Title page

Original article

Title

Pouchitis Disease Activity Index (PDAI) does not predict patients with symptoms of pouchitis who will respond to antibiotics.

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Short title

Diagnosis of pouchitis by PDAI

Keywords

pouchitis, PDAI, ulcerative colitis

ABSTRACT

Purpose. To evaluate whether the pouchitis disease activity index (PDAI) alone is sufficient to design appropriate treatment plans for ulcerative colitis patients with bowel movement problems following ileal pouch-anal anastomosis (IPAA).

Methods. The study included 70 patients undergoing an IPAA . For patients evaluation by PDAI was performed prospectively at 1-2 years after ileostomy closure. When symptoms relevant to bowel movement appeared, PDAI was evaluated and metronidazole or ciprofloxacin was administered. Pouchitis was diagnosed in patients with PDAI scores of 7 or more. Patients whose PDAI score was less than 7 points who responded to antibiotic therapy were defined as treatment responders having disease not diagnosed by PDAI (TR-NDPDAI).

Results. Pouchitis was diagnosed in 16 of 70 enrolled patients (22.9%) using the PDAI scoring system. Of these, 11 had acute pouchitis and 5 had chronic pouchitis. Twenty-one patients whose PDAI score was less than 7 were symptomatic. Among them, 12 were TR-NDPDAI. In patients with TR-NDPDAI, antibiotic treatment resulted in significant improvements

after treatment in the PDAI score ($p<0.001$) and in clinical symptoms ($p<0.001$).

Conclusion. Antibiotic treatment was effective in a considerable number of ulcerative colitis patients whose PDAI score was less than 7 after IPAA.

Introduction

Since the ileal pouch-anal anastomosis (IPAA) was first described[1], IPAA has become the preferred operation for ulcerative colitis (UC). While surgical advancements for IPAA have decreased short-term morbidity, long-term complications such as pouchitis[2], small bowel obstruction[3] and portal vein thrombi[4], continue to be a problem.

Pouchitis is an idiopathic inflammatory disease of the ileal reservoir that may occur after IPAA. The frequency of pouchitis varies from 7% to 59% [4,5]. There are no universal diagnostic criteria, and differences in the diagnostic criteria between institutions may account for the wide range of occurrence. The pouchitis disease activity index (PDAI) was proposed by the Mayo Clinic and has three components: clinical symptoms, endoscopic

findings, and pathological findings[6]. A diagnosis of pouchitis made from only subjective measures of disease activity, such as the symptoms, may lead to over-assessment[2,6]. Therefore, incorporation of objective data such as endoscopic and pathological findings is considered necessary for an accurate evaluation. So the PDAI was more widely-used criteria for diagnosis of pouchitis and preferable tool for clinical study.

However, the diagnostic ability of the PDAI itself is difficult to assess because an absolute diagnosis of pouchitis cannot be made using other diagnostic criteria[7]. In addition, the information from the PDAI does not give a clear diagnosis and prediction of the best treatment. Pouchitis is often not diagnosed using the PDAI, even in symptomatic patients. Antibiotic therapy is successful in some of these patients not diagnosed by PDAI[2,8].

The objective of the current study was to examine whether the PDAI alone was sufficient to design a treatment strategy for symptomatic patients after ileal pouch-anal anastomosis. Two indices – the PDAI and the response to antibiotics – were used to classify patients who had ileal pouch-anal anastomosis and exhibited bowel movement symptoms.

MATERIALS AND METHODS

Study population

Subjects were selected from all patients who had undergone a total colectomy and ileal pouch-anal anastomosis for ulcerative colitis with simultaneous temporary ileostomy between January 1997 and December 2003 at the First Department of Surgery, Hiroshima University, and for whom 1 to 2 years had passed since the ileostomy closure. None of them had been previously diagnosed with pouchitis by PDAI. Patients were excluded if they were 12 years old or younger, took antibiotics recently (within 2 weeks before they entered this study), had infection enteritis, or were suspected of having Crohn's disease postoperatively or had nonfunctioning ileal pouches (e.g., patients with evacuation tubes).

