Modified Pouchitis Disease Activity Index

A Simplified Approach to the Diagnosis of Pouchitis

Bo Shen, M.D.,* Jean-Paul Achkar, M.D.,* Jason T. Connor, M.S.,†
Adrian H. Ormsby, M.D.,‡ Feza H. Remzi, M.D.,§ Charles L. Bevins, M.D., Ph.D.,*§
Aaron Brzezinski, M.D.,* Marlene L. Bambrick, R.N.,§ Victor W. Fazio, M.B., M.S.,§
Bret A. Lashner, M.D., M.P.H.*

*From the Center for Inflammatory Bowel Disease, Departments of *Gastroenterology, †Biostatistics and Epidemiology, ‡Anatomic Pathology, and §Colorectal Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio*

PURPOSE: Pouchitis is the most common complication of ileal pouch-anal anastomosis for ulcerative colitis. Our previous study suggested that symptoms alone are not reliable for the diagnosis of pouchitis. The most commonly used diagnostic instrument is the 18-point pouchitis disease activity index consisting of three principal component scores: symptom, endoscopy, and histology. Despite its popularity, the pouchitis disease activity index has mainly been a research tool because of costs of endoscopy (especially with histology), complexity in calculation, and time delay in determining histology scores. It is not known whether pouch endoscopy without biopsy can reliably diagnose pouchitis in symptomatic patients. The aim of the present study was to determine whether omitting histologic evaluation from the pouchitis disease activity index significantly affects the sensitivity and specificity of diagnostic criteria for pouchitis. METHODS: Ulcerative colitis patients with an ileal pouch-anal anastomosis and symptoms suggestive of pouchitis were evaluated. Patients with chronic refractory pouchitis and Crohn's disease were excluded. Patients with pouchitis disease activity index scores of seven or more were diagnosed as having pouchitis. Different diagnostic criteria were compared on the basis of the pouchitis disease activity index component scores. Nonparametric receiver-operating-characteristic curves were used to measure proposed pouchitis scores' diagnostic accuracy compared with diagnosis from the pouchitis disease activity index. The receiver-operating-characteristic area under the curve measured how much these diagnostic strategies differed from each other. RESULTS: Fifty-eight consecutive symptomatic patients were enrolled; 32 (55 percent) patients were diagnosed with pouchitis. With the use of the pouchitis disease activity index as a criterion standard, the use of only symptom and endoscopy scores (modified pouchitis disease activity index) produced an area under the curve of 0.995. Establishing a cut-point of five or more for diseased patients resulted in a sensitivity equal to 97 percent and specificity equal to 100 percent. CONCLUSIONS: Diagnosis based on the modified pouchitis disease activity index offers similar sensitivity and specificity when compared with the pouchitis disease activity index for patients with acute or acute relapsing pouchitis. Omission of endoscopic biopsy and histology from the standard pouchitis disease activity index would simplify pouchitis diagnostic criteria, reduce the cost of diagnosis, and avoid delay associated with determining histology score, while providing equivalent sensitivity and specificity. [Key words: Diagnosis; Pouchitis]

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Total proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the surgical treatment of choice for refractory ulcerative colitis (UC). Pouchitis is the most common long-term complication of this surgery, with a ten-year cumulative incidence ranging from 24 to 48 percent.[1–5] The most frequently reported symptoms of pouchitis are increased stool frequency, fecal urgency, abdominal cramping, and pelvic discomfort. In clinical practice, pouchitis often is diagnosed on the basis of symptoms alone and empirically treated with metronidazole. Patients who do not respond to initial therapy usually undergo further diagnostic tests, including pouch endoscopy. However, symptoms are not specific for pouchitis, and they can instead be caused by inflammation of the rectal cuff, a condition resembling irritable bowel syndrome,[6,7] jejunal bacterial overgrowth,[8,9] Crohn's disease,[10] and pouch-outlet obstruction.[11] Symptoms do not necessarily correlate with endoscopic and histologic findings.[1,6-9,12–15]

Ideally, pouchitis should be diagnosed on the basis of combined assessment of symptom, endoscopy, and histology. Semi-objective assessments to diagnose pouchitis in patients with IPAA have been proposed using composite scores such as the Pouchitis

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Address reprint requests to Dr. Shen: Department of Gastroenterology/Desk A30, The Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, Ohio 44195.

