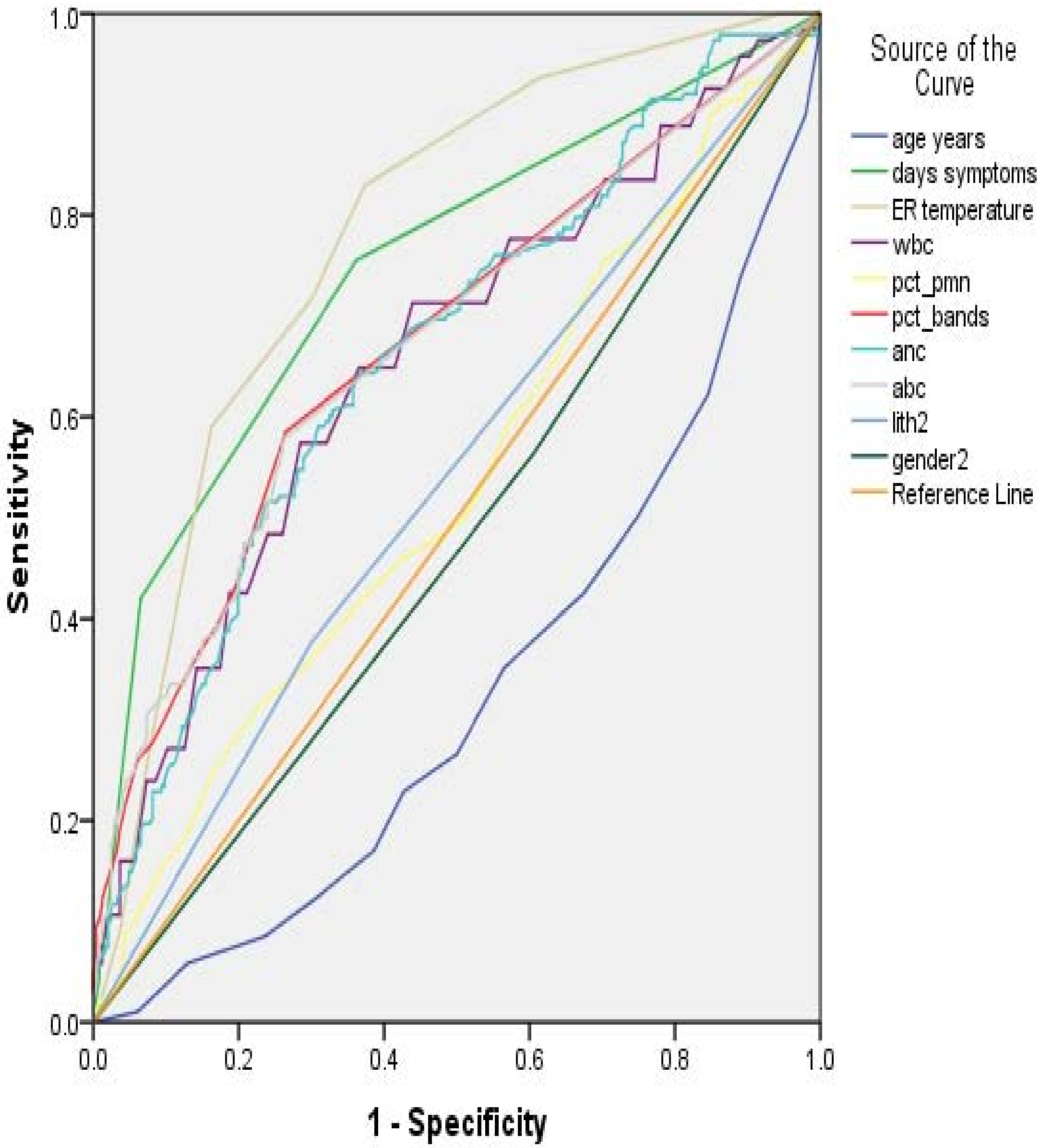
- Appendicitis: visualization of an enlarged appendix measuring $\geq$7 mm in diameter in addition to inflammatory signs including hyperemia in the wall, peri-appendiceal fat stranding, or appendicolith