Study design

Outpatient endoscopy was performed in patients with or without symptoms 1–2 years after the closure of ileostomy to evaluate inflammatory changes of the pouch. A prospective evaluation was

performed on endoscopic findings of ileal pouch mucosa and on pathological findings from a biopsy. In addition, for patients whose bowel movement symptoms worsened during the study period, evaluation by PDAI was performed and metronidazole 750 mg/day or ciprofloxacin 1000 mg/day was orally administered for 14 days. The worsening of symptoms was defined as increase in PDAI symptoms score of one or more points. The daily-recommended dose of metronidazole is 1200 mg or 15-20 mg/kg [9]. However, we set the dose of metronidazole at 750 mg/day, because UC patients in Japan weigh less than patients in Europe or the US, and Japanese patients tend to have more gastrointestinal symptoms at the dose used in Europe or the US. The protocol for this study was conducted with the written consent of each participant.

Method of diagnosis of pouchitis

Clinical symptoms, endoscopic findings, and pathological findings were assigned scores using the PDAI as proposed by the Mayo Clinic[6]. The PDAI has three components: clinical symptoms, endoscopic findings, and pathological findings. The highest score for each component is 6, and a

total score of 7 is considered to indicate pouchitis (PDAI-diagnosed pouchitis). The patients were interviewed and their clinical symptoms scored during outpatient visits by the same physician. Endoscopies were performed by one of the three specified endoscopists. Films taken during endoscopy were examined and used to evaluate endoscopic findings. During the endoscopies, biopsies were taken from pouches with or without particular findings of inflammation. Pathological findings were reexamined and scored at the same time in a blinded fashion by one pathologist.

A PDAI endoscopy score of 1 or more was defined as indicating positive endoscopic findings, a PDAI pathological score of 3 or more as indicating positive pathological findings, and a clinical score of 1 or more as indicating positive clinical findings.

Definition of pouchitis, TR-NDPDAI, cuffitis, and irritable pouch syndrome (IPS)

Therapeutic effects were evaluated by examining clinical symptom changes during the 2 weeks following the start of antibiotic treatment for symptomatic patients. Outcome was evaluated by PDAI, which is based on

symptomatic, endoscopic, and pathological findings (Table 1). Patients were defined as treatment responders having disease not diagnosed by PDAI if they responded to antibiotics and their PDAI scores were less than 7 points (TR-NDPDAI). Responsiveness in TR-NDPDAI was defined as reduction in PDAI symptom score by one or more points within 2 weeks after antibiotic treatment. Cuffitis was diagnosed in patients with a PDAI score of less than 7 and significant inflammatory findings in the residual rectum. Irritable pouch syndrome (IPS) was diagnosed in nonresponders with a PDAI score of less than 7 who underwent mucosectomy or had no inflammatory changes in the residual rectum [10].

Statistical analysis

A chi-square test was used for categorical data (comparisons of patient background data). The Student *t*-test was used for continuous data. The Mann-Whitney *U*-test was used to compare the scores of each PDAI component between the two groups. A comparison between before and after the antibiotic treatment was performed for every component using the Wilcoxon test. Logistic regression models were used to determine which

components were significantly related to PDAI score less than 7 in TR-NDPDAI as compared with pouchitis. A p-value of 0.05 or less was considered statistically significant. All data are indicated as mean ± SD.

RESULTS

Within the study period, 102 patients underwent surgeries for ulcerative colitis. Each surgery was performed by the same surgeons. A hand-sewn ileal pouch-anal anastomosis with mucosectomy was performed in 65 patients and a double-stapled technique was used in 5 patients. In 20 and 12 patients, we were unable to obtain consent to perform post-surgical endoscopy and biopsies during endoscopy, respectively. All of these patients were asymptomatic. Thus, a total of 32 patients were excluded, and the remaining 70 patients were entered into the study. The median follow-up period at the endoscopic examination in these 70 patients was 22 months (range, 12-81 months) after ileostomy closure.

