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ORIGINAL ARTICLE

Characterization of risk factors for floppy pouch complex in ulcerative colitis

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Abstract

Background Restorative proctocolectomy with ileal pouch–anal anastomosis can be associated with a variety of complications, including floppy pouch complex (FPC). FPC is defined as the presence of pouch prolapse, afferent limb syndrome, enterocele, redundant loop, and folding pouch on pouchoscopy or contrasted pouchogram. The main symptoms of patients with FPC are dyschezia, incomplete evacuation, and bloating. The aims of the study were to evaluate the relative frequency of each disorder of FPC and to characterize its risk factors.

Methods This case–control study included all eligible patients with FPC from our prospectively maintained, IRB-approved Pouchitis Registry from 2011 to 2017. The control group included the patients without any of the above conditions. Univariate and multivariate analyses were performed.

Results A total of 437 eligible patients were analyzed including 97 (22.2%) with FPC and 340 (77.8%) without FPC, 188 (43.0%) being female, 360 (82.4%) being Caucasians, and 66 (15.1%) having a family history of inflammatory bowel disease (IBD). There were 427 patients (97.7%) having J pouches and 10 (2.2%) having S pouches and the median duration from pouch construction to data sensor was 6.0 years (interquartile range 0.962–1.020). In the whole cohort, 64 (66.0%) patients had pouch prolapse, 38 (39.2%) patients had afferent limb syndrome, 10/42 (23.8%) patients had redundant loop, and 3/42 (7.1%) had folding pouch. In multivariable analysis, lower body weight (odds ratio [OR] 0.944; interquartile range; 95% confidence interval [CI] 0.913–0.976, $P = 0.001$) and the presence of family history of IBD (OR 4.098; 95% CI 1.301–12.905, $P = 0.013$) were associated with a higher risk of FPC.

Conclusion We found that pouch prolapse and afferent limb syndrome are the most common forms of FPC. A lower body weight as well as family history of IBD was found to be risk factors for FPC. The findings will have implications in both diagnosis and investigation of etiopathogenesis of this group of challenging disorders.

Keywords Afferent limb syndrome · Body mass index · Dyschezia · Enterocoele · Floppy pouch complex · Gender · Ileal pouch–anal anastomosis · Pouch · Prolapse · Ulcerative colitis

Introduction

Restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) has become the surgical treatment of choice for the majority of the patients with refractory ulcerative colitis (UC), colitis-associated dysplasia, or familial adenomatous polyposis (FAP) [1, 2]. Approximately 30% of patients with UC eventually require total proctocolectomy [3].

IPAA improves patient's health-related quality of life but is often associated with adverse events, including acute pouchitis, anastomotic leakage or stricture, chronic antibiotic refractory pouchitis, abscesses, fistula, sinus, Crohn's disease (CD), and cuffitis [4]. For the past decade, we have encountered a growing number of patients with symptoms of dyschezia, bloating, abdominal pain, and incomplete evacuation, which results from afferent limb syndrome (ALS), efferent limb syndrome (ELS), and pouch prolapse [5–7]. We previously proposed a classification system for ileal pouch disorders [8]. In the classification system, pouch prolapse and ALS

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can cause mechanical, functional, dysplastic, inflammatory, as well as systemic complications. Based on the clinical presentation and underlying mechanism, those pouch disorders can be grouped into a complex, named floppy pouch complex (FPC).

FPC is defined as the presence of pouch prolapse, ALS, enterocele, redundant loop, and folding pouch on pouchoscopy, gastrografin enema (GGE), or barium defecography (BD). Clinical features and risk factors have not been evaluated. The aims of the study were to evaluate the relative frequency of each disorder of FPC and to characterize its risk factors.

Patients and methods

This case–control study included all eligible patients with FPC from our prospectively maintained, IRB-approved Pouchitis Registry from 2011 to 2017. The control group included the patients without any of the above conditions on pouchoscopy or contrasted pouchogram. Demographics, comorbidities, and pouch complications were extracted from a prospectively maintained pouch database. Office visit notes, follow-up notes, admission records, operation reports, and other medical records were carefully reviewed. The Institutional Review Board (IRB) of the Cleveland Clinic Foundation approved this study.

