The Simple Pediatric Activity Ultrasound Score (SPAUSS) for the Accurate Detection of Pediatric Inflammatory Bowel Disease

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ABSTRACT

Objective: The aim of the study was to identify the most significant ultrasound (US) parameters that predict inflammatory activity and develop a simple US activity score.

Methods: Patients were identified through retrospective evaluation of an established database of children with inflammatory bowel disease (IBD). Patients with endoscopy and US within 60 days were included (N = 75). US parameters evaluated included: bowel wall thickness (BWT), mesenteric inflammatory fat, lymphadenopathy, and hyperemia. The weighted kappa statistic was calculated to assess agreement between sonographic and endoscopically identified disease location. Using a proportional odds model and ordinal logistic regression, statistically significant ($P < 0.05$) parameters were used to generate a score. Variables were weighted to classify individuals into severity classes. Receiver operating characteristic curves were plotted to demonstrate the score's discriminative and predictive capacity.

Results: There was substantial agreement between US and endoscopy for all disease locations (weighted kappa = 0.85) and substantial agreement for ileocolonic disease (weighted kappa = 0.96). Two sonographic parameters were identified as contributing significantly to disease activity: BWT and mesenteric inflammatory fat ($P < 0.05$). A predictive score was developed incorporating BWT, hyperemia and inflammatory fat, and receiver operating characteristic curve curves demonstrated good predictive capacity to distinguish between the absence of disease (normal) and active disease with an area under the curve of 82.1%.

Conclusions: The most important sonographic parameters for predicting disease activity were BWT and mesenteric inflammatory fat. When combined with hyperemia into a simple score, there was accurate detection of inflammatory activity in children with inflammatory bowel disease. This score may facilitate noninvasive, bedside detection of inflammation, and standardize the use of US in children.

Key Words: inflammatory bowel disease, monitoring, ultrasound

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What Is Known

- Inflammatory bowel disease is often progressive, resulting in growth restriction with significant potential impact on early psychosocial development in children if inflammation is not controlled; however, early targeted medical intervention has been shown to improve outcomes.
- Ultrasound of the bowel exhibits comparable accuracy to both computed tomography and magnetic resonance imaging, and is readily available, well tolerated, and a considerably less expensive, easily repeated noninvasive imaging modality.

What Is New

- We have developed the Simple Pediatric Activity Ultrasound Score to accurately detect inflammatory disease activity noninvasively, vital to attempts to standardize use of ultrasound in children.
- This score may facilitate easy access to bedside detection of inflammation during routine clinical pediatric assessment.

Inflammatory bowel disease (IBD) is a chronic condition of inflammation of the gastrointestinal tract characterized by relapse and remission, with childhood onset occurring in up to 20% of patients (1). The global incidence of pediatric Crohn disease (CD) is increasing and the prevalence of pediatric IBD in Canada is high (2). IBD is progressive and may be complicated by growth restriction, hospitalization, and surgery in children, with the potential for adverse impact on early psychosocial development (3). Early, targeted medical intervention has been shown to improve pediatric outcomes (4).

Endoscopic evaluation poses challenges in children, because general anesthetic is required. Cecal and ileal intubation rates tend to be lower in children in comparison to adults (5). Although endoscopy is fundamental to diagnosis, factors such as requirement for anesthesia and bowel preparation, and duration of hospital stay limit its utility as a routine and frequently implemented monitoring

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tool. Dedicated small bowel imaging is recommended at diagnosis. Computed tomography (CT) has safety limitations given ionizing radiation exposure, particularly in children (5). Magnetic resonance (MR) imaging is safe; however, it limited by cost, access, and need for intravenous medications, including contrast. Ultrasound (US) of the bowel is not yet widely available, but exhibits similar accuracy to CT and MR, but is well tolerated with no requirement for anesthesia or contrast; it is nonradiating, repeatable, and inexpensive (6). In addition, US provides a unique opportunity to engage parents and children by providing immediate, real-time images and videos to help patients and families better understand their disease.

The purpose of this study was to identify statistically significant US parameters that best predict disease activity in pediatric patients with IBD compared to endoscopy (the criterion standard), and then use these parameters in a weighted manner to generate an activity score.

METHODS

This retrospective study was approved by the University of Calgary Ethics Board with informed consent waived given the retrospective study design. Children younger than 18 years with an established diagnosis of CD or ulcerative colitis (UC) followed at the Alberta Children's Hospital who underwent transabdominal bowel US between 2009 and 2014 were identified through the Picture Archiving Communication System. Included participants had high-quality images (at least 4 images of the large bowel and at least 2 images of the small bowel/ileum) from the US examination and had endoscopy completed within 60 days. Any patient having medical therapies initiated during the intervening time period were excluded. All patient charts were reviewed to ascertain disease location, character/phenotype using the Montreal Classification, prior surgical history, and medications (7). Relevant laboratory investigations within the 60-day time frame (hemoglobin, C-reactive protein, and albumin) were also collected.