Among the 70 patients, 37 (52.9%) were symptomatic, all of whom were treated with antibiotics. The treatment was successful in 23 of these 37 patients. Of the 70 patients, 16 (22.9%) had PDAI-diagnosed pouchitis

(PDAI scores of 7 or more); however, the occurrence rate was 15.7% of the 102 eligible patients, including the asymptomatic patients who did not consent to endoscopic examinations and biopsies. There were 12 TR-NDPDAI (8 with positive endoscopic findings [≥ 1 point] and 4 with positive pathological findings [≥3 points]). Six of the 12 were unaware of the worsening of their symptoms because the deterioration was gradual. We found that their symptoms were worsening only after checking previous data in the medical records. Of the 12 TR-NDPDAI, 8 (67%) had objective evidence based on endoscopy and 4 (33%) had objective evidence based on pathological findings.

Table 2 shows the demographic characteristics of all study patients. There were no significant differences between the three groups in age, gender, duration of disease before surgery, dose of steroid, or surgical indication. Figure 1 shows the diagnostic tree for each patient group. Of the 16 PDAI-diagnosed pouchitis patients, 11 had acute pouchitis and 5 had chronic pouchitis. Of the 37 symptomatic patients, 21 had PDAI scores of less than 7; 12 of these 21 patients were TR-NDPDAI and 9 were nonresponders. Furthermore, 2 of these 9 had cuffitis and the other 7 had

IPS. During the study period, 33 patients were asymptomatic and therefore not suspected of having pouchitis that required treatment. The PDAI score was 2.8±1.1 for asymptomatic patients and 6.9±2.8 for symptomatic patients ($p<0.001$).

Figure 2 shows changes in the pretreatment and posttreatment scores of 12 TR-NDPDAI. The PDAI score and clinical symptom score showed significant improvement (total PDAI score, 5.0±1.1 *vs.* 3.2±1.1 [p= 0.002]; clinical symptoms score, 1.6±0.8 *vs.* 0.2±0.4 [p=0.002]). Because the scores for endoscopic findings were initially low in TR-NDPDAI, no significant improvement was observed after the treatment (1.0±1.0 *vs.* 0.8±1.1; p= 0.157). In addition, the scores for pathological findings did not reveal improvement (2.4±0.7 *vs.* 2.2±0.4; p=0.083).

The mean total PDAI score and each component score in patients with PDAI-diagnosed pouchitis and in TR-NDPDAI are compared in Table 3. There was no significant difference between the two groups in clinical symptoms score (2.7±1.4 *vs.* 1.9±0.8; p=0.103). TR-NDPDAI, however, had significantly lower scores for endoscopic and pathological findings (endoscopic findings; 3.3±1.7 *vs.* 1.0±1.0 [p= 0.001], pathological findings;

3.5±0.9 *vs.* 2.4±0.7 [p=0.003]). The contributor to low PDAI score in TR-NDPDAI was the particularly low score for endoscopic and pathological findings. In univariate logistic regression models, scores for endoscopic and pathological findings were the main predictors of PDAI score 7 or more in PDAI diagnosed pouchitis compared with TR-NDPDAI (endoscopic findings; odds ratio 3.257, 95% confidence interval [1.319-8.044], pathological findings; odds ratio 4.645, 95% confidence interval [1.520-14.200]). Clinical symptoms score, however, was not a significant factor (symptoms; odds ratio 1.761, 95% confidence interval [0.869-3.571]).

Table 4 shows scores of subgroups that were classified on the basis of PDAI score and response to antibiotics. There was no significant difference in the PDAI score between the TR-NDPDAI and IPS groups (5.3±0.7 *vs.* 5.2±1.1; p=0.857). There was a significant difference only in the clinical symptoms score (1.9±0.8 *vs.* 1.1±0.4; p=0.028), but not in the objective scores for endoscopic findings (1.0±1.0 *vs.* 1.3±1.3; p=0.505) or pathological findings (2.4±1.7 *vs.* 2.8±0.9; p=0.253).

