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Successful nonoperative management of uncomplicated appendicitis: predictors and outcomes

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Abstract

Background—Our objective was to identify predictors of successful nonoperative management (NOM) of uncomplicated appendicitis. We hypothesized that the absence of diabetes, absence of an appendicolith, short duration of symptoms, absence of systemic inflammation, and low modified Alvarado score would predict successful NOM.

Methods—We performed a retrospective cohort analysis of 81 consecutive patients who underwent NOM of uncomplicated appendicitis. Successful NOM was defined as resolution of appendicitis with antibiotics alone and no recurrent appendicitis within 180 days. Patients with successful NOM ($n = 36$) were compared with patients who failed NOM ($n = 45$). Multivariable logistic regression was used to identify predictors of successful NOM, expressed as odds ratios (ORs) with 95% confidence intervals. Model strength was assessed by calculating area under the receiver operating characteristic curve (AUC).

Results—Patient age (35 years), the American Society of Anesthesiologists class (2.0), and Charlson comorbidity index (0.0) were similar between groups. Independent predictors of successful NOM were duration of symptoms prior to admission >25 hours: OR 4.17 (1.42–12.24), maximum temperature within 6 hours of admission <37.3°C: OR 8.07 (1.79–36.38), modified Alvarado score <4: OR 9.06 (1.26–64.93), and appendiceal diameter <13 mm: OR 17.55 (1.30–237.28); model AUC: 0.81 (0.72–0.90).

Conclusions—Patients with a longer duration of symptoms prior to admission were more likely to have successful NOM. Other independent predictors of successful NOM included lower temperature, lower modified Alvarado score, and smaller appendiceal diameter. These findings

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Disclosure

This manuscript is not under consideration elsewhere, and the authors have nothing to disclose.

provide a framework for clinical decision-making and large-scale derivation and validation of a model to predict successful NOM of uncomplicated appendicitis.

Keywords

Appendicitis; Appendectomy; Nonoperative management; Antibiotics; Recurrent appendicitis

Introduction

Nonoperative management (NOM) with antibiotic therapy alone has emerged as an alternative to appendectomy for the treatment of acute uncomplicated appendicitis, and is often preferred by patients.¹⁻⁴ However, NOM may fail due to persistent inflammation, appendiceal perforation, or recurrent appendicitis.^{1,5,6} Complications associated with these events may be equal to or worse than complications associated with appendectomy.⁶ In the recently published Jerusalem guidelines, Di Saverio *et al.*⁷ did not find adequate evidence to recommend routine NOM of appendicitis, and both strategies remain viable options for most patients.

Rather than seeking to establish the superiority of operative *versus* NOM of appendicitis, a more effective approach may be used to determine which strategy is best for each individual patient. Several studies have identified risk factors for failing NOM of uncomplicated appendicitis. Shindoh *et al.*⁸ demonstrated that high serum C-reactive protein levels and the presence of an appendicolith are associated with failed NOM, Vons *et al.*⁹ also found that appendicoliths were associated with complicated appendicitis, and Tsai *et al.*¹⁰ recently described diabetes as a risk factor for requiring appendectomy after NOM of uncomplicated appendicitis. However, the relative importance of other potential risk factors remains unclear, and multivariable clinical prediction models have not been reported.

The aims of this study were to identify conditions present on admission that are independent predictors of successful NOM and to provide a framework for derivation and validation of clinical prediction models. We hypothesized that the absence of comorbid diabetes, absence of an appendicolith, short duration of symptoms, absence of systemic inflammation, and low modified Alvarado score would predict successful NOM.

Methods

We performed a retrospective cohort analysis of 81 consecutive patients who underwent NOM of acute uncomplicated appendicitis at our university hospital during a 4-year period ending July 1, 2016. The Institutional Review Board approval was obtained. We searched our institutional database for all adults (age ≥ 18 years) with acute appendicitis. Pregnant women, patients with complicated appendicitis (i.e., perforation or abscess), patients who did not have computed tomography (CT) scan evidence of appendicitis, patients with a prior episode of appendicitis, and patients with incomplete documentation of history and physical examination findings were excluded. Successful NOM was defined as the resolution with antibiotics alone and no recurrent appendicitis within the 180-day follow-up period. One hundred eighty days was selected as the end point of the study based on the evidence that within 2 years of NOM, the incidence of late failures occurring between 6 months and 2

years is approximately 3%, and 6-month follow-up allowed for inclusion of a greater number of patients in the study population by extending the end date of the study period.¹ During the study period, there were 667 patients presenting with acute uncomplicated appendicitis, and 81 patients underwent NOM. Patients with successful NOM ($n = 36$) were compared with patients who failed NOM ($n = 45$). Derivation of the study population is illustrated in Figure.

