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Endoscopic scoring indices for assessing disease severity in familial adenomatous polyposis: Systematic review

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ABSTRACT

Background and study aims There is limited consensus on the optimal method for measuring disease severity in familial adenomatous polyposis (FAP). We aimed to systematically review the operating properties of existing endoscopic severity indices for FAP.

Methods We searched MEDLINE, EMBASE, and the Cochrane Library from inception to February 2023 to identify randomized controlled trials (RCTs) that utilized endoscopic outcomes or studies that evaluated the operating properties of endoscopic disease severity indices in FAP.

Results A total of 134 studies were included. We evaluated scoring indices and component items of scoring indices, such as polyp count, polyp size, and histology. Partial validation was observed for polyp count and size. The most commonly reported scoring index was the Spigelman classification system, which was used for assessing the severity of duodenal involvement. A single study reported almost perfect interobserver and intra-observer agreement for this system. The InSIGHT polyposis staging system, which was used for assessing colorectal polyp burden, has been partially validated. It showed substantial interobserver reliability; however, the intra-observer reliability was not assessed. Novel criteria for high-risk gastric polyps have been developed and assessed for interobserver reliability. However, these criteria showed a poor level of agreement. Other scoring indices assessing the anal transition zone, duodenal, and colorectal polyps have not undergone validation.

Conclusions There are no fully validated endoscopic disease severity indices for FAP. Development and validation of a reliable and responsive endoscopic disease severity instrument will be informative for clinical care and RCTs of pharmacological therapies for FAP.

Introduction

Familial adenomatous polyposis (FAP) is an inherited polyposis syndrome characterized by development of numerous polyps in the gastrointestinal tract [1]. Of particular importance are polyps that develop in the colorectum and duodenum that confer an increased risk of cancer [2]. Frequent endoscopic surveillance with polypectomy starts in adolescence; however, a colectomy is often inevitable for patients with FAP to prevent colorectal cancer [3,4]. Most often, a total colectomy with ileorectal anastomosis or proctocolectomy with ileal pouch-anal anastomosis (IPAA) is performed. There is limited guidance on timing of prophylactic surgery, and currently the decision is multifactorial including scoring indices as well as other factors in the patient's life. After colectomy, most patients will develop polyps in the retained rectum or ileal pouch, which require further surveillance and treatment [5,6]. Unlike the large intestine, prophylactic removal of the duodenum to prevent progression of polyps to cancer is not needed in most patients, and endoscopic surveillance with polypectomy is sufficient [7].

There is considerable interest in developing therapeutics to reduce polyp burden or even prevent polyp formation in the colorectum, pouch, and duodenum and subsequently ideally decrease the incidence of cancer and prevent or postpone surgery in FAP. Recent data suggest that multiple pharmacologic agents might reduce the polyp burden in FAP, including aspirin, selective COX-2 inhibitors, sulindac, erlotinib, eicosapentaenoic acid, interleukin-23 inhibitors, and sirolimus [8,9,10,11,12,13,14]. Given that FAP can result in development of hundreds of polyps, counting and estimating the size of polyps are inherently prone to inaccuracy. Reproducible and reliable methods of quantifying polyp burden are needed for clinical care, research, and to rigorously study pharmacologic effects on polyp burden in FAP.

The most commonly used endoscopic disease severity classification systems in FAP include the Spigelman classification for duodenal polyposis and the InSiGHT staging system for colorectal polyposis [15,16]. We aimed to conduct a systematic review of all existing endoscopic indices for upper and lower gastrointestinal tract polyposis used to evaluate disease severity in FAP. A comprehensive understanding of the components required for assessment of endoscopic disease severity in FAP is needed to improve clinical care and is imperative for evaluation and regulatory approval of future therapeutics.

Methods

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and was conducted using an a priori protocol which can be made available upon request [17].

Search methods for identification of studies

We conducted a systematic literature search of MEDLINE (Ovid), EMBASE (Ovid), and the Cochrane Central Register of Controlled Trials (CENTRAL) databases from inception to 23 February 2023 to identify studies that assessed the operating properties of indices measuring endoscopic disease severity in FAP. We also searched for randomized controlled trials (RCTs) of FAP that utilized endoscopic scoring indices to assess disease severity. The search strategies are reported in **Supplementary Appendix 1**. To identify other potentially pertinent studies, we manually searched the references of relevant manuscripts and review articles as well as conference abstracts from Digestive Disease Week and the United European Gastroenterology Week.

Selection criteria

Any study design that evaluated endoscopic disease severity in patients with FAP (adults or children, diagnosed clinically or by family history with genetic testing) was considered for inclusion. The search was conducted without language restrictions. Studies must have reported scoring indices or component items reflective of FAP severity, such as polyp counting, used to measure endoscopic disease severity to be eligible for inclusion. Case reports and case series with fewer than 10 patients were excluded unless they reported on use of a unique endoscopic scoring tool for assessing disease severity in patients with FAP. Two authors [ALS and AA or AZ and JL] independently screened the search results.