There was also no significant difference in pathological findings

between the TR-NDPDAI and asymptomatic patients (2.4±1.7 *vs.* 2.5±0.7; p=0.890). Clinical symptoms and endoscopic findings scores were significantly higher in TR-NDPDAI than in asymptomatic patients (symptoms, 1.9±0.8 *vs.* 0.0±0.0 [p<0.001]; endoscopic findings, 1.0±1.0 *vs.* 0.3±0.6 [p=0.015]). In the two cases of cuffitis, endoscopic findings score was 0.

DISCUSSION

Various problems have been identified in the PDAI [6-9, 11-13], and some have proposed that objective findings such as endoscopy and pathology should be emphasized more than subjective assessment of clinical symptoms[9,11]. On the other hand, in one report, the clinical symptoms of chronic pouchitis improved following treatment with metronidazole, while the objective (endoscopy and pathology) findings did not [13], suggesting that the therapeutic effect cannot effectively be determined from objective findings. Furthermore, various problems have been identified in relating the assessment by pathological findings to the PDAI[7,12]. Shen et al. stated that sensitivity and specificity of the modified

PDAI, which excludes pathological findings, should be accepted[7] and that biopsies are probably unnecessary from the viewpoint of economic efficiency[12]. From the Japanese group, the Japanese criteria which was consisted of clinical symptoms and endoscopic findings and did not contain pathological findings and scoring system, was proposed as more simple and useful criteria in clinical practice[14]. In this paper we selected the PDAI which was widely-used criteria to evaluate also pathological findings and severity.

Furthermore, Heuschen et al.[9] suggested that the cutoff of 7 points is too high for the diagnosis of pouchitis and that if the cutoff point were one or two points lower, the PDAI would be more accurate. In addition, a question has been raised regarding the treatment of patients with PDAI scores of less than 7 but who are responsive to antibiotics[8]. Therefore, in the current study, we combined two indices (diagnosis using the PDAI and estimation according to the response to antibiotics) and then subclassified the symptomatic patients. We found a significant number of cases in which antibiotic treatment was effective in patients with low PDAI scores. Of the 70 patients, 37 were symptomatic but only 16 had PDAI-diagnosed

pouchitis. Of the remaining 21 symptomatic patients, 12/21(57.1%) responded to antibiotics. So using the PDAI score (≥7), 12 patients who were relieved symptoms by antibiotics were missed. Although the PDAI is a useful way of objectively quantifying the severity of pouchitis, it did not predict treatment success in our study.

We considered that TR-NDPDAI included symptomatic patients that were not diagnosed by the PDAI scoring system and patients with proximal small bowel bacterial overgrowth. Multiple studies have shown that some patients with irritable bowel syndrome, analogous to IPS, have small bowel bacterial overgrowth, and this is believed to occur in 40% of patients with ileal pouches [15].

We examined where the differences in PDAI scores lie between the TR-NDPDAI and the PDAI-diagnosed pouchitis group. Although there was no significant difference in the clinical symptoms, a large difference in the endoscopic and pathological findings contributed to the difference in the total PDAI scores among these two groups. PDAI-diagnosed pouchitis occurred in 22.9% of all patients in this study and 15.7% of all eligible patients including those excluded because they did not give consent for

endoscopy owing to lack of symptoms. Considering that some TR-NDPDAI can have pouchitis, the incidence of pouchitis could be higher than this value.

Shen et al. defined IPS by the presence of low PDAI scores in symptomatic patients, stated that the treatment for irritable bowel syndrome was successful in these patients, and reported that a very high frequency (42.6%) of symptomatic patients had IPS[10]. The frequency is high because IPS is a diagnosis that covers a wide range of nonspecific inflammatory conditions with symptoms similar to pouchitis[16]. Instead, we classified these symptomatic patients with a PDAI score of less than 7 as follows. Patients successfully treated with antibiotics were classified as TR-NDPDAI (12 cases). Cuffitis was diagnosed in patients, not successfully treated with antibiotics, who had inflammation in the residual rectum and had normal endoscopic findings in the pouch (2 cases). IPS was diagnosed in all other patients (7 cases). Although we examined where were any differences between TR-NDPDAI and non-pouchitis groups, in objective findings there was little difference between TR-NDPDAI and non-pouchitis groups as Table 4 showed.