- *Non-perforated* appendicitis: criteria for appendicitis above without any evidence of intra-abdominal abscess/phlegmon, extra-luminal air, extra-luminal appendicolith, or focal defect in enhancing appendiceal wall*

- *Perforated* appendicitis: criteria for appendicitis above with evidence of either intra-abdominal abscess/phlegmon, extra-luminal air, extra-luminal appendicolith, or focal defect in enhancing appendiceal wall*

*Reference 19

FIGURE 2. ROC curve analyses for 10 individual clinical/laboratory variables



wbc: CBC white blood cell count

pct pmn: % polymorphonuclear leukocytes

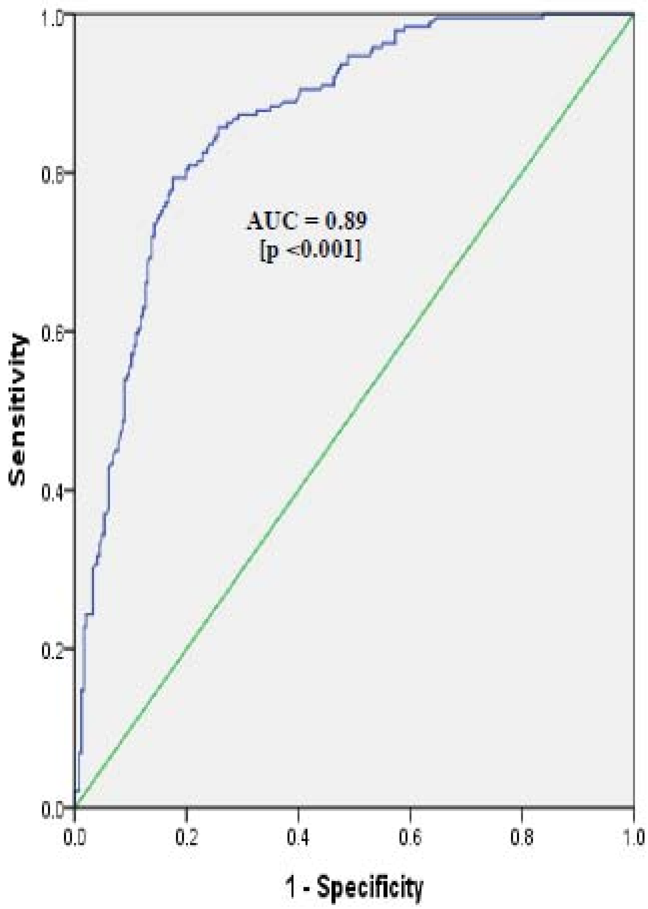
pct bands: %-band form neutrophils

anc: absolute neutrophil count

abc: absolute band count

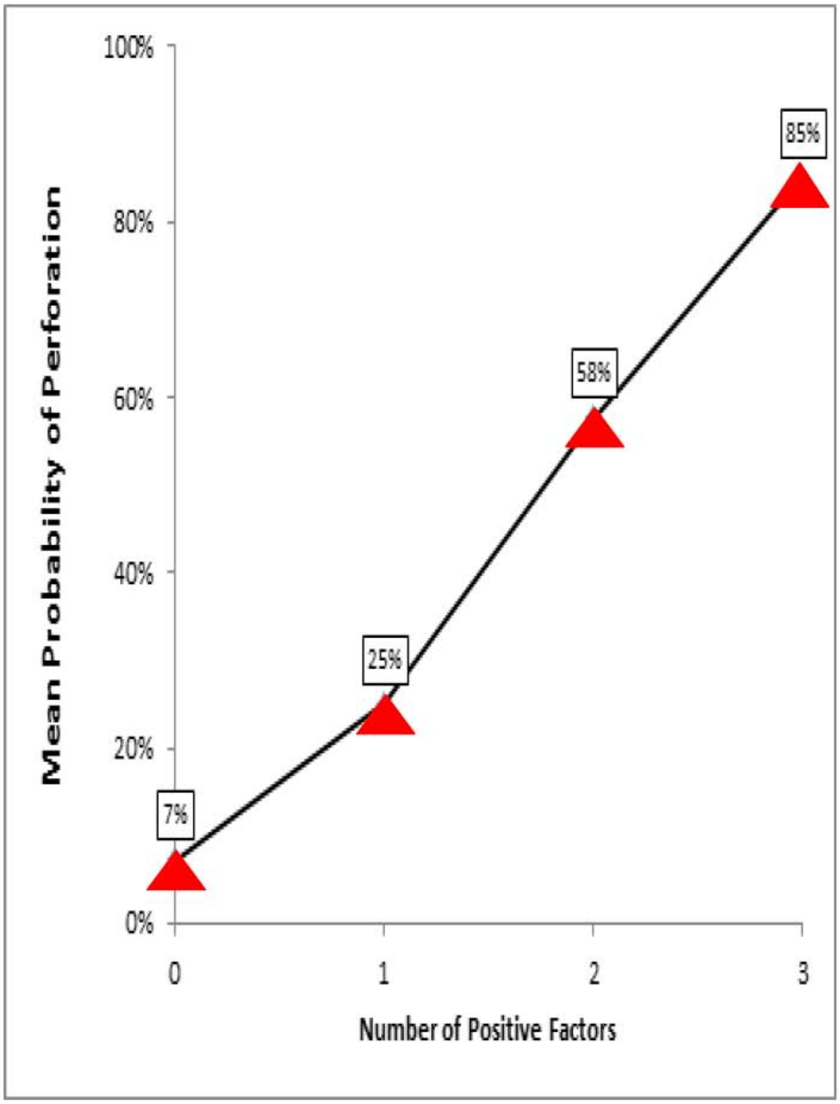
lith 2: appendicolith

FIGURE 3. ROC curve analysis of 3 significant variables for perforation after multivariate regression



POSITIVE-PREDICTIVE VARIABLES	THRESHOLD VALUES
Duration of symptoms	> 1 day
ED-measured fever	body temperature $\geq 38^0$C