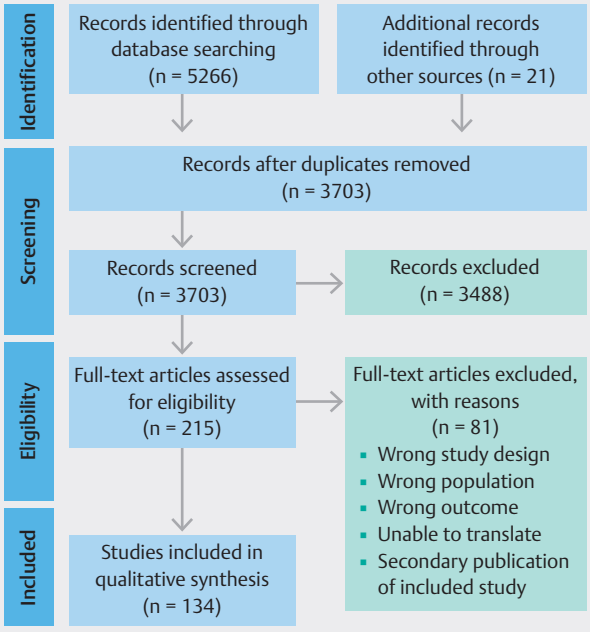
Data abstraction and risk of bias assessment

Two authors [ALS and HB or AZ and JL] independently extracted data from the included studies. Arbitration by a third author [JKM] was conducted when consensus was unable to be achieved. A meta-analysis was not planned due to the expected heterogeneity across studies in the reliability and validity of different indices used to assess endoscopic disease severity in FAP. For each instrument, operating properties including validity, reliability, responsiveness, and feasibility were assessed. The definitions of operating properties can be found in **Supplementary Appendix 2,** and details on how reliability and validity were assessed can be found in **Supplementary Table 1**. Evaluation of the methodological quality of studies was performed independently by two authors [ALS and HB or AZ and JL]. The risk of bias was assessed with respect to selection bias, detection bias, attrition and reporting bias, and other potential biases (**Supplementary Table 2**) [18]. For studies with formal scale validation, methodological quality was independently assessed by two authors [ALS and HB] using the quality assessment of diagnostic accuracy studies (QUADAS-2) tool (**Supplementary Table 3**) [19].

Results

Search results and included studies

The systematic database search yielded a total of 5266 references (▶**Fig. 1**). Twenty-one additional records were identified from other sources. After removing duplicates, 3703 records underwent initial title and abstract screening, and 3488 were excluded as non-relevant. Full-text review was performed for 215 articles. Eighty-one full-text articles were excluded. A list of the excluded studies and reasons for exclusion are reported in **Supplementary Table 4**. A total of 134 studies met the inclu-



▶ **Fig. 1** PRISMA flow diagram [20] depicting study selection results.

sion criteria. The characteristics of included studies are reported in **Supplementary Table 5**.

Overview of included studies

A total of 87 studies reported on use of scoring items and 52 studies reported on use of scoring indices to assess endoscopic disease severity in FAP (▶**Table 1**). Five studies reported on both scoring items and scoring indices [21, 22, 23, 24, 25], and one study reported on two scoring indices [11]. Among the studies that reported on scoring items, polyp count was most commonly described (n = 80), followed by polyp size (n = 30), and histology (n = 5).

The most frequently reported scoring index was the Spigelman classification score (n = 41), which is a classification system used to assess the severity of duodenal polyposis. Several studies (n = 9) used an updated Spigelman classification, which differs from the original instrument in the approach used to categorize the degree of dysplasia [7, 22, 26, 27, 28, 29, 30, 31, 32]. Three studies reported use of a modified Spigelman classification score [23, 33, 34]. The InSiGHT Polyposis Staging System was reported in three studies and was used to classify the severity of lower gastrointestinal tract polyposis [11, 16, 35]. A study by Lee et al [36] focused on assessing severity of the anal transition zone in patients with FAP following ileoanal pouch construction, based on parameters such as size, distribution, and histology. One study by Mankaney et al [37] presented novel criteria for identifying high-risk gastric polyps in patients with FAP. The criterion for high-risk gastric polyp was fulfilled if any of the following parameters were found: polyp color (lighter or darker than background mucosa), open pit pattern, similar appearance under high-definition endoscopy and narrow-band imaging, and irregular, bumpy, or nodular surface architecture. Two studies reported on video assessment scores for the qualitative assessment of the endoscopic appearance of duodenal [24] and colorectal [21] polyposis. Richard et al. [38] reported on use of the FAP duodenal polyp classification for a cancer registry.

▶ **Table 1** Reporting of familial adenomatous polyposis endoscopic scoring items and indices in included studies.

	Total studies (n = 134) Number of studies (% total)
Scoring items	**87*** **(64.9)**
Polyp count	80† (59.7)
Gastric	12 (9.0)
Duodenal, jejunal, and ileal	18 (13.4)
Colorectal	57 (42.5)
Pouch	6 (4.5)
Polyp size	30‡ (22.4)
Gastric	5 (3.7)
Duodenal, jejunal, and ileal	10 (7.5)
Colorectal	19 (14.2)
Pouch	0
Polyp histology	5 (3.7)
Gastric	2 (1.5)
Duodenal, jejunal, and ileal	3 (2.2)
Colorectal	0
Pouch	0
Scoring indices	**52 (38.8)**
Upper gastrointestinal tract indices	**48 (35.8)**
Spigelman classification	42 (31.3)
Modified Spigelman classification	3 (2.2)
Criteria to identify high-risk gastric polyps	1 (0.7)
Video assessment score for duodenal polyposis	1 (0.7)
FAP duodenal polyp classification	1 (0.7)
Lower gastrointestinal tract indices	**5 (3.7)**
InSiGHT Polyposis Staging System (IPSS)	3 (2.2)
Grade severity of anal transition zone	1 (0.7)
Video assessment score for colorectal polyposis	1 (0.7)

*Twenty-eight papers reported on two scoring items.
†Nine papers reported on two types of polyps and three papers on three types of polyps.
‡Four papers reported on two types of polyps.