Inclusion and exclusion criteria

In order to qualify for the study, patients were required to meet all of the following inclusion criteria: (1) being evaluated and regularly followed up in our Pouchitis Clinic, (2) diagnosed with UC, (3) history of IPAA, and (4) evidence of any of the above pouch disorders on pouchoscopy or the pelvic imaging. Exclusion criteria were the following: (1) IPAA for FAP or colon neoplasm, (2) patients with CD of the pouch, or (3) Kock pouch or other continent ileostomies.

Definitions of variables and diagnosis

Demographic and clinical variables are self-explanatory. Pouch prolapse is defined as protrusion of pouch walls or mucosa into pouch lumen, which can be detected by pouchoscopy or pouchogram. Prolapse is often highlighted with patient straining (Fig. 1a). Afferent limb syndrome (ALS) is defined as the sharp angulation at the distal afferent limb, from the pouch inlet, in the absence of intrinsic stricture (Fig. 1b). ALS is often caused by patients with redundant loop of bowel or long mesentery in the area or scar tissue outside the bowel segment [7]. Redundant loop is defined as the presence of too long intestinal loop proximal to the pouch inlet revealed on GGE or BD (Fig. 1c). Pouch folding is defined as angulation of the pouch body axis revealed by pouchoscopy or GGE or BD (Fig. 1d). Enterocele is defined as a peritoneum-lined sac herniating down between the vagina and pouch filled with small intestine revealed by GGE or BD [9]. Perineal descent is defined as the perineum prolapsed below the bony outlet of the pelvis known as the pubococcygeal line demonstrated by GGE or BD.

FPC is defined as the presence of any of above conditions.

Outcome measurement

The primary outcomes were relative frequency of the various phenotypes of FPC and risk factors associated with FPC.

Statistical analysis

An independent sample t test or non-parametric test (Wilcoxon) was used for compare continuous variables between two groups as appropriate. Fisher exact or chi-square test was used for categorical variables as appropriate. Univariate and multivariate analyses were performed to explore risk factors of FPC. Multiple logistic analysis was enforced using stepwise regression and all of the factors with potential clinical significance were included into the multiple regression analysis. The enter limit and remove limit were $p = 0.05$ and $p = 0.10$, respectively. $P < 0.05$ (two-sided) was considered as statistically significant. All of the analyses were performed with SPSS 17.0 (Chicago, IL).

Results

A total of 437 eligible patients were analyzed including 97 (22.2%) with FPC and 340 (77.8%) without FPC, 188 (43.0%) being female, 360 (82.4%) being Caucasians, and 66 (15.1%) having family history of inflammatory bowel disease (IBD). Out of 437 patients, 427 (97.7%) had J pouches and 10 (2.3%) had S pouches. The mean age at IBD diagnosis was 26.4 ± 12.4 years. The mean age at pouch construction was 34.0 ± 13.1 years, and the mean age at pouch evaluation was 42.5 ± 14.1 years. The median duration from pouch construction to data sensor was 6.0 years (interquartile range [IQR] 0.962–1.020). Seventeen (3.9%) patients underwent 1-stage pouch surgery, 179 (41.0%) had 2-stage pouch surgery, 129 (29.5%) had 3-stage pouch surgery, and 112 (25.6%) patients had unknown stage of pouch surgery.

Twenty six patients (26.8%) had smoking history, and 18 (18.6%) had history of excessive alcohol consumption. Eleven (11.3%) patients had extra-intestinal manifestations (EIM) of IBD.