Triad,[13] Heidelberg Pouchitis Activity Score,[16] and pouchitis disease activity index (PDAI).[4] Each of these diagnostic instruments consists of three components: clinical symptoms, endoscopy, and histology. With the lack of a criterion standard for the diagnosis of pouchitis, an 18-point PDAI was proposed by Sandborn *et al*.[4] and has become the most commonly used diagnostic instrument. The 18-point PDAI consists of three principal component scores: symptoms (range, 0–6 points), endoscopy (range, 0–6 points), and histology (range, 2–6 points). We found that symptom, endoscopy, and histology did not correlate with each other and that a combination of two or more components of assessment (symptom, endoscopy, and histology) is needed to make a diagnosis.[6] Use of a diagnostic instrument that allows for assessment of symptoms and endoscopic and histologic evaluations provides an optimal approach to accurately diagnose pouchitis. From a cost standpoint, however, the cost of endoscopy with biopsy may deter cost-conscious clinicians from routinely performing this procedure to make a diagnosis. Therefore, diagnostic instruments such as the PDAI remain mostly research tools. Other obstacles for the routine clinical application of the PDAI include the complexity in calculation of the score and the time delay in scoring necessitated by a histologic evaluation. To find a compromise between achieving accurate diagnosis and cost savings, a diagnostic instrument that is simple to apply and that does not sacrifice sensitivity and specificity would be ideal. It is not known whether a simplified approach of using pouch endoscopy without biopsy can reliably diagnose pouchitis in symptomatic patients. Therefore, the aim of the study was to analyze the PDAI component scores in symptomatic patients with and without pouchitis to determine whether omitting histologic evaluation significantly affects the sensitivity and specificity of the diagnostic criteria.

PATIENTS AND METHODS

Study Subjects

As a part of a larger project on the investigation of pathogenesis and management of pouchitis, 58 consecutive UC patients with IPAA and PDAI symptom scores of one or more who responded to an advertisement in our pouch registry newsletter were studied. Some of these patients were included in our previous study of irritable pouch syndrome.[7] Although some of the study patients had been treated with antibiotics for presumed pouchitis in the past, none of them had been previously diagnosed with pouchitis on the basis of PDAI criteria, and none had been treated for pouchitis in the previous two weeks. Exclusion criteria included age less than 18 years, suspected Crohn's disease, maintenance therapy with antibiotics for chronic pouchitis, or use of 5-aminosalicylate products or corticosteroids.

Diagnostic Criteria

The 18-point PDAI was used (Table 1). A single investigator (BS) collected demographic data and scored symptoms before pouch endoscopy. Endoscopic scores were determined by consensus between two endoscopists. Biopsies were taken from the posterior wall of the pouch if the pouch had a normal endoscopic appearance or from areas of maximal inflammation. A single gastrointestinal pathologist (AHO), blinded to the clinical presentations and

Table 1.
The Pouchitis Disease Activity Index[4]

Criteria	Score
Clinical	
Stool frequency	
Usual postoperative stool frequency	0
1–2 stools/day > postoperative usual	1
3 or more stools/day > postoperative usual	2
Rectal bleeding	
None or rare	0
Present daily	1
Fecal urgency or abdominal cramps	
None	0
Occasional	1
Usual	2
Fever (temperature > 37.8° C)	
Absent	0
Present	1
Endoscopic inflammation	
Edema	1
Granularity	1
Friability	1
Loss of vascular pattern	1
Mucous exudates	1
Ulceration	1
Acute histologic inflammation	
Polymorphic nuclear leukocyte infiltration	
Mild	1
Moderate + crypt abscess	2
Severe + crypt abscess	3
Ulceration per low-power field (mean)	
>25%	1
25–50%	2
>50%	3

endoscopic findings, assessed the pouch biopsies for grade of inflammation. On the basis of the criteria proposed by Sandborn *et al.*,[4] patients with a total PDAI of seven or more were classified as having pouchitis. Symptomatic patients without endoscopic and histologic evidence of pouchitis and a PDAI less than seven points were defined as not having pouchitis.