Assessment of endoscopic scoring items

Most of the studies included in this review reported on individual scoring items, with the item most often reported being polyp counting. Operating properties that were evaluated for endoscopic scoring items include content validity, construct validity, and interobserver reliability (▶ **Table 2**). Polyp counting was found to be partially validated, with the interobserver reliability evaluated in only two studies [39, 40]. Mallappa et al [39] determined interobserver reliability of polyp counting in patients receiving pre-operative colonoscopy by comparing the endoscopic and post-colectomy pathologic count. The study reported none to slight interobserver reliability, with a kappa value of 0.172 among endoscopists and pathologists. The study by Lynch et al [40] developed five models to assess the burden of colorectal polyps, including two models that focused solely on polyp count and three models that assessed both polyp count and size. Three blinded reviewers, consisting of two gastroenterologists and one surgeon experienced in FAP, scored the videos based on polyp count and size. The first model summed all polyp counts, revealing almost perfect interobserver reliability with kappa values ranging from 0.841 to 0.969. The second model, which summed only polyps > 2 mm, showed an almost perfect interobserver reliability ranging from 0.803 to 0.957. For polyp count and size, the model that performed best had almost perfect interobserver reliability, ranging from 0.846 to 0.978. Bussey et al [41] assessed interobserver variability of duplicate polyp counts by two different observers at the same patient visit in 21 patients with colorectal polyposis. After calculating the polyp count, a coefficient of variation was calculated for each patient. The mean coefficient of variation was 27%, suggesting that interobserver variability was not large and that variability of measurements by a single observer would be minimal. We were uncertain how this measure of variability would equate with reliability; hence, we rated interobserver reliability as "limited data preclude firm conclusions" for this study. Polyp size was evaluated for interobserver reliability in two studies [22, 26]. One study reported almost perfect interobserver reliability with a kappa value of 0.851 for duodenal lesions > 1 cm and a kappa value of 0.641, indicating substantial agreement, for smaller lesions [26]. Another study evaluated interobserver reliability for duodenal lesions > 1 cm which was substantial with a kappa value of 0.651 [26]. Intra-observer reliability was not reported for the scoring items.

Assessment of endoscopic upper gastrointestinal tract scoring indices

The Spigelman classification system, which is widely used to assess severity of duodenal involvement in FAP, was the most frequently reported scoring index. Validation of this index was partial and involved assessment of content validity, construct validity, interobserver reliability, intra-observer reliability, and responsiveness (▶ **Table 3**). Only one study evaluated both the interobserver and intra-observer reliability of the Spigelman classification [42]. Interobserver reliability of both the Spigelman score and stage were almost perfect with kappa values of 0.95 (95% confidence interval [CI]: 0.91–0.98) and 0.93 (95% CI: 0.86–0.96), respectively. Corresponding values for the intra-observer reliability were 0.91 (95% CI: 0.83–0.96) for the Spigelman score and 0.88 (95% CI: 0.76–0.94) for the Spigelman stage.

One study developed new criteria for assessing high-risk gastric polyps associated with gastric cancer in patients with FAP [37]. These criteria were evaluated for content validity, construct validity, and interobserver reliability (▶ **Table 3**). Interobserver reliability was found to be fair to moderate with a kappa value of 0.45 (95% CI: 0.38–0.54). Intra-observer reliability was not reported. Phillips et al [24] reported on a video assessment score for endoscopic appearance of duodenal polyposis. Five blinded physicians scored endoscopic appearance of duodenal polyposis as no change (scored as 0), clinical improvement (scored as 1), or deterioration in number or density of adenoma (scored as -1). However, this score did not undergo any validation (▶ **Table 3**). Richard et al [38] reported on use of the FAP duodenal polyp classification, which classifies polyps based on size. This polyp classification did not undergo any validation (▶ **Table 3**).

Assessment of endoscopic lower gastrointestinal tract scoring indices

The InSIGHT polyposis staging system underwent partial validation, which included an assessment of content validity, construct validity, and interobserver reliability (▶ **Table 3**).

One study evaluated interobserver reliability and reported a kappa value of 0.710 (95% CI: 0.651–0.759), which corresponds with substantial agreement [16]. However, no data were reported on intra-observer reliability. In another study, a staging system was reported for severity of the anal transition zone in patients following pouch construction [36]. However, this system did not undergo any validation (▶ **Table 3**). Steinbach et al [21] reported on a video assessment score for assessment of endoscopic appearance of colorectal polyposis. Five blinded endoscopists scored endoscopic appearance of colorectal polyposis as "no change" (scored as 0), "better" (scored as 1), or "worse" (scored as -1). However, this score did not undergo any validation (▶ **Table 3**).

Study quality and risk of bias assessment

▶ **Fig. 2** summarizes study-level risk of bias assessment using the QUADAS-2 tool for formal validation studies. The index test, reference standard, and flow and timing were found to be unclear due to lack of a reference standard for assessing disease severity in FAP. Results of risk of bias assessment for studies that assessed the operating properties of scoring items and indices are reported in **Supplementary Table 6** and **Supplementary Table 7**, respectively.