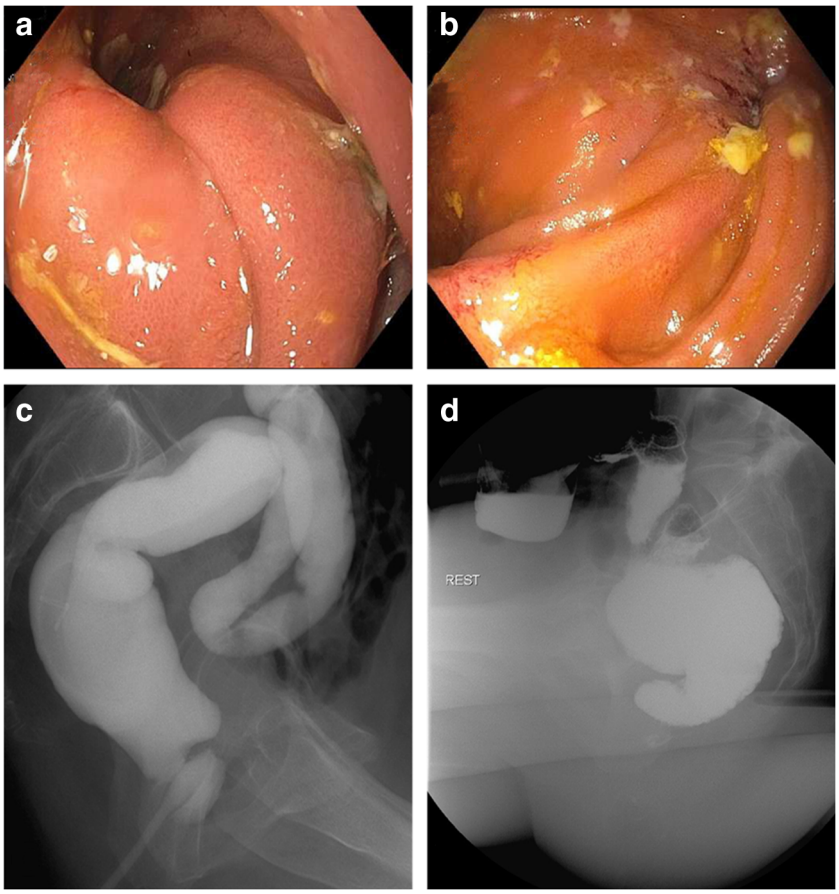

Fig. 1 Images of pouch prolapse, afferent limb syndrome, redundant loop, and folding pouch. **a** Pouch prolapse revealed by pouchoscopy, showing a prolapsed fold within the anal transitional zone, almost completely blocked the anal canal when straining. **b** Angulation of the pouch inlet, showing twist of the distal afferent limb above the pouch inlet. **c** Redundant loop, showing a very low-lying afferent limb in defecography, which may contribute to the sensation that the pouch is not emptying. **d** Folding pouch, pouchoscopy showing a huge and folding pouch

Relative frequency of floppy pouch complex

Out of 97 patients with FPC, 64 (66.0%) patients had pouch prolapse, 38 (39.2%) patients had ALS, and 58 (59.8%) patients had chronic pouchitis. Of 42 patients with available pouchogram, 10 (23.8%) patients had redundant loop, 8 (19.0%) had enterocele, 12 (28.6%) had perineal descent, and 3 (7.1%) had a folding pouch. The flow diagram for inclusion of patient inclusion is shown in Fig. 2.

Univariable and multivariable analyses of risk factors for floppy pouch complex

Patients in the FPC group had significantly lower body weight (68.7 ± 20.3 vs. 76.7 ± 18.0 kg, $P < 0.001$) and a lower BMI (23.3 ± 5.1 vs. 25.6 ± 5.5 kg/m^2, $P < 0.001$) than controls. Female patients are more likely to develop FPC than male patients (56.7% vs. 39.1%, $P = 0.002$) (Table 1).

Univariable comparison showed that family history of IBD (25.8% vs. 12.1%, $P = 0.001$) is strongly related to FPC. No statistically significant association was found between family history of colon cancer (16.5% vs. 17.1%, $P = 0.896$) and history of hysterectomy (10.9% vs. 9.0%, $P = 0.689$). EIM seem to have no impact on FPC (11.3% vs. 12.6%, $P = 0.730$). Paradoxical contraction (40.9% vs. 39.1%, $P = 0.840$) and chronic pouchitis (59.8% vs. 51.8%, $P = 0.162$) do not seem to be strongly related to FPC (Table 1).

Univariate analysis showed that a lower median weight (0.975, interquartile range [IQR] 0.961–0.988, $P < 0.001$), a taller height (0.974, IQR 0.954–0.994, $P = 0.013$), lower BMI (0.914, IQR 0.870–0.961, $P < 0.001$), and family history of IBD (2.532, IQR 1.446–4.433, $P = 0.001$) were associated with FPC.

Smoking history (0.745, IQR 0.451–1.233, $P = 0.252$) and excessive alcohol consumption (1.386, IQR 0.764–2.516, $P = 0.283$) were not found to be associated with FPC. No significant association found between family history of colon cancer and FPC (0.960, IQR 0.524–1.761, $P = 0.896$). History of hysterectomy seems to have no impact on FPC (1.235, IQR 0.439–3.475, $P = 0.690$). EIM do not seem to be related to FPC (0.883, IQR 0.437–1.787, $P = 0.730$). Univariate analysis was used to compute above results (Table 2).