Validation of the modified PDAI (mPDAI), in which the histology component was omitted, was performed by applying it to our previously published randomized clinical trial of metronidazole and ciprofloxacin for acute pouchitis in which the standard PDAI was used for diagnosis and for assessment of treatment response.[17]

Statistical Model

The primary endpoint was diagnosis of pouchitis made by the PDAI. Different diagnostic strategies were compared on the basis of the PDAI scores. Nonparametric (empiric) receiver-operating-characteristic curves were used to measure diagnostic ability of proposed tests. When comparing a continuous or ordinal diagnostic tool to a known dichotomous diagnosis, receiver-operating-characteristic curves illustrate the sensitivity-specificity trade-off for all possible cutoffs of the continuous or ordinal variable. Lacking a true standard, the PDAI was used as a criterion standard. Cutoffs were chosen on the basis of optimizing the sensitivity-specificity tradeoff. S-PLUS 6.0® (Insightful, Inc., Seattle WA) was used for all analyses.

RESULTS

Fifty-eight consecutive symptomatic patients were enrolled; 32 (55 percent) patients were diagnosed with pouchitis whereas 26 (45 percent) patients were categorized as not having pouchitis. The mean total PDAI, symptom, endoscopy, and histology scores in patients with or without pouchitis are shown in Table 2. For patients with pouchitis, symptom and endoscopic scores contributed the most to the total PDAI scores, whereas for patients without pouchitis, symptom scores made the greatest contribution. These results suggest that the endoscopic evaluation in the PDAI scoring system has the most discriminating power in differentiating patients with pouchitis from those without pouchitis. The discriminating power of histology scores, on the other hand, appears to be minimal. On this basis, we then investigated the effect of omitting the histology component to determine whether it significantly affected the diagnostic accuracy of the PDAI.

Various combinations of symptom, endoscopy, and histology components were introduced into the statistical model (Table 3). Different cutoff levels were tried to optimize the sensitivity and specificity (Fig. 1; Table 3). The optimal cutoff was chosen by inspecting Table 4. Using a cutoff of five or more to diagnose pouchitis resulted in 97 percent sensitivity and 100 percent specificity. Cutoffs of either four or six would result in significant decreases in specificity or sensitivity, respectively. The area under the curve was 0.995. Table 4 shows the results of comparison of diagnoses made by the PDAI and mPDAI. In only 1 of 58 (2 percent) cases did the two instruments offer different diagnoses. In comparison with the PDAI criteria as a criterion standard, mPDAI criteria yielded 0 percent false-positive tests and 4 percent (1/27) false-negative tests.

All six endoscopic subcomponent scores (edema, granularity, friability, loss of vascular pattern, mucus exudates, and ulcer) contributed to the total endoscopic score with a similar degree of magnitude. Therefore, it is reasonable to give the same weight for each the endoscopic components of the PDAI to the mPDAI.

The mPDAI was further validated by applying it to the results of our previous published randomized clinical trial of metronidazole *vs.* ciprofloxacin for acute pouchitis in which the standard PDAI was used for diagnosis and for assessment of treatment response.[17] In this study, 16 patients with acute pouchitis, diagnosed by the 18-point PDAI with a cut-point of seven, were treated with either ciprofloxacin or metronidazole. All patients (n = 7) in the ciprofloxacin group and six (67 percent) patients in the metronidazole group responded to the

Table 2.
Comparison of Mean Total PDAI Score and Component Scores Between Symptomatic Patients With Pouchitis and Without Pouchitis*

	Pouchitis n = 32	Nonpouchitis n = 26
Total PDAI score	9.8 ± 2.1	4.6 ± 1.3
Symptom score	3.2 ± 1.0	2.1 ± 1.1
Endoscopy score	3.7 ± 1.5	0.3 ± 0.5
Histology score	2.9 ± 1.0	2.2 ± 0.6

PDAI = pouchitis disease activity index.
* Values reported are mean ± one standard deviation.

Table 3.
Comparison of Diagnostic Accuracy of the PDAI and Modified PDAI*

Components	ROC AUC	Scale Range	Pouchitis Cut-Point	Sensitivity	Specificity
Symptom + endoscopy + histology (PDAI)	1.00	2–18	≥7	1.00	1.00
Symptom + endoscopy (mPDAI)	0.995	0–12	≥5	0.97	1.00
Symptom only	0.77	0–6	≥3	0.74	0.63

PDAI = pouchitis disease activity index; mPDAI = modified pouchitis disease activity index; AUC = receiver-operating-characteristic area under curve.