Conditions present on admission that were significantly different between groups were assessed for the capacity to predict successful NOM. Continuous variables were transformed to binary variables by determining the optimal cutoff value on Youden's index,¹¹ that is, the single value with optimal sensitivity and specificity for predicting successful NOM was calculated by coordinating points on the receiver operating characteristic curve. These optimal cutoff values were converted to ranges (e.g., duration of symptoms prior to admission was converted to duration of symptoms prior to admission >25 hours). Both continuous and binary variables were individually assessed for the capacity to predict successful NOM on univariate logistic regression. Variables that were statistically significant on univariate regression were entered into one of two multivariable models: one model for continuous variables, and one model for binary variables. Model strength was assessed by calculating the area under the receiver operating characteristic curve with 95% confidence intervals (CIs).

Patient demographics, comorbidities, clinical presentation, timing of admission, systemic inflammatory response syndrome criteria,¹² the modified Alvarado score,^{13–15} CT findings,¹⁶ procedural management, pathology findings, complications, and outcomes within 180 days were obtained from our institutional data repository and review of the electronic medical record. Admissions occurring between 6 PM and 6 AM were considered nighttime admissions. This study used the modified Alvarado score^{13–15} that includes eight parameters, assigning one or two points to each: pain migrating to the right lower quadrant (+1), anorexia (+1), nausea or vomiting (+1), right lower quadrant tenderness (+2), rebound tenderness (+1), temperature > 37.5°C (+1), white blood cell count > $10.0 \times 10^9/L$ (+2), and neutrophil percentage > 75 (+1). Radiology reports from CT scans performed at outside hospitals ($n = 4$ per group) were not consistently available and were not included in the analysis. Outcome variables included hospital length of stay, days on antibiotics, readmissions, complications, and mortality.

A protocol to select patients for NOM was implemented at our institution in July 1, 2015. The protocol recommended that patients with a modified Alvarado score ≥ 6 and no appendicolith would be offered NOM. Patients undergoing NOM were admitted for close observation with serial abdominal examinations and intravenous (IV) antibiotic therapy with ceftriaxone 2 g IV every 12 hours plus metronidazole 500 mg IV every 8 hours. Ceftriaxone plus metronidazole was selected as an initial antibiotic therapy based on pediatric literature demonstrating the efficacy of this approach and guidelines from the Surgical Infection Society and the Infectious Diseases Society of America.^{17–19} On admission, patients were prescribed narcotic pain medications to be taken as needed. If a patient undergoing NOM developed worsening pain or increasing leukocytosis, then appendectomy was recommended. Worsening pain was assessed subjectively by interviewing and examining

each patient at 4-hour intervals. The decision to perform appendectomy under these circumstances was at the discretion of the patient following a comprehensive discussion of the risks, benefits, and alternatives of operative and NOM, consistent with the ethical principle of patient autonomy. If a patient undergoing NOM improved clinically and tolerated nutrition, then IV antibiotics were transitioned to ciprofloxacin plus metronidazole by mouth or amoxicillin/clavulanate by mouth, to be administered until the patient received seven total days of antibiotic therapy. For patients who improved with NOM and were transitioned to oral antibiotics, amoxicillin/clavulanate was considered a suitable alternative to oral ceftriaxone plus metronidazole based on literature demonstrating the efficacy of this approach for adults with uncomplicated appendicitis.⁹ Prior to protocol implementation, although there was general agreement among surgical staff regarding patient selection for NOM, there was no formal protocol, and decisions regarding NOM were ultimately at the discretion of the attending surgeon. To assess the impact of protocol implementation on patient selection and outcomes, patients admitted before *versus* after protocol implementation were compared in Supplemental Tables 1 and 2.