Univariate analysis showed that type of pouch surgery (S pouch vs. J pouch) has no impact on FPC (0.874, IQR 0.182–4.183, $P = 0.866$). Stage of pouch surgery ((2–3) vs.1) does not seem to be related to FPC (0.974, IQR 0.308–3.080, $P = 0.964$). Chronic pouchitis was not associated with FPC (1.386, IQR 0.876–2.191, $P = 0.163$) (Table 2).

Multivariate analysis showed that lower weight (0.944, IQR 0.913–0.976, $P = 0.001$) and family history of IBD

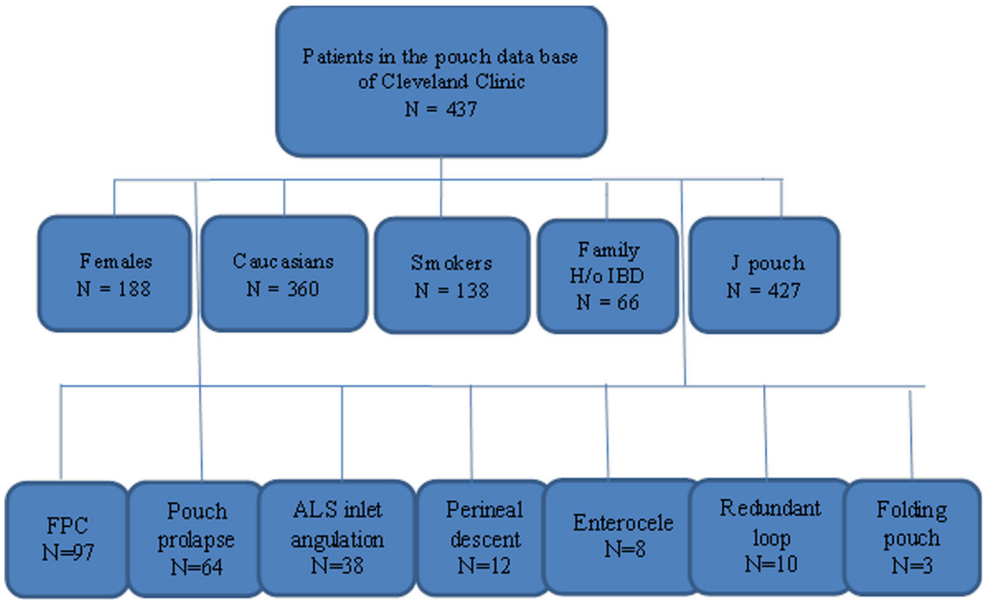

Fig. 2 Patient selection flow diagram

Table 1 Univariable comparison of demographic and clinical data in patients with or without floppy pouch complex

		Floppy pouch complex		*P*
		Yes ($n = 97$)	No ($n = 340$)	
Female gender		55.0 (56.7%)	133 (39.1%)	*0.002*
Age at IBD diagnosis (years)		26.4 ± 12.4	28.4 ± 13.6	0.221
Age at pouch construction (years)		34.0 ± 13.1	35.5 ± 13.9	0.362
Age at evaluation (years)		42.5 ± 14.1	42.3 ± 14.7	0.299
Weight (kg)		68.7 ± 20.3	76.7 ± 18.0	*< 0.001*
Height (cm)		169.3 ± 16.0	173.0 ± 9.6	0.037
Body mass index (kg/m^2)		23.3 ± 5.1	25.6 ± 5.5	*< 0.001*
Median pouch duration (years)		6 (2–13)	6 (3–13)	0.252
Smoking		26 (26.8%)	112 (32.9%)	0.251
Excessive alcohol use		18 (18.6%)	48 (14.1%)	0.282
Family history of IBD		25 (25.8%)	41 (12.1%)	*0.001*
Family history of colon cancer		16 (16.5%)	58 (17.1%)	0.896
History of hysterectomy		6/55 (10.9%)	12/133 (9.0%)	0.689
Pouch type	J pouch	95 (97.9%)	332 (97.6%)	1.000
	S pouch	2 (2.1%)	8 (2.4%)	
Stage of pouch surgery	Unknown	22 (22.7%)	90 (26.5%)	0.771
	1	4 (4.1%)	13 (3.8%)	
	2	41 (47.7%)	138 (39.3%)	
	3	21 (24.4%)	108 (30.8%)	
Presence of any extra-intestinal manifestations		11 (11.3%)	43 (12.6%)	0.730
Afferent limb syndrome		38 (39.2%)	0 (0.0%)	*< 0.001*
Prolapse		64 (66.0%)	0 (0.0%)	*< 0.001*
Enterocele or pouchocele		8/42 (19.0%)	0/70 (0.0%)	*< 0.001*
Redundant loop		10/42 (23.8%)	0/70 (0.0%)	*< 0.001*
Pelvic descent		12/42 (28.6%)	7/70 (10.0%)	*0.011*
Folding pouch		3/42 (7.1%)	0/70 (0.0%)	*0.023*
Dyschezia symptom		14 (14.4%)	25 (7.4%)	*0.031*
Paradoxical contraction on manometry		18/44 (40.9%)	34/87 (39.1%)	0.840
Chronic pouchitis		58 (59.8%)	176 (51.8%)	0.162