* To calculate sensitivity and specificity, the PDAI was used as a critereon standard.

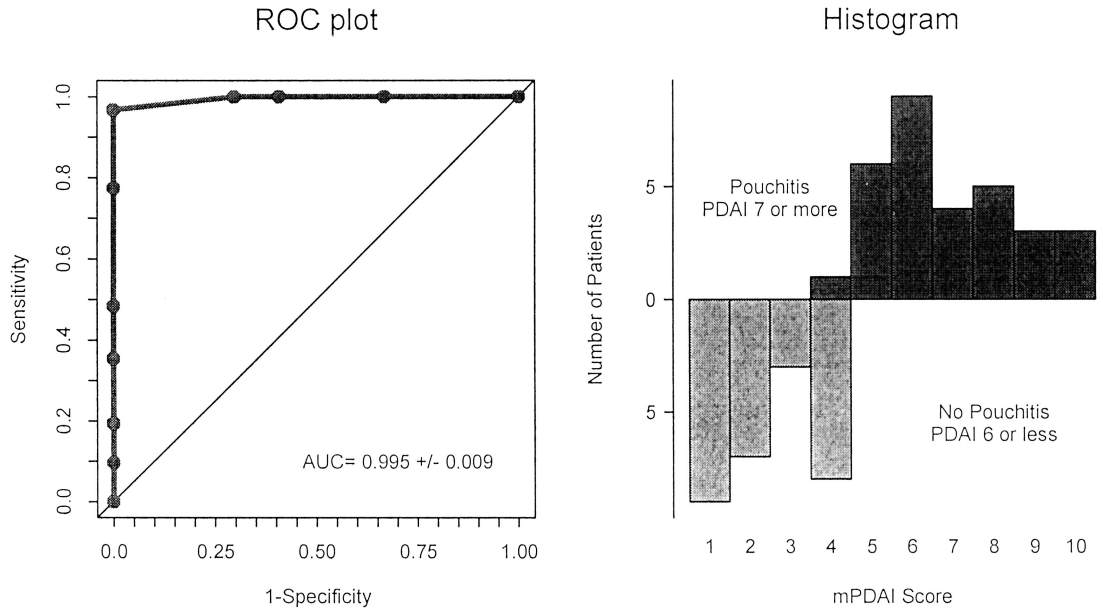

Figure 1. The left plot shows that the receiver-operating characteristic (ROC) curve with area under curve (AUC) = 0.995, indicating extremely good prediction. The right plot shows the histogram of modified pouchitis disease activity index (mPDAI) scores for the two groups: pouchitis above the horizontal and nonpouchitis below the horizontal.

antibiotic therapy, with response defined as a reduction in the PDAI score of three or more. We then applied the 12-point mPDAI to the same study population and defined response as a reduction in mPDAI score of two or more (proportional to ≥3 points in the 18-point PDAI); the response rates in both groups were identical (*i.e.*, 100 percent of response rate in the ciprofloxacin group and 67 percent of response rate in the metronidazole group).

DISCUSSION

Pouchitis-like symptoms in UC patients after total proctocolectomy and IPAA are common. Such symptoms may be caused by pouchitis, sphincter dysfunction, anastomotic stricture, pouch-outlet obstruction, rectal-cuff inflammation, or an irritable bowel syndrome-like condition. Pouchitis often is diagnosed on the basis of symptoms alone, but previous studies have shown that symptoms in patients with IPAA do not always correlate with the diagnosis of pouchitis.[6] In this study, using the PDAI criteria, 55 percent of symptomatic patients were diagnosed with pouchitis. Consistent with our previous studies and reports in the literature, the results suggest that patients with symptoms suggestive of pouchitis do not necessarily have pouchitis.