From the perspective of treatment, TR-NDPDAI must be differentiated from IPS patients. So in terms of etiology we considered that the IPS was analogous to irritable bowel syndrome as Shen described[10], and TR-NDPDAI was analogous to pouchitis. Although TR-NDPDAI had slightly higher clinical symptom scores than IPS patients, the differences in the scores of total PDAI, endoscopic findings, or pathological findings were not significant. Therefore, differentiation between the two groups is difficult using the components of the PDAI. It may be a treatment option to administer anticholinergic or antidepressant to symptomatic patients with PDAI scores less than 7 before administration of antibiotics. However, it is not clear whether the treatment strategy for IPS would be less costly and have fewer side effects than antibiotic use. At this time, we cannot recommend which treatment strategy should be started first.

Benefits of mucosectomy are lower rates of inflammation and dysplasia in the retained mucosa in UC. However recent meta-analysis suggested that nighttime seepage of stool and resting and squeeze pressure were worse after mucosectomy than stapled anastomosis[17]. High percentage of patients undergoing mucosectomy and hand-sewn

anastomosis in this study may attribute high incidence of symptomatic patients other than PDAI-diagnosed pouchitis.

This study is limited by the absence of a placebo treatment arm to understand how much of the improvement was due to antibiotics *versus* mild random variation in symptoms, especially in TR-NDPDAI. In conclusion, the PDAI was not a good indicator of treatment success in symptomatic patients who have undergone IPAA. A considerable number of symptomatic patients with PDAI scores less than 7 showed clinical improvements upon antibiotic treatment. Because the symptoms after ileal pouch-anal anastomosis had several causes, investigation of appropriate treatment for each of the conditions is necessary. For this reason, we believe that a detailed analysis should be performed to develop treatment plans in symptomatic patients even if their PDAI scores are less than 7.

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Figure 1

Patient classification by PDAI score and response to antibiotics treatment PDAI, pouchitis disease activity index ; TR-NDPDAI, treatment responders having disease not diagnosed by PDAI

Figure 2

Changes in PDAI scores and each components score of PDAI in TR-NDPDAI between pre and post treatment. PDAI, pouchitis disease activity index; TR-NDPDAI, treatment responders whose disease is not diagnosed by PDAI

Table 1 List of outcome measurements

・Symptomatic findings
Stool frequency
Rectal bleeding
Fecal urgency
Fever
・Endoscopic findings
Edema
Granularity
Friability
Loss of vascular pattern
Mucus exudates
Ulceration
・Pathological findings
Polymorphonuclear leukocyte infiltration
Ulceration
・PDAI score

PDAI, pouchitis disease activity index

Table 2 Demographic characteristics of ulcerative colitis patients after IPAA

	pouchitis (n=16)	TR-NDPDAI (n=12)	non-pouchitis (n=42)	*P* value
Median age (range)	38 (23-64)	39 (24-68)	33 (19-62)	＞0.212*
Male : female ratio	9 : 7	4 : 8	18 : 24	0.462
Extents of colitis (pancolitis : left side involved colitis)	13 : 3	12 : 0	32 : 10	0.174
Median total doses of preoperative steroid [g](range)	10.0 (2-26.6)	15.0 (12.9-32.4)	10.8 (1-64.8)	＞0.068*
Median duration of UC before operation [months] (range)	55 (10-324)	72 (21-156)	84 (3-128)	＞0.259*
Indication of surgery				
・toxic colitis or perforation or massive bleeding	4	3	13	0.872
・cancer	1	0	0	
・refractory to medical treatment	12	8	28	
Stage operation (2 stage : 3 stage)	5 : 11	6 : 6	13 : 29	0.452
Mucosectomy / double stapler method	16 : 0	11 : 1	38 : 4	0.446
Median months after ileostomy closure (range)	15 (12-80)	24 (12-80)	24 (12-81)	＞0.408*
Metronidazole : Ciprofloxacin	12 : 4	10 : 2	9 : 0	