Table 2 Univariate and multivariate logistic analyses for risk factors of floppy pouch complex

	Univariate analysis		Multivariate analysis	
	95%CI	*P*	95%CI	*P*
Gender (male vs. female)	0.491 (0.311–0.775)	*0.002*		
Age at IBD diagnosis	0.988 (0.970–1.007)	0.221		
Age at pouch construction	0.992 (0.974–1.010)	0.361		
Age at evaluation	0.992 (0.976–1.007)	0.299		
Weight (kg)	0.975 (0.961–0.988)	*< 0.001*	0.944 (0.913–0.976)	*0.001*
Height (cm)	0.974 (0.954–0.994)	*0.013*		
BMI (kg/m^2)	0.914 (0.870–0.961)	*< 0.001*		
Pouch duration	0.991 (0.962–1.020)	0.528		
Smoking	0.745 (0.451–1.233)	0.252		
Excessive alcohol use	1.386 (0.764–2.516)	0.283		
Family history of IBD	2.532 (1.446–4.433)	*0.001*	4.098 (1.301–12.905)	*0.013*
Family history of colon cancer	0.960 (0.524–1.761)	0.896		
History of hysterectomy	1.235 (0.439–3.475)	0.69		
Pouch type (S pouch vs. J pouch)	0.874 (0.182–4.183)	0.866		
Stage of pouch surgery ((2–3) vs.1)	0.974 (0.308–3.080)	0.964		
Extra-intestinal manifestation	0.883 (0.437–1.787)	0.730		
Chronic pouchitis	1.386 (0.876–2.191)	0.163		
Pouch complications	0.782 (0.399–1.532)	0.473		

(4.098, IQR 1.301–12.905, $P = 0.013$) were independent risk factors for FPC. Smoking history, excessive alcohol consumption, family history of colon cancer, history of hysterectomy, and EIM did not seem to be associated with FPC (Table 2).

Discussion

FPC is defined as the presence of pouch prolapse, ALS, redundant loop, enterocoele, or pouch folding. This study characterized FPC and its phenotypes and identified several risk factors for FPC. Pouch prolapse is the most common form of FPC. We found that lower weight is associated with FPC.

While pouch prolapse was found to be the most common form of FPC, its etiology remains unclear. It is defined as excessive protrusion of pouch walls through the anus. Reported cumulative incidence of prolapse was 0.3% (11/3176) from Cleveland Clinic [6] and 0.35% (83/23,541) from the American Society of Colon and Rectal Surgeons [5]. Prolapse compromises pouch function and affects patients' quality of life [10]. It is speculated that pouch prolapse results from low pouch tone or redundant mesentery of the small bowel. Prolapse can be classified into the following: (1) mucosal prolapse vs. full thickness prolapse, based on the depth of wall of bowel involved; (2) partial vs. complete, based on the degree of lumen occupation; and (3) primary vs. secondary (to other functional, mechanical, inflammatory disorders), based on the etiology [6].