Discussion

We identified 134 studies evaluating eight existing FAP indices and three component items for assessing endoscopic disease severity. Notably, none of the indices identified have undergone external validation in a separate cohort of patients. In addition, outside of polyp counting, it is unclear if the indices

▶ **Table 2** Operating properties of familial adenomatous polyposis endoscopic scoring items.

Study author/year	Scoring item	Content validity	Construct validity	Intra-observer reliability	Interobserver reliability	Respon-siveness	Feasi-bility
Anele/2017	Polyp count	0	0	0	0	0	0
Anele/2022	Polyp count	0	0	0	0	0	0
Attard/2004	Polyp count	0	0	0	0	0	0
Baba/1990	Polyp count	0	0	0	0	0	0
Bunyan/1995	Polyp count	–	–	0	0	0	0
Burke/2017	Polyp count	0	0	0	0	0	0
Church/2001	Polyp count	0	0	0	0	0	0
Crabtree/2001	Polyp count	0	0	0	0	0	0
DeCosse/1989	Polyp count	0	0	0	0	0	0
Friedl/2001	Polyp count	0	0	0	0	0	0
Ghorbanoghli/ 2016	Polyp count	0	0	0	0	0	0
Goldstein/2015	Polyp count	0	0	0	0	0	0
Grover/2012	Polyp count	0	0	0	0	0	0
Groves/2005	Polyp count	0	0	0	0	0	0
Iida/1988	Polyp count	0	0	0	0	0	0
Ishikawa/2021	Polyp count	0	0	0	0	0	0
Jung/2016	Polyp count	0	0	0	0	0	0
Kadmon/2001	Polyp count	0	0	0	0	0	0
Kanter-Smoler/2008	Polyp count	0	0	0	0	0	0
Kariv/2019	Polyp count	0	+	0	0	0	0
Kono/2018	Polyp count	0	0	0	0	0	0
Kono/2019	Polyp count	0	0	0	0	0	0
Kurtz/1987	Polyp count	0	0	0	0	0	0
Lefevre/2009	Polyp count	0	0	0	0	0	0
Li/2019	Polyp count	0	0	0	0	0	0
Lynch/2010	Polyp count	0	0	0	0	0	0
Lynch/2013	Polyp count	+	0	0	+	0	0
Lynch/2016	Polyp count	0	+	0	0	0	0
Mallappa/2012	Polyp count	0	0	0	-	0	0
Matsumoto/2002	Polyp count	+	+	0	0	0	0
Nagase/1992	Polyp count	0	0	0	0	0	0
Nielsen/2007	Polyp count	0	0	0	0	0	0
Nilbert/2008	Polyp count	0	0	0	0	0	0
O'Shea/2017	Polyp count	0	0	0	0	0	0
Papp/2016	Polyp count	0	0	0	0	0	0
Parc/2001	Polyp count	0	0	0	0	0	0
Plum/2009	Polyp count	0	0	0	0	0	0
Polese/2003	Polyp count	0	0	0	0	0	0
Ponz de Leon/1999	Polyp count	0	0	0	0	0	0

▶ **Table 2** (Continuation)

Study author/year	Scoring item	Content validity	Construct validity	Intra-observer reliability	Interobserver reliability	Responsiveness	Feasibility
Rivera/2011	Polyp count	0	0	0	0	0	0
Samadder/2016	Polyp count	0	0	0	0	0	0
Scott/2001	Polyp count	0	0	0	0	0	0
Shawki/2016	Polyp count	0	0	0	0	0	0
Sinicrope/2004	Polyp count	0	0	0	0	0	0
Tescher/2010	Polyp count	0	0	0	0	0	0
Thomas/1993	Polyp count	0	0	0	0	0	0
Thompson-Fawcett/ 2001	Polyp count	0	0	0	0	0	0
Torrezan/2013	Polyp count	0	?	0	0	0	0
Valanzano/1996	Polyp count	0	0	0	0	0	0
West/2010	Polyp count	0	0	0	0	0	0
Winde/1995	Polyp count	0	0	0	0	0	0
Winde/1997	Polyp count	0	0	0	0	0	0
Wu/1998	Polyp count	0	?	0	0	0	0
Yamaguchi/2016	Polyp count	0	0	0	0	0	0
Yang/2022	Polyp count	0	0	0	0	0	0
Bertoni/1996	Polyp count and histology	0	0	0	0	0	0
Bertoni/1999	Polyp count and histology	0	0	0	0	0	0
Bertoni/1995	Polyp count and size	0	0	0	0	0	0
Burn/2011	Polyp count and size	0	0	0	0	0	0
Bussey/1982	Polyp count and size	0	0	0	?	0	0
Cruz-Correa/2018	Polyp count and size	0	0	0	0	0	0
Cruz-Correa/2002	Polyp count and size	0	0	0	0	0	0
Giardiello/1993	Polyp count and size	0	0	0	0	0	0
Giardiello/2002	Polyp count and size	0	0	0	0	0	0
Gilad/2022	Polyp count and size	0	0	0	0	0	0
Guldenschuh/ 2001	Polyp count and size	0	0	0	0	0	0
Higuchi/2003	Polyp count and size	0	0	0	0	0	0
Hisamuddin/2005	Polyp count and size	0	0	0	0	0	0
Ishikawa/2013	Polyp count and size	0	0	0	0	0	0
Iwama/2006	Polyp count and size	0	0	0	0	0	0
Nugent/1993	Polyp count and size	0	0	0	0	0	0
Park/2021	Polyp count and size	0	0	0	0	0	0
Phillips/2002	Polyp count and size	0	0	0	0	0	0
Sample/2018	Polyp count and size	0	0	0	0	0	0
Seow-Choen/1996	Polyp count and size	0	0	0	0	0	0
Spagnesi/1994	Polyp count and size	0	0	0	0	0	0