IPAA, ileal pouch-anal anastomosis ; PDAI, pouchitis disease activity index; TR-NDPDAI, treatment responders having disease not diagnosed by PDAI. *P* value represents the results of Chi-square test unless otherwise specified. * Student's *t*-test

Table 3 Comparison of total PDAI score and each component score in patients with pouchitis and TR-NDPDAI

	PDAI-diagnosed pouchitis (n=16)	TR-NDPDAI (n=12)	*P* value
PDAI	9.4±2.4	5.3±0.7	<0.001
Clinical	2.7±1.4	1.9±0.8	0.103
stool frequency	1.4±0.6	1.3±0.5	0.525
bleeding	0.5±0.5	0.2±0.4	0.074
urgency	0.4±0.5	0.3±0.5	0.491
fever	0.4±0.5	0.2±0.4	0.236
Endoscopic inflammation	3.3±1.7	1.0±1.0	0.001
edema	0.8±0.4	0.2±0.4	0.003
granularity	0.3±0.5	0.0±0.0	0.036
friability	0.6±0.5	0.0±0.0	0.002
loss of vascular pattern	0.8±0.4	0.2±0.4	0.003
mucous exudate	0.2±0.4	0.0±0.0	0.120
ulcer	0.7±0.5	0.7±0.5	0.909
Pathological inflammation	3.5±0.9	2.4±0.7	0.003
polymorphonuclear leukocyte inflammation	1.7±0.5	1.2±0.4	0.007
ulceration per low-power field	1.8±0.7	1.3±0.5	0.019

PDAI, pouchitis disease activity index ; TR-NDPDAI, treatment responders having disease not diagnosed by PDAI. Values reported are mean ± one standard deviation. *P* value represents the results of the Mann –Whitney *U* test.

Table 4

Comparison of total PDAI score and each component scores between each subgroups

	PDAI ≥7		PDAI <7			
	acute pouchitis (n=11)	chronic pouchitis (n=5)	TR-NDPDAI (n=12)	IPS (n=7)	cuffitis (n=2)	asymptomatic cases (n=33)
PDAI	9.0±2.2 *	10.4±2.7	5.3±0.7	5.2±1.1	4.5±0.7	2.8±1.1 †
Clinical symptoms	2.9±1.2 *	2.2±1.9	1.9±0.8	1.1±0.4 **	2.5±0.7	0.0±0.0 †
Endoscopic findings	2.6±1.6 *	4.6±1.1	1.0±1.0	1.3±1.3	0.0±0.0	0.3±0.6 ††
Pathological findings	3.5±1.0 *	3.6±0.5	2.4±1.7	2.8±0.9	2.0±0.0	2.5±0.7

PDAI, pouchitis disease activity index; TR-NDPDAI, treatment responders having disease not diagnosed by PDAI; IPS, irritable pouch syndrome; Values reported are means ± one standard deviation; *P* value represents the results of the Mann –Whitney *U* test; * p<0.001 (*vs* TR-NDPDAI); ** p=0.028 (*vs* TR-NDPDAI); † p<0.001 (*vs* TR-NDPDAI); †† p=0.015 (*vs* TR-NDPDAI)