Common clinical presentations include dyschezia, excessive straining, incomplete evacuation, external prolapse of tissue, seepage, anal pain, nausea, or fecal incontinence [5, 10]. Full thickness prolapse can be diagnosed based on symptoms and physical examinations [8], while the diagnosis of mucosal prolapse usually requires pouchoscopy and radiological test, including GGE or BD [6]. Our previous study has indicated that pouch prolapse is more common in female patients with lower BMI and patients with family history of IBD [11].

ALS is another common form of FPC. It is defined as the sharp angulation in any segment of distal afferent limb, from the pouch inlet to previous loop ileostomy site, in the absence of intrinsic stricture. Two common pouch configurations are J pouch and S pouch [3]. J-pouch procedures are preferred for refractory UC. Common symptoms include dyschezia, straining, incomplete evacuation, recurrent intermittent abdominal pain, bloating, constipation, or perianal pain [7]. The etiology of ALS is not known. The construction of J and S pouches is technically similar and different. Literature shows that ALS, pouch outlet angulation, and ELS are much more common in the S pouch than in the J pouch [12]. It was suggested that afferent limb obstruction occurs due to a loop of ileum just proximal to the pelvic pouch becoming trapped posteriorly between the sacrum and the pouch. A study of six patients with ALS suggested that afferent limb obstruction should be suspected in patients with recurrent obstructive symptoms after IPAA [13]. We found that female gender

and lower BMI may be risk factors, which is consistent with what we encountered in clinical practice.

Redundant loop, enterocele, and folding pouch are less common forms of FPC. Redundant loop may represent a milder form of ALS, which may nor may not cause obstruction. Enterocele may share the same risk factors of pouchocele, which is related to tone of pouch wall. We speculate that pouch folding may result from excessively long pouch body or low pouch tone.

Risk factors for pouch disorders and pouch failure have been extensively studied. Female patients were found to have a greater risk for pouch dysfunction [14], pouch failure [15], or fistula formation [16]. It is speculated that childbirth or repeated straining at stool stretches and injures the pelvic floor musculature and pudendal nerve and causes pelvic floor descent and rectal prolapse [9, 17]. In this study, we did not find any association between history of hysterectomy and FPC. However, our study showed that female patients are more likely to have FPC than male patients.

For the first time, we propose that FPC is a disease spectrum of overlapping disorders, with overlaps between the phenotypes. Pouch prolapse, ALS, and folding pouch share common features of redundant or floppy bowel segment. A study reported three case of pouch prolapse and found that all three of the patients with pouch prolapse had large redundant pouches [18]. This study reinforces our findings as suggested by data analysis. Another study described that ALS may have similar mechanism as pouch prolapse [7]. Our results showed overlaps between pouch prolapse, ALS, and other forms of FPC. It is safe to say that pouch prolapse, folding pouch, ALS, and redundant loop have similar underlying mechanism. It is reasonable to combine these entities under FPC.

The findings of our study have clinical implication. Since the risk of developing FPC is higher in slender females, surgeon may develop new techniques in the management of redundant bowel and mesentery during construction of the pouch. Patients with typical symptoms and risk factors can be evaluated with proper diagnostic modalities. The identification of risk factors will open the door for future therapeutic intervention.

There are limitations to our study. First, there might have been referral bias, since all the patients in the current study were seen in the setting of a subspecialty Pouchitis Clinic where patients with a spectrum of pouch disorders were diagnosed and managed. Second, the high prevalence of pouch disorders in our Pouchitis Clinic may not reflect the true prevalence of the disease. Because of the sample size, not all potential risk factors for FPC were included in the model. Also due the sample size, we were not able to identify risk factors associated with each individual phenotype of FPC. Finally, we are not clear what would be therapeutic intervention for FPC.

In conclusion, our study demonstrated that pouch prolapse and afferent limb syndrome are the most common forms of FPC. A lower BMI and female gender were found to be risk factors for FPC. These findings suggest that the symptomatic patients at risk for FPC can be evaluated with proper diagnostic modality.

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Author contribution Freeha Khan and Xian Hua Gao contributed equally to this article.

Freeha Khan and Xian Hua Gao: Data gathering and entry, imaging measurement, and manuscript preparation.

Bo Shen and Tracy Hull: Concept, general supervision, and manuscript revisions.

Compliance with ethical standards

The Institutional Review Board (IRB) of the Cleveland Clinic Foundation approved this study.

Conflict of interest The authors declare that they have no conflict of interest.

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