▶ **Table 2** (Continuation)

Study author/year	Scoring item	Content validity	Construct validity	Intra-observer reliability	Interobserver reliability	Responsiveness	Feasibility
Steinbach/2000	Polyp count and size	0	0	0	0	0	0
Tajika/2022	Polyp count and size	0	0	0	0	0	0
Tonelli/2000	Polyp count and size	0	0	0	0	0	0
Wang/2022	Polyp count and size	0	0	0	0	0	0
Kunnathu/2018	Polyp size	0	0	0	0	0	0
Lopez-Ceron/2013	Polyp size	+	+	0	+	0	0
Nakamura/2019	Polyp size	+	0	0	0	0	0
Van Heumen/2013	Polyp size	0	0	0	0	0	0
Martin/2021	Polyp size and histology	+	0	0	0	0	0
Moozar/2002	Polyp size and histology	+	+	0	0	0	0
Sanabria/1996	Polyp size and histology of the ampulla	0	0	0	0	0	0

+ = present, - = absent,? = limited information available, and 0 = no information available.

identified are effective for differentiating responsiveness in patients receiving investigational therapies for FAP. This systematic review brings to light evidence gaps surrounding existing indices that measure endoscopic disease severity in FAP. Further work is needed to assess current endoscopic disease severity indices in FAP, and to possibly develop a new, validated, FAP endoscopic disease severity index to support clinical practice and clinical trials.

The most common FAP endoscopic disease severity measure (scoring item) used in the included studies was polyp counting. Although appealing for its simplicity and face validity, the large number of polyps commonly seen in FAP, often on the order of hundreds of polyps, makes counting and estimating the size of polyps inherently prone to inaccuracy. Moreover, polyp size may confer more serious disease severity as opposed to total polyp count.

The Spigelman classification was introduced in 1989 to quantify severity of duodenal polyposis and stratify patients for surveillance based on their risk of cancer [15]. Polyposis severity is evaluated using the Spigelman score (0–12 points) based on polyp number, polyp size, histology, and dysplasia. Higher scores are assigned for high-risk features. The score was developed from a prospective cohort of 102 patients with FAP who underwent protocolized upper endoscopies with biopsies. The total score results in a grade (stages 0-IV) and informs recommendations for frequency of upper endoscopy surveillance. Multiple studies have found that high Spigelman scores correlate with duodenal cancer, and a recent study found good inter-rater reliability among five experts [2, 42, 43]. The InSiGHT staging system was created by the International Society for Gastrointestinal Hereditary Tumors in 2016 as a result of the U.S. Food and Drug Administration decision that a decrease in polyp burden was not a sufficient clinical trial endpoint for approval of new chemo-preventive agents in FAP [16]. This staging system consists of ordinal stages from 0 to 4 corresponding with polyp number, polyp size, ability of polyps to be completely removed endoscopically, and presence of high-grade dysplasia. Each stage corresponds with recommendations for fre-

▶ **Fig. 2** Summary of study-level risk of bias assessment using the QUADAS-2 tool.

▶ **Table 3** Operating properties of familial adenomatous polyposis endoscopic scoring indices.

Study author/year	Index	Content validity	Construct validity	Intra-observer reliability	Interobserver reliability	Responsiveness	Feasibility
Anele/2017	Spigelman classification	+	0	0	0	0	0
Balmforth/ 2012	Spigelman classification	+	+	0	0	0	0
Bjork/2001	Spigelman classification	+	–	0	0	0	0
Bülow/2013	Spigelman classification	+	+	0	0	0	0
Calabrese/2013	Spigelman classification	+	+	0	?	0	0
Debinski/1995	Spigelman classification	0	0	0	0	0	0
Dekker/2009	Spigelman classification	+	+	0	0	0	0
Fukushi/2023	Spigelman classification	0	0	0	0	0	0
Groves/2002	Spigelman classification	+	+	0	0	0	0
Huneburg/ 2022	Spigelman classification	0	0	0	0	0	0
Inoki/2018	Spigelman classification	+	0	0	0	0	0
Jang/2011	Spigelman classification	+	0	0	0	0	0
Kallenberg/ 2016	Spigelman classification	+	+	0	0	0	0
Karstensen/ 2022	Spigelman classification	+	+	+	+	0	0
Leone/2019	Spigelman classification	0	0	0	0	0	0
Lepisto/2009	Spigelman classification	+	+	0	0	0	0
Lopez-Ceron/2013	Spigelman classification	0	0	0	0	0	0
Matsumoto/ 2008	Spigelman classification	0	0	0	0	0	0
Mehta/2020	Spigelman classification	+	+	0	0	+	0
Monkemuller/2007	Spigelman classification	+	+	0	0	0	0
Moussata/ 2014	Spigelman classification	+	+	0	0	+	0
Papagni/2016	Spigelman classification	0	0	0	0	0	0
Parc 2012	Spigelman classification	0	0	0	0	0	0
Park/2011	Spigelman classification	0	0	0	0	0	0
Roos/2021	Spigelman classification	+	+	0	0	0	0
Samadder/ 2023	Spigelman classification	0	0	0	0	0	0
Sato/2019	Spigelman classification	0	?	0	0	0	0
Sato/2020	Spigelman classification	0	?	0	0	0	0
Schulmann/ 2019	Spigelman classification	0	0	0	0	0	0
Silva/2020	Spigelman classification	0	0	0	0	0	0
Singh/2022	Spigelman classification	0	0	0	0	0	0
Stigliano/2016	Spigelman classification	0	0	0	0	0	0
Sulburan/2016	Spigelman classification	0	0	0	0	0	0
Takeuchi/2022	Spigelman classification	+	+	0	0	0	0
Tanaka/2022	Spigelman classification	0	0	0	0	0	0
Thiruvengadam/ 2015	Spigelman classification	0	0	0	0	0	0
Thiruvengadam/ 2019	Spigelman classification	0	0	0	0	0	0
Van Kouwen/2006	Spigelman classification	0	0	0	0	0	0