Statistical analysis was performed using SPSS software, version 24 (IBM, Armonk, NY). Continuous variables were compared by the Kruskal–Wallis test and reported as median (interquartile range). Discrete variables were compared by Fisher’s exact test and reported as *n* (%). Predictors of successful NOM were reported as odds ratio (OR) (95% CI). Significance was set at $\alpha = 0.05$. Ideally, a multivariable logistic regression model should contain ten outcome events for each variable in the model.²⁰ In our model, there were 36 cases of successful NOM, such that the appropriate number of predictors would be 3.6; with four covariates in the multivariable model, the analysis was slightly underpowered. Alternatively, the multivariable model could be presented with the strongest three factors alone, but this approach may underestimate the significance of a fourth factor, which contributed significantly to the model.

Results

Baseline characteristics for the study population are listed in Table 1. Patients with successful and failed NOM had similar age (35 years), the American Society of Anesthesiologists class (2.0), and Charlson comorbidity index (0.0). A smaller proportion of the successful NOM group was admitted on a weekend (17% *versus* 36%), though the difference was not statistically significant ($P = 0.079$). Patients with successful NOM had a significantly longer duration of symptoms prior to admission (44 *versus* 24 hours, $P = 0.023$), a lower maximum temperature within 6 hours of admission (36.9 *versus* 37.2°C, $P = 0.005$), and lower modified Alvarado score (4.5 *versus* 5.0, $P = 0.048$). A lower proportion of patients in the successful NOM group had rebound tenderness (11% *versus* 29%), though the difference was not statistically significant ($P = 0.060$). CT scan findings are listed in Table 2. All patients had a CT scan, and all CT scans had evidence of appendicitis. Appendiceal diameter was significantly lower among patients with successful NOM (9.0 *versus* 10.5 mm, $P = 0.021$). Other imaging findings were similar between groups.

Outcomes are listed in Table 3. Patients with successful NOM had shorter hospital length of stay (1.4 *versus* 2.2 days, $P < 0.001$) and more days on antibiotic therapy (6.7 *versus* 2.0

days, $P < 0.001$). Of the patients who failed NOM, most (80%) failed early and required appendectomy during the index admission (Figure). Of the 36 patients who failed NOM during admission, intraoperative and pathologic assessment demonstrated perforation in 11 patients and a normal appendix in two patients. Of the nine patients who failed NOM after the initial admission, six failures occurred within 30 days. The successful NOM group had no infectious complications; 11% of all patients who failed NOM had an infectious complication ($P = 0.062$, Table 3). Interval elective laparoscopic appendectomy was performed for three patients, two of whom required overnight admission, one of whom had a malignant tumor requiring reoperation for right hemicolectomy. This patient was 70 years old, never had a previous colonoscopy, and presented with a 2-day history of nonmigratory right lower quadrant pain and mild tenderness in the absence of anorexia, nausea, vomiting, fever, or leukocytosis. CT scan demonstrated right lower quadrant fat stranding and appendiceal wall thickening, but no apparent mass. The right hemicolectomy specimen contained a 3.5-cm T4N0 low-grade mucinous adenocarcinoma with negative margins. Forty-six of 81 total patients followed up in clinic; an additional six patients were readmitted to the hospital within 2 weeks of discharge prior to clinical follow-up. There were no mortalities during the study period.

The analyses performed to describe the patient population were also performed to compare patients admitted before *versus* after protocol implementation. These comparisons are listed in Supplemental Tables 1 and 2. Patient demographics, comorbidities, admission vital signs, and admission laboratory values were similar before and after protocol implementation (Supplemental Table 1). After protocol implementation, median modified Alvarado scores were one point lower (5.0 *versus* 6.0, $P = 0.038$). CT scan findings were similar before and after protocol implementation (Supplemental Table 2).

Univariate logistic regression was performed for the four variables that were significantly different between groups (duration of symptoms prior to admission, maximum temperature within 6 hours of admission, modified Alvarado score, and appendiceal diameter). Modified Alvarado score was not significant on univariate analysis, and so the other three variables were included in a multivariable model (Table 4). All three variables contributed significantly to the multivariable model (duration of symptoms prior to admission: OR 4.26 [95% CI 1.51–12.05], maximum temperature within 6 hours of admission: 0.16 [0.04–0.58], and appendiceal diameter: 0.10 [0.01–0.90]). Area under the receiver operating characteristic curve for this model was 0.82 (0.70–0.95).