ANC	> 13,000/mm^3

FIGURE 4. Average probability of perforation based on additive number of positive predictive variables which exceed threshold values



POSITIVE-PREDICTIVE VARIABLES	THRESHOLD VALUES
Duration of symptoms	> 1 day
ED-measured fever	body temperature $\geq 38^{0}$C
ANC	> 13,000/mm^3

Table 1. Results of univariate and multivariate logistic regressions

Predictor		Univariate			Multivariate		
		Odds ratio	95% CI^	p-value	Odds ratio	95% CI^	p-value
Days of symptoms		2.56	2.02-3.25	<0.001	2.36	1.82-3.06	<0.001
ED-measured fever*		1.78	1.58-2.00	<0.001	1.47	1.27-1.69	<0.001
Patient age (years)		0.85	0.81-0.89	<0.001	0.95	0.89-1.02	0.15
CBC	Differential %-bands	1.16	1.10-1.22	<0.001	1.15	0.92-1.45	0.22
	ABC/1000[a]	2.15	1.64-2.80	<0.001	0.68	0.20-2.26	0.52
	ANC/1000[b]	1.14	1.09-1.19	<0.001	1.27	1.02-1.57	0.03
	Total WBC count	1.13	1.08-1.18	<0.001	0.88	0.71-1.09	0.24

^ confidence interval

* body temperature $\geq 38.0^{o}C$

[a] absolute band count per 1000 cells

[b] absolute neutrophil count per 1000 cells