▶ **Table 3** (Continuation)

Study author/year	Index	Content validity	Construct validity	Intra-observer reliability	Interobserver reliability	Responsiveness	Feasibility
Watanabe/2017	Spigelman classification	0	0	0	0	0	0
Yamada/2014	Spigelman classification	0	0	0	0	0	0
Pyle/2017	Modified Spigelman classification (inclusion of the ampulla)	0	0	0	0	0	0
Sample/2018	Modified Spigelman classification	0	0	0	0	0	0
Spigelman/1989	Spigelman classification (original)	0	0	0	0	0	0
Yoon/2021	Modified Spigelman classification (inclusion of jejunal polyps)	0	0	0	0	0	0
Burke/2020	Spigelman classification/InSiGHT Polyposis Staging System (IPSS)	0	0	0	0	0	0
De Oliveira/2019	InSiGHT Polyposis Staging System (IPSS)	+	+	0	0	0	0
Lynch/2016	InSiGHT Polyposis Staging System (IPSS)	+	0	0	+	0	0
Lee/2021	IPAA anal transition zone severity stages	0	0	0	0	0	0
Mankaney/ 2020	novel criteria to identify high-risk gastric polyps	+	+	0	–	0	0
Phillips/2002	video assessment score for duodenal polyposis	0	0	0	0	0	0
Steinbach/ 2000	video assessment score for colorectal polyposis	0	0	0	0	0	0
Richard/1997	FAP duodenal polyp classification	0	0	0	0	0	0

+ = present, - = absent,? = limited information available, and 0 = no information available.
IPAA, ileal pouch-anal anastomosis; FAP, familial adenomatous polyposis.

quency of surveillance endoscopies, timing of colectomy, and initiation of chemoprevention.

Recently, however, concerns have arisen regarding several limitations with the Spigelman classification system. Two studies found that Spigelman stage was not an accurate predictor for duodenal and especially ampullary cancer [44, 45]. Moreover, gastric findings are not incorporated into the Spigelman classification because gastric adenomas and cancer are a more recently recognized challenge in surveillance of the upper gastrointestinal tract in patients with FAP [46, 47]. Lack of a clear indication for endoscopic polypectomy or surgery outside of Spigelman stage IV limits use of the Spigelman score in clinical practice. Finally, there have been considerable technological advances in endoscopy since the development of the Spigelman score in 1989. Widespread use of high-definition endoscopes has resulted in more and smaller polyps being identified, which may inflate the Spigelman score while risk of cancer may not be increased [48].

For lower gastrointestinal polyps, the InSiGHT staging system had excellent inter-rater reliability when sigmoidoscopy videos from 24 patients with FAP were reviewed by 26 expert clinicians who assigned a stage to the case using the proposed system. Similar to the Spigelman classification, the InSiGHT staging system has not undergone rigorous validation. Our work highlights that very few studies have evaluated interobserver reliability of endoscopic disease severity indices in FAP. Another notable gap in the literature is the lack of intra-observer reliability.

Our systematic review has several strengths, including its broad scope and size, with identification of all endoscopic severity scoring items and indices used in RCTs for FAP and a comprehensive description of all the operating properties that have been assessed for these scoring items and indices. The RCTs

and validation studies were identified by an explicit, prespecified, and reproducible search strategy. However, we acknowledge some important limitations. The limitations of our work include the heterogeneous nature of the reported FAP indices, which prevented pooling of the data and meta-analysis. The quality of the existing evidence is quite poor due to the observational nature of most of the included studies, many of which were retrospective with small sample size. Also, we did not assess publication bias; however, we included conference abstracts to minimize the effect of possible publication bias. Despite this, it is possible we have incomplete information about certain studies due to the content limitations imposed by abstract publications. In addition, heterogeneity of index parameters, limited parameter severity classification, and minimal inter-rater reliability evaluation preclude direct comparison of indices. Finally, the quality of index validation was suboptimal in many studies, and many studies did not assess operating properties of scoring items and indices.

Conclusions

In conclusion, this comprehensive review of endoscopic disease severity indices in FAP highlights that there are few endoscopic disease severity indices in FAP, and there is limited understanding of the operating properties of these scores. Additional work is needed to fully validate the existing scores or develop and validate new FAP endoscopic disease severity indices. Fully validated endoscopic disease severity indices in FAP will be imperative to support consistent reporting both for clinical care and clinical trials to rigorously study pharmacologic effects on polyp burden in FAP.