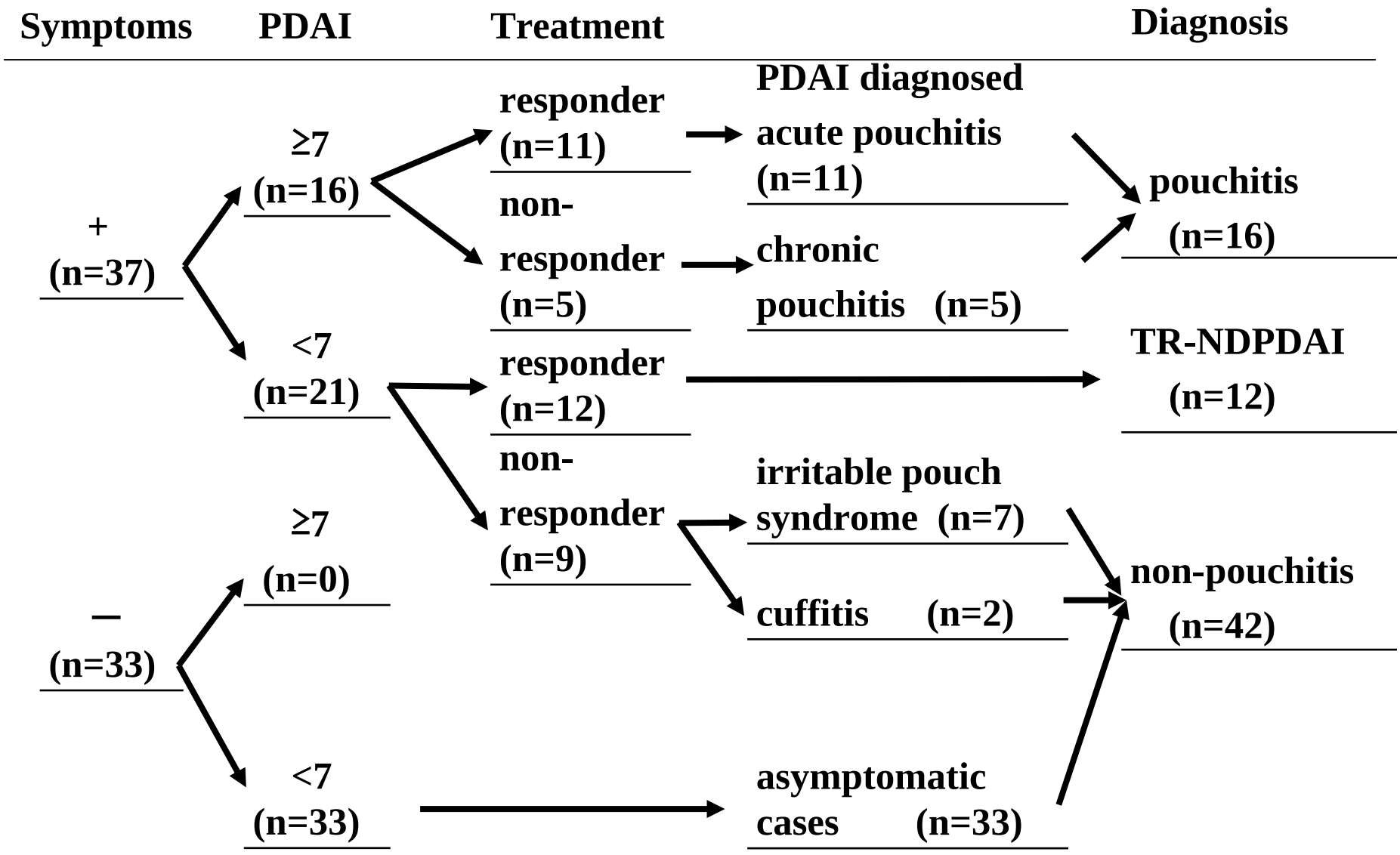
Symptoms
PDAI
Treatment
Diagnosis
+
(n=37)
≥7
(n=16)
<7
(n=21)
responder
(n=11)
non-
responder
(n=5)
responder
(n=12)
non-
responder
(n=9)
PDAI diagnosed
acute pouchitis
(n=11)
chronic
pouchitis (n=5)
irritable pouch
syndrome (n=7)
cuffitis (n=2)
pouchitis
(n=16)
TR-NDPDAI
(n=12)
non-pouchitis
(n=42)
–
(n=33)
≥7
(n=0)
<7
(n=33)
asymptomatic
cases (n=33)