The four variables that were significantly different between groups were converted to binary variables, and univariate logistic regression was performed for these variables as well. All four variables were statistically significant on univariate analysis; therefore, all were included in the multivariable model. All four variables contributed significantly to the multivariable model (duration of symptoms prior to admission >25 hours: OR 4.17 [95% CI 1.42–12.24], maximum temperature within 6 hours of admission $<37.3^{\circ}\text{C}$: 8.07 [1.79–36.38], modified Alvarado score <4 : 9.06 [1.26–64.93], and appendiceal diameter <13 mm: 17.55 [1.30–237.28]). Area under the receiver operating characteristic curve for this model was 0.81 (0.72–0.90). There were no patients in the study population meeting all four criteria. There were nine patients meeting three criteria; six (67%) had successful NOM.

There were 37 patients meeting two criteria; 20 (54%) had successful NOM. There were 31 patients meeting one criterion; nine (29%) had successful NOM. There were four patients meeting no criteria; one (25%) had successful NOM.

Discussion

Our findings suggest that several conditions present on admission are the independent predictors of successful NOM. Although we hypothesized that patients with a shorter duration of symptoms would have less advanced disease that would be more amenable to resolution with antibiotic therapy alone, the opposite was true. We speculate that patients who more than one full day of symptoms but still hadn't progressed to complicated appendicitis represent a subgroup with a relatively indolent clinical trajectory and are therefore more likely to have successful NOM. The other predictors of successful NOM were more intuitive. Although the absence of systemic inflammatory response syndrome on admission was not associated with successful NOM, lower maximum temperature is a reasonable surrogate for the systemic inflammatory response and was predictive of successful NOM. Modified Alvarado score had mediocre performance as a continuous variable, and only a very low score (<4) was significantly associated with successful NOM. Although patients with a modified Alvarado score <4 are unlikely to have appendicitis, these patients were included in this study because they had CT scan evidence of appendicitis. Finally, smaller appendiceal diameter was associated with successful NOM, likely because greater dilation increases the likelihood of rupture according to LaPlace's Law. Although the prevalence of diabetes and the incidence of an appendicolith were similar between groups, this study may have been under-powered to detect a true difference. As expected, patients with successful NOM had shorter hospital length of stay, fewer readmissions related to appendicitis, and fewer infectious complications. These observations underscore the importance of identifying appropriate candidates for NOM who are likely to succeed with antibiotics alone.

The rate of failed NOM in this study was very high. In the Non Operative Treatment for Acute Appendicitis study, Di Saverio *et al.*¹ reported that NOM failed within 1 week for approximately 12% of all patients, compared to an early NOM failure rate of 44% in our study. Several factors may have contributed to this disparity. There were three patients with an appendicolith who failed NOM, and this finding has been previously associated with complicated appendicitis and failed NOM.^{8,9} NOM was attempted despite the presence of an appendicolith for two patients because their clinical presentation was atypical, initially casting uncertainty on the diagnosis of appendicitis, and for a third patient because it was difficult to assess whether perforation had occurred on their initial CT scan. There were also thirteen patients with rebound tenderness who failed NOM. Although rebound tenderness has not been firmly established as a contraindication to NOM and the difference between groups did not reach statistical significance in this study ($P = 0.060$), NOM be inappropriate for a patient with localized peritonitis. Finally, our threshold for considering NOM to have failed may have been too low, that is, some patients who were deemed to have failed NOM and underwent appendectomy may have had successful NOM if antibiotic therapy had been given more time to succeed. Ultimately, the high rate of failed NOM in this study and others calls into question the practice of offering NOM to a patient with uncomplicated

appendicitis, unless there is a contraindication to operative management.^{21,22} Our process for selecting patients for NOM is currently being revised based on findings from this study and emerging evidence supporting the use of the Appendicitis Inflammatory Response score.²³ When NOM is successfully employed for patients with advanced age, interval colonoscopy should be performed to assess for appendiceal and cecal tumor.