Conflict of Interest

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References

[1] Jasperson KW, Tuohy TM, Neklason DW et al. Hereditary and familial colon cancer. Gastroenterology 2010; 138: 2044–2058 doi:10.1053/j.gastro.2010.01.054

[2] Bülow S, Bjork J, Christensen IJ et al. Duodenal adenomatosis in familial adenomatous polyposis. Gut 2004; 53: 381–386 doi:10.1136/gut.2003.027771

[3] Yang J, Gurudu SR, Koptiuch C et al. American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in familial adenomatous polyposis syndromes. Gastrointest Endosc 2020; 91: 963–982 doi:10.1016/j.gie.2020.01.028

[4] Monahan KJ, Bradshaw N, Dolwani S et al. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). Gut 2020; 69: 411–444

[5] Church J, Burke C, McGannon E et al. Risk of rectal cancer in patients after colectomy and ileorectal anastomosis for familial adenomatous polyposis: a function of available surgical options. Dis Colon Rectum 2003; 46: 1175–1181 doi:10.1007/s10350-004-6710-2

[6] Friederich P, de Jong AE, Mathus-Vliegen LM et al. Risk of developing adenomas and carcinomas in the ileal pouch in patients with familial adenomatous polyposis. Clin Gastroenterol Hepatol 2008; 6: 1237–1242

[7] Moussata D, Napoleon B, Lepilliez V et al. Endoscopic treatment of severe duodenal polyposis as an alternative to surgery for patients with familial adenomatous polyposis. Gastrointest Endosc 2014; 80: 817–825

[8] Samadder NJ, Neklason DW, Boucher KM et al. Effect of sulindac and erlotinib vs placebo on duodenal neoplasia in familial adenomatous polyposis: a randomized clinical trial. JAMA 2016; 315: 1266–1275 doi:10.1001/jama.2016.2522

[9] Yuksekkaya H, Yucel A, Gumus M et al. Familial adenomatous polyposis; successful use of sirolimus. Am J Gastroenterol 2016; 111: 1040–1041 doi:10.1186/1750-1172-4-22

[10] West NJ, Clark SK, Phillips RK et al. Eicosapentaenoic acid reduces rectal polyp number and size in familial adenomatous polyposis. Gut 2010; 59: 918–925 doi:10.1136/gut.2009.200642

[11] Burke CA, Dekker E, Lynch P et al. Eflornithine plus sulindac for prevention of progression in familial adenomatous polyposis. N Engl J Med 2020; 383: 1028–1039 doi:10.1056/NEJMoa1916063

[12] Meyskens FL, McLaren CE, Pelot D et al. Difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas: a randomized placebo-controlled, double-blind trial. Cancer Prev Res (Phila) 2008; 1: 32–38 doi:10.1158/1940-6207.CAPR-08-0042

[13] Lynch PM, Burke CA, Phillips R et al. An international randomised trial of celecoxib versus celecoxib plus difluoromethylornithine in patients with familial adenomatous polyposis. Gut 2016; 65: 286–295

[14] Vilar-Sanchez E, Burke C, Correa MRC et al. A phase 1b, multicenter, randomized, blinded, placebo-controlled study to evaluate the efficacy of guselkumab in subjects with familial adenomatous polyposis. Cancer Res 2020; 80: CT236

[15] Spigelman AD, Williams CB, Talbot IC et al. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet 1989; 2: 783–785

[16] Lynch PM, Morris JS, Wen S et al. A proposed staging system and stage-specific interventions for familial adenomatous polyposis. Gastrointest Endosc 2016; 84: 115–125 doi:10.1016/j.gie.2015.12.029

[17] Liberati A, Altman DG, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009; 151: W65–W94

[18] Ma C, MacDonald JK, Nguyen TM et al. Systematic review: disease activity indices for immune checkpoint inhibitor-associated enterocolitis. Aliment Pharmacol Ther 2022; 55: 178–190 doi:10.1111/apt.16718

[19] Whiting PF, Rutjes AW, Westwood ME et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011; 155: 529–536 doi:10.7326/0003-4819-155-8-201110180-00009

[20] Page MJ, McKenzie JE, Bossuyt PM et al. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. J Clin Epidemiol 2021; 134: 103–112 doi:10.1016/j.jclinepi.2021.02.003

[21] Steinbach G, Lynch PM, Phillips RK et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med 2000; 342: 1946–1952 doi:10.1056/NEJM200006293422603

[22] Lopez-Ceron M, Van Den Broek FJC, Mathus-Vliegen EM et al. The role of high-resolution endoscopy and narrow-band imaging in the evaluation of upper GI neoplasia in familial adenomatous polyposis. Gastrointestinal Endoscopy 2013; 77: 542–550 doi:10.1016/j.gie.2012.11.033

[23] Sample DC, Samadder NJ, Pappas LM et al. Variables affecting penetrance of gastric and duodenal phenotype in familial adenomatous polyposis patients. BMC Gastroenterology 2018; 18: 115 doi:10.1186/s12876-018-0841-8

[24] Phillips RK, Wallace MH, Lynch PM et al. A randomised, double blind, placebo controlled study of celecoxib, a selective cyclooxygenase 2 inhibitor, on duodenal polyposis in familial adenomatous polyposis. Gut 2002; 50: 857–860 doi:10.1136/gut.50.6.857

[25] Anele C, Chauhan J, McGinty P et al. Attenuated FAP-how should it be defined and what are the clinical outcomes? Familial Cancer 2017; 16: S70