Figure 1

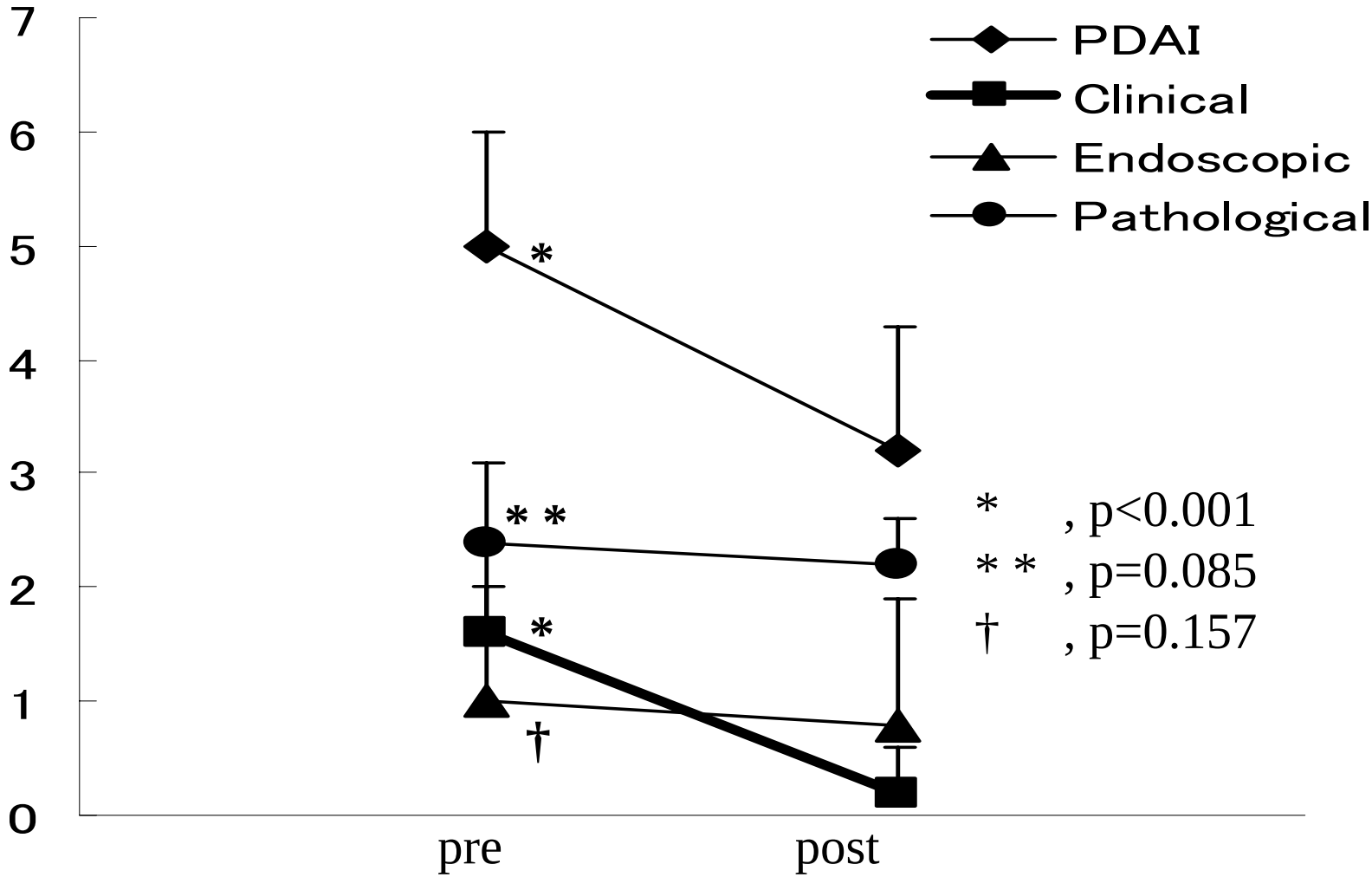
7
6
5
4
3
2
1
0
PDAI
Clinical
Endoscopic
Pathological
*
* *
*
†
pre
post
* , p<0.001
* * , p=0.085
† , p=0.157

Figure 2