Biomarkers for the Evaluation of Pouch Inflammation: A Systematic Review

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Introduction

- IPAA is the main surgical approach of choice in patients with UC requiring surgery
- Following IPAA, ~60% of patients develop pouch inflammation
- Diagnosis of pouch inflammation is multimodal
- Current gold standard for objective assessment of pouch is pouchoscopy, which is invasive and costly
- Several surrogate markers have been proposed and utilized but none have been validated

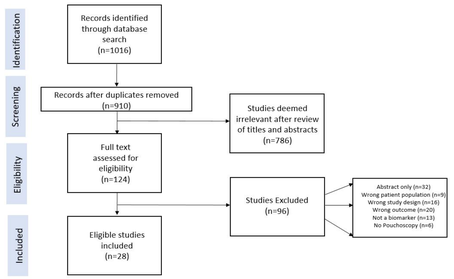
Materials and Methods

- Systematic review conducted according to PRISMA Guidelines
- Outcomes of interest:
  - Comparison of the biomarker to inflammation
  - Status as assessed via pouchoscopy using either correlative statistics or sensitivity and specificities
  - Prediction of future episodes of pouchitis via biomarkers
  - Longitudinal evaluation of pouchitis using biomarkers
- Two reviewers (KF and TQ) independently screened all titles and abstracts and identified and selected studies for inclusion based on eligibility criteria
- KF and TQ independently assessed all non-randomized studies for risk of bias using the Newcastle-Ottawa Scale

Table 1 Inclusion and Exclusion Criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
Study design: randomized or non-randomized observational cohort studies, case control studies, or case series involving at least 10 patient	Narrative reviews or editorials
Patients with an IPAA (including J, W, and S pouches) regardless of pre-operative diagnosis	Languages other than English
Age 18 years or older	Studies with fewer than 10 patients
Utilization of easily attainable clinical biomarkers obtained from serum, stool, urine, or breath for the evaluation and/or prediction of pouch inflammation	Studies investigating only microbiome and/or genetic markers
Comparison of the biomarker against the gold standard of pouch endoscopy	Patients with a diverting ileostomy, Kock pouch, or alternative enteric-colonic anastomoses

PRISMA DIAGRAM



Results

Study Approach:

- **25** studies assessed role of biomarkers in association with pouch inflammation
  - None reliably demonstrated high sensitivity and specificity
- **3** studies evaluated biomarkers as predictors of subsequent pouch inflammation
  - All demonstrated some degree of prediction though association was not robust
- **6** studies reported longitudinal assessments of biomarkers in relation to pouch inflammation
  - Only 3 reported a predictive role of biomarkers in diagnosing endoscopic inflammation

Included Biomarkers :

- **6** studies evaluated **serum biomarkers**
  - Evaluated serum biomarkers: C-reactive protein, alpha-1-antitrypsin, serotonin, perinuclear anti-neutrophil cytoplasmic antibody, and serum immunoglobulin glycoprotein 2
  - None of the biomarkers demonstrated a high sensitivity or specificity
- **23** studies assessed **fecal biomarkers**, with or without serum biomarkers
  - Evaluated fecal biomarkers: fecal calprotectin, fecal lactoferrin, stool alpha-1-antitrypsin, matrix metalloproteases, fecal pyruvate kinase
  - Fecal calprotectin was most commonly studied (Table 1)
- **4** studies examined use of **whole gut lavage fluid**
  - None demonstrated high sensitivity or specificity

Table 2. Association of Fecal Calprotectin with Pouch Inflammation

Author	Year	Study Design	Patient #	Median Age (Range)	Pre-Op Diagnosis	Pouchitis Definition	Cut Off (µg/g)	Association Between Pouch Biomarker and PDAI	Sensitivity (%)	Specificity (%)
Thomas[1]	2000	Prospective Cohort	24	NP	UC: 16 FAP: 8	Macroscopic inflammation and histologic inflammation	NP	All patients with inflammation had elevated fecal calprotectin	NP	NP
Pronio[2]	2016	Prospective Cohort	40	52 (33-71)	UC	PDAI ≥7	66.2 37.6	*Endoscopy subscore*: NP *Total PDAI*: r=0.55 p=0.002 AUC: 0.832	85 92	38 19
Johnson[3]	2009	Prospective Cohort	54	47	UC: 46 FAP: 8	PDAI ≥7	92.5	*Endoscopy subscore:* t=0.605 p≤0.0001 *Total PDAI:* r=0.71 p≤0.001	90	76.5
Farkas[4]	2015	Prospective Cohort	33	30-40	UC	Histologic Neutrophil Count + Episodes of Pouchitis	262	*Endoscopy subscore:* p=0.001 *Total PDAI:* AUC: 0.78	67	89
Pakarinen[5]	2010	Prospective Cohort	32	24 (17-31)	UC	PDAI ≥7	300	*Histologic Neutrophil Count:* r=0.715 p<0.001 *Episodes of pouchitis* r=0.457 p<0.01	57	92
Ollech[6]	2021	Prospective Cohort	156	43 (35-58)	UC	Endoscopic PDAI ≥5	462	*Severity of Pouchitis* r=0.526 p=0.0017	66.7	82.4

Conclusions

- Biomarkers are appealing as a potential option to help improve the management of pouch inflammation given the relative ease of sampling compared to pouchoscopy
- Though the literature is limited, this systematic review found that no available biomarker can reliably predict or diagnose pouch inflammation
- Based on the evidence, we cannot recommend the use of any available biomarker alone for the diagnosis or prediction of pouch inflammation
- Identification of novel, validated biomarkers for pouchitis should be a research priority

Contact

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Legend

IPAA = ileal pouch anal anastomosis
UC: ulcerative colitis
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis
FAP: Familial Adenomatous Polyposis
PDAI: Pouchitis Disease Activity Index

References

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