[26] Calabrese C, Pratico C, Calafiore A et al. Eviendep reduces number and size of duodenal polyps in familial adenomatous polyposis patients with ileal pouch-anal anastomosis. World journal of gastroenterology : WJG 2013; 19: 5671–5677

[27] Monkemuller K, Fry LC, Ebert M et al. Feasibility of double-balloon enteroscopy-assisted chromoendoscopy of the small bowel in patients with familial adenomatous polyposis. Endoscopy 2007; 39: 52–57

[28] Park SY, Ryu JK, Park JH et al. Prevalence of gastric and duodenal polyps and risk factors for duodenal neoplasm in Korean patients with familial adenomatous polyposis. Gut and Liver 2011; 5: 46–51

[29] Takeuchi Y, Hamada K, Nakahira H et al. Efficacy and safety of intensive endoscopic intervention (IDP) for multiple duodenal adenomas in patients with familial adenomatous polyposis: A prospective cohort study. Endoscopy 2023; 55: 515–523

[30] Tanaka K, Sato Y, Ishikawa H et al. Small Intestinal involvement and genotype-phenotype correlation in familial adenomatous polyposis. Techniq Innovations Gastrointest Endosc 2022; 24: 26–34

[31] Van Kouwen MCA, Drenth JPH, Van Krieken JHJM et al. Ability of FDG-PET to detect all cancers in patients with familial adenomatous polyposis, and impact on clinical management. European Journal of Nuclear Medicine and Molecular Imaging 2006; 33: 270–274

[32] Singh AD, Bhatt A, Joseph A et al. Natural history of ampullary adenomas in familial adenomatous polyposis: a long-term follow-up study. Gastrointest Endosc 2022; 95: 455–467 doi:10.1016/j.gie.2021.09.036

[33] Pyle B, Waller H, Chalmers-Watson T et al. Including ampullary polyposis staging in the Spigelman classification: Modifying the modified. Familial Cancer 2017; 16: S29–S30

[34] Yoon JY, Mehta N, Burke CA et al. The prevalence and significance of jejunal and duodenal bulb polyposis after duodenectomy in familial adenomatous polyposis retrospective cohort study. Ann Surgery 2021; 274: E1071–E1077 doi:10.1097/SLA.0000000000003740

[35] de Oliveira JC, Viana DV, Zanardo C et al. Genotype-phenotype correlation in 99 familial adenomatous polyposis patients: A prospective prevention protocol. Cancer Medicine 2019; 8: 2114–2122 doi:10.1002/cam4.2098

[36] Lee C, Kalady M, Burke C et al. Proposed classification system for ileal pouch adenomas in patients with familial adenomatous polyposis. Dis Colon Rectum 2021; 64: 171

[37] Mankaney GN, Cruise M, Sarvepalli S et al. Surveillance for pathology associated with cancer on endoscopy (SPACE): criteria to identify high-risk gastric polyps in familial adenomatous polyposis. Gastrointest Endosc 2020; 92: 755–762

[38] Richard CS, Berk T, Bapat BV et al. Sulindac for periampullary polyps in FAP patients. Int J Colorectal Dis 1997; 12: 14–18 doi:10.1007/s003840050071

[39] Mallappa S, Samarasinghe M, Neale K et al. Pre-operative colonoscopy in the management of familial adenomatous polyposis (FAP) patients: We need to do better. Colorectal Dis 2012; 14: 37

[40] Lynch PM, Morris JS, Ross WA et al. Global quantitative assessment of the colorectal polyp burden in familial adenomatous polyposis by using a Web-based tool. Gastrointest Endosc 2013; 77: 455–463 doi:10.1016/j.gie.2012.11.038

[41] Bussey HJ, DeCosse JJ, Deschner EE et al. A randomized trial of ascorbic acid in polyposis coli. Cancer 1982; 50: 1434–1439 doi:10.1002/1097-0142(19821001)50:7<1434::aid-cncr2820500733>3.0.co;2-f

[42] Karstensen JG, Bulow S, Burisch J et al. Validation of the endoscopic part of the Spigelman classification for evaluating duodenal adenomatosis in familial adenomatous polyposis: a prospective study of interrater and intrarater reliability. Am J Gastroenterology 2022; 117: 343–345 doi:10.14309/ajg.0000000000001582

[43] Groves CJ, Saunders BP, Spigelman AD et al. Duodenal cancer in patients with familial adenomatous polyposis (FAP): results of a 10 year prospective study. Gut 2002; 50: 636–641

[44] Latchford AR, Neale KF, Spigelman AD et al. Features of duodenal cancer in patients with familial adenomatous polyposis. Clin Gastroenterol Hepatol 2009; 7: 659–663

[45] Thiruvengadam SS, Lopez R, O'Malley M et al. Spigelman stage IV duodenal polyposis does not precede most duodenal cancer cases in patients with familial adenomatous polyposis. Gastrointest Endosc 2019; 89: 345–354

[46] Mankaney G, Leone P, Cruise M et al. Gastric cancer in FAP: a concerning rise in incidence. Fam Cancer 2017; 16: 371–376 doi:10.1007/s10689-017-9971-3

[47] Martin I, Roos VH, Anele C et al. Gastric adenomas and their management in familial adenomatous polyposis. Endoscopy 2021; 53: 795–801

[48] Mathus-Vliegen EM, Boparai KS, Dekker E et al. Progression of duodenal adenomatosis in familial adenomatous polyposis: due to ageing of subjects and advances in technology. Fam Cancer 2011; 10: 491–499 doi:10.1007/s10689-011-9433-2