This study is limited by a small sample size ($n = 81$), the lack of a standardized approach to NOM for most of the study period, the limited generalizability inherent to single-center studies, and the propensity for overfitting the prediction models. Although the sample size could have been expanded by including patients with complicated appendicitis, this would also introduce considerable heterogeneity. The risk of overfitting could be abrogated by randomizing patients to derivation and validation cohorts, but this would require a larger sample to make meaningful comparisons. Despite these limitations, our findings may be used to inform conversations with patients in the shared decision-making process of selecting operative *versus* NOM of uncomplicated appendicitis and provide a framework for future research in large multicenter data sets. In particular, the finding that a longer duration of symptoms prior to admission was associated with successful NOM deserves further attention.

Several conditions present on admission are independent predictors of successful NOM for patients with acute uncomplicated appendicitis, including lower temperature, lower modified Alvarado score, and smaller appendiceal diameter. Interestingly, patients with a longer duration of symptoms prior to admission were more likely to have successful NOM. These findings may be used to inform conversations with patients in the shared decision-making process of selecting operative *versus* NOM of uncomplicated appendicitis. Accurate prediction of successful NOM has the potential to reduce the significant morbidity associated with failed NOM. Therefore, our findings, as well as those from previous studies,^{8–10} should be validated in a large multi-center data set.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure.
Derivation of the study population. ^aPerforation or abscess.

Table 1

Characteristics on admission for patients with successful *versus* failed nonoperative management of appendicitis.

Patient characteristics	Successful NOM (<i>n</i> = 36)	Failed NOM (<i>n</i> = 45)	<i>P</i>
Age	35 [23–59]	35 [23–50]	0.797
Female	23 (64%)	22 (49%)	0.260
ASA physical status classification	2.0 [1.0–2.0]	2.0 [1.0–2.0]	0.208
Charlson comorbidity index	0.0 [0.0–1.0]	0.0 [0.0–1.0]	>0.999
Crohn's disease	0	0	-
Diabetes	7 (19%)	5 (11%)	0.354
Without complications	7 (19%)	4 (9%)	0.203
With complications	1 (3%)	1 (2%)	>0.999
Steroid/immunosuppressant use	0	2 (4%)	0.500
Body mass index	28.2 [24.5–33.0]	27.2 [23.1–31.8]	0.421
Former smoker	6 (17%)	9 (20%)	0.779
Current smoker	10 (28%)	6 (13%)	0.160
Nighttime admission	16 (44%)	17 (38%)	0.650
Weekend admission	6 (17%)	16 (36%)	0.079
Duration of symptoms (h)			
Prior to admission	44.0 [24.1–79.1]	24.1 [15.5–52.6]	0.023
From admission to CT	2.3 [1.3–3.1]	2.0 [1.2–2.9]	0.498
T _{max} within 6 hours	36.9 [36.7–37.1]	37.2 [36.8–37.3]	0.005
T _{min} within 6 hours	36.7 [36.5–36.9]	36.8 [36.6–37.0]	0.325
Heart rate	86 [76–94]	90 [74–99]	0.518
Respiratory rate	17 [16–20]	16 [16–18]	0.129
C-reactive protein (mg/L)	15.1 [6.4–69.8]	20.3 [4.1–60.2]	0.669
White blood cell count ($\times 10^9/L$)	9.8 [8.0–14.0]	11.0 [8.5–13.6]	0.645
% Neutrophils	77.9 [61.5–84.5]	76.9 [66.3–85.5]	0.653
SIRS	8 (22%)	9 (20%)	>0.999
Absolute neutrophil count ($\times 10^9/L$)	7.7 [4.9–11.8]	7.8 [6.2–10.8]	0.681
Absolute lymphocyte count ($\times 10^9/L$)	1.4 [1.1–2.1]	1.4 [0.9–2.3]	0.862
Neutrophil:lymphocyte ratio	6.1 [2.4–10.7]	6.3 [3.3–11.6]	0.530
Alvarado score	4.5 [4.0–6.0]	5.0 [4.0–6.0]	0.048
Migratory RLQ pain	11 (31%)	19 (42%)	0.356
Anorexia	27 (75%)	31 (69%)	0.624
Nausea or vomiting	23 (64%)	27 (60%)	0.819
RLQ tenderness	32 (89%)	43 (96%)	0.399
Rebound tenderness	4 (11%)	13 (29%)	0.060

ASA = American Society of Anesthesiologists; SIRS = systemic inflammatory response syndrome; RLQ = right lower quadrant. Data are presented as median (interquartile range) or *n* (%).