Diagnosis of pouchitis in this study was based on the PDAI. No independent diagnosis of those patients was made by other diagnostic instruments. This complicates the analysis because it makes measuring the diagnostic ability of the PDAI itself impossible. We

Table 4.
Comparison of Diagnoses Made by the PDAI to Potential Diagnoses Made by the mPDAI

mPDAI Score	PDAI < 7	PDAI ≥ 7	Cutoff	Sensitivity	Specificity
0	0	0	≥0	1.00	0.00
1	9	0	≥1	1.00	0.00
2	7	0	≥2	1.00	0.33
3	3	0	≥3	1.00	0.59
4	8	1	≥4	1.00	0.70
5	0	6	≥5	0.97	1.00
6	0	9	≥6	0.77	1.00
7	0	4	≥7	0.48	1.00
8	0	5	≥8	0.35	1.00
9	0	3	≥9	0.19	1.00
10	0	3	≥10	0.10	1.00
11	0	0	≥11	0.00	1.00

PDAI = pouchitis disease activity index; mPDAI = modified pouchitis disease activity index.

assumed that the PDAI accurately classified all patients. The overall goal of this analysis was to make the diagnostic instrument more efficient and less costly.

Symptoms, endoscopy, and histology did not correlate with each other, implying that all were needed for the diagnosis of pouchitis.[6–9,12–15] However, the costs and inherent delay in calculating PDAI scores, especially the histology component, are major obstacles for clinicians to routinely apply this diagnostic instrument in daily practice. In our initial study, we noted that histology scores were similar in symptomatic patients with pouchitis and symptomatic patients without pouchitis diagnosed on the basis of the PDAI.[6] This prompted us to see whether the histology score in the PDAI contributed much to the sensitivity and specificity of the diagnostic instrument. In this study, we have demonstrated that omitting biopsy and histologic evaluation is justifiable for the diagnosis of acute pouchitis or relapsing pouchitis because it does not compromise diagnostic sensitivity or specificity of the PDAI. Omitting biopsy and histologic evaluation would shorten procedure time, reduce cost, and allow immediate calculation of mPDAI scores. This, in turn, would help the clinician direct appropriate therapy without the delay associated with awaiting histologic interpretation. This simplified approach using the mPDAI was effective in assessing the patients' response to treatment in our previously published randomized clinical trial.[17] We and others showed that symptoms, endoscopy, and histology did not correlate with each other.[6–9,12–15] Therefore, relying on a single component, like symptom score, may not accurately diagnose pouchitis.[6,11] We believe that two or more components are necessary to make a correct diagnosis. The current study shows that symptom assessment and endoscopic evaluation together are nearly as good as using all three components of the PDAI to accurately diagnose acute and acute relapsing pouchitis.

However, in the subset of patients with chronic refractory pouchitis who are resistant to antibiotic therapy or require long-term maintenance therapy, we would recommend endoscopic biopsies and histologic evaluation to rule out conditions such as Crohn's disease or cytomegalovirus infection.[18] Pouchitis secondary to Crohn's disease or to cytomegalovirus is uncommon. Only a minority of patients (less than 15 percent) with pouchitis had endoscopic features of Crohn's disease.[15,19,20] Furthermore, rarely are features of Crohn's disease, such as granulomas, detected in mucosal biopsy. As for cytomegalovirus, there are only case reports in the literature.[18,21,22] Clinical course in patients with IPAA and with either Crohn's disease or cytomegalovirus infection is often chronic and refractory to routine antibiotic therapy. Other causes of pouch symptoms, such as pouch-outlet obstruction or intussusception, could be diagnosed on pouch endoscopy without biopsy. We believe that the standard PDAI is an excellent research tool. For example, inclusion of histologic evaluation in the diagnosis and outcome measurement is important in future clinical trials.

CONCLUSION

Although the standard PDAI remains an optimal way to diagnose pouchitis, the mPDAI, consisting of symptom and endoscopy scores from the PDAI but omitting histology scores, offers similar sensitivity and specificity in diagnosing patients with acute or acute relapsing pouchitis. This approach simplifies pouchitis diagnostic criteria, reduces cost of diagnosis, and avoids delay in determining histology. In addition, the mPDAI offers better sensitivity and specificity when compared with symptom assessment alone. Therefore, we believe that the mPDAI simplifies the PDAI and is a practical and alternative diagnostic instrument that is readily applicable to routine clinical practice.

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