Table 2

Findings on admission computed tomography for patients with successful *versus* failed nonoperative management of appendicitis.

CT scan findings	Successful NOM (<i>n</i> = 36)	Failed NOM (<i>n</i> = 45)	<i>P</i>
Had a CT scan	36 (100%)	45 (100%)	-
CT performed at OSH [*]	4 (11%)	4 (9%)	>0.999
CT with intravenous contrast	32 (100%)	38 (93%)	0.251
Right lower quadrant fluid	3 (9%)	8 (20%)	0.328
Fat stranding	21 (66%)	32 (78%)	0.294
Appendicolith	1 (3%)	3 (7%)	0.626
Appendix diameter (mm)	9.0 [8.0–10.0]	10.5 [9.0–14.3]	0.021
Wall thickening	7 (22%)	3 (7%)	0.093
Mural enhancement	11 (34%)	13 (32%)	>0.999
Phlegmon/abscess/perforation	0	0	-

OSH = outside hospital.

Data are presented as *n* (%) or median (interquartile range).

* Findings from outside hospital CT scans were not consistently reported and were not included in the analysis.

Table 3

Outcomes for patients with successful *versus* failed nonoperative management of appendicitis.

Outcomes	Successful NOM (<i>n</i> = 36)	Failed NOM (<i>n</i> = 45)	<i>P</i>
Hospital length of stay (days)	1.4 [1.0–2.0]	2.2 [1.7–3.2]	<0.001
Total antibiotic days	6.7 [3.9–8.3]	2.0 [0.9–5.8]	<0.001
Inpatient antibiotic days	1.3 [0.9–1.8]	1.5 [0.9–2.7]	0.372
Outpatient antibiotic days	5.0 [3.0–7.0]	0.0 [0.0–2.5]	<0.001
Clinic follow-up	14 (39%)	32 (71%)	0.006
Days to clinic follow-up	26 [19–30]	20 [14–23]	0.031
Readmission within 180 days	3 (8%)	10 (22%)	0.129
For surgical site infection	0	1 (2%)	>0.999
For appendicitis	0	9 (20%)	0.004
For elective appendectomy	3 (8%)	0	0.084
Infectious complications	0	5 (11%)	0.062
Surgical site infection	0	3 (7%)	0.250
Superficial	0	2 (4%)	0.500
Deep	0	1 (2%)	>0.999
Organ/space	0	0	-
Other nosocomial infection	0	2 (4%)	0.500
Mortality within 180 days	0	0	-

SIRS = systemic inflammatory response syndrome.

Data are presented as median (interquartile range) or *n* (%).

Table 4

Univariate and multivariable predictors of successful NOM.

Variable type	Factors	Univariate regression			Multivariable models*		
		OR	95% CI	P	OR	95% CI	P
Continuous variables	Duration of symptoms PTA (h)	1.02	1.01–1.03	0.011	4.26	1.51–12.05	0.006
	T _{max} on admission (°C)	0.14	0.03–0.61	0.009	0.16	0.04–0.58	0.006
	Modified Alvarado score	0.71	0.50–1.01	0.053	-	-	-
Binary variables [†]	Appendiceal diameter (mm)	0.77	0.60–0.99	0.038	0.10	0.01–0.90	0.040
	Duration of symptoms PTA >25 h	3.00	1.20–7.49	0.019	4.17	1.42–12.24	0.009
	T _{max} on admission <37.3°C	4.41	1.32–14.73	0.016	8.07	1.79–36.38	0.007
	Modified Alvarado score <4	5.19	1.01–26.77	0.049	9.06	1.26–64.93	0.028
	Appendiceal diameter <13 mm	10.00	1.21–82.35	0.032	17.55	1.30–237.28	0.031

PTA = prior to admission.

* Area under the receiver operating characteristic curve (AUC) for continuous variable model: 0.82 (0.70–0.95); AUC for discrete variable model: 0.81 (0.72–0.90).

[†]Optimal limits were selected by Youden's index.