Abdominal Ultrasound

Patients were instructed to fast for 8 hours before the examination, as is standard preparation. All abdominal US examinations were performed by 1 of 2 expert radiologists (S.W. and C.O.) using one of the following commercially available US machines: Aplio (Toshiba, Tokyo, Japan), iU22 (Philips, Bothell, WA), and S2000 (Siemens, Mountain View, CA) and a range of transducers were used to optimally image the bowel including high-frequency (9–12 MHz), high-resolution curved and linear array probes. Annotated cine-loop and still image files were captured from each examination and stored on the Picture Archiving Communication System as standard protocol for abdominal/ intestinal imaging.

From each examination, sonographic variables were assessed and documented for each bowel segment (terminal ileum, right-sided colon, transverse, descending colon, sigmoid colon, and rectum). This included bowel wall thickness (BWT) graded as normal (1–3.9 mm), mild (4–6.9 mm), or moderate/severe ($\geq$7 mm) (adapted from (8)). Presence of mesenteric inflammatory fat and lymphadenopathy were documented as absent (0), mild (1), or moderate/severe (2). Hyperemia, as assessed by color Doppler signal, was graded as 0, 1, or 2, representing absent, mild, or moderate to severe, respectively. Presence of complications were recorded and included fixed luminal apposition or stricture with or without elements of mechanical bowel obstruction (evidenced by proximal bowel dilation), fistula, phlegmon/inflammatory mass and abscess(es). Subjective commentary regarding overall disease severity was also recorded and was graded as absent, mild, or moderate/severe. Disease activity according to bowel segment on US was categorized as present or absent based on the radiologist's overall assessment.

Endoscopy

All endoscopic evaluations were completed as per standard of care by pediatric gastroenterologists at the Alberta Children's Hospital using pediatric PENTAX (Mississauga, ON) endoscopes. Endoscopic reports and images were retrieved from the Endopro database (New Jersey). Two independent, blinded IBD specialists reviewed the endoscopic records (K.L.N. and G.K.) to determine the presence or absence of inflammation, descriptions of severity, and disease location. In addition, commentary regarding intubation of the ileocecal valve with visualization of the ileum was recorded. Given the absence of a validated retrospective scoring system, assessment of inflammation was documented as normal (complete absence of disease activity), mild (<5 aphthous ulcerations, <0.5 cm in diameter, no bridging inflammation), or active (signifying activity that was more extensive than mild and within the range of moderate and severe inflammation). This assessment was performed for disease in terminal ileum, right-sided colon, transverse colon, descending colon, and sigmoid colon. In the event of a disagreement, a third reviewer was asked to evaluate the patient's report to ascertain agreement.

Statistical Analysis

Demographic Data

Demographic data were analyzed using descriptive statistics. Chi-square and Fisher exact tests were used to analyze categorical data. The post hoc test with Tukey pairwise comparison and Spearman rank order correlation statistics were used to analyze significant differences between variables. Statistical significance was defined as a P value of <0.05.

Ultrasound Comparison to Endoscopy

The accuracy of US in assessing disease severity was determined by comparison to endoscopy in a segmental manner. The sensitivity, specificity, positive and negative predictive value, and overall accuracy were calculated, based on the presence/absence of disease as assessed by US compared to ileocolonoscopy. Comparisons were made for overall ileocolonic location and for separate colonic segments. Ileocolonic disease was defined as disease originating distal to the jejunum and including any segment of the large intestine.

Generation of the Simple Pediatric Activity Ultrasound Score

US parameters found to significantly predict disease activity were identified using multivariable ordinal logistic regression and proportional odds model. The chi-squared test was then used to assess whether or not the proportional odds assumptions were violated. Variables that were not significant were removed by backward elimination with the exception of hyperemia. The estimate of the coefficient of the parameter for each significant variable was transformed by dividing each coefficient with the smallest coefficient of the fitted model, rounded to the nearest integer, and then assigned as the weighting factor for that variable. Based on the weights assigned to the variables that were found to be significantly associated with IBD disease severity, a total score was calculated for each patient, which was used to classify individuals into the

different severity levels. Receiver operating characteristic curves were plotted to assess the overall predictive and discriminative value of the score. All statistical analysis was performed using SAS statistical software for Windows (version 9.2; Statistical Analysis System, Toronto, Canada).

RESULTS

Demographics

Seventy-five patients comprised the study cohort with a mean age of 14.4 years (±3.12 years). Of those, 56 (75.6%) were diagnosed with Crohn disease, 4 (5.3%) had IBD-unclassified, and 15 (20.2%) had ulcerative colitis (Table 1). All patients were in follow-up with the exception of the cases of IBD-unclassified. Of those, 19 (26.3%) patients had prior surgery and 53 (70.7%) were on medication at the time of the US and endoscopic examination. All data were analyzed according to diagnosis and disease location. Although disease severity was assessed for each segment of the bowel, data were grouped into ileal, colonic, or ileocolonic disease for analysis. The most common disease location for patients with CD was ileocolonic (N = 26 [34.6%]), followed by colonic (N = 11 [14.6%]) then ileal disease (N = 7 [9.3%]). For patients with UC, 1 patient (1.3%) had left-sided disease, 9 (12%) had pancolitis N = 9 (12%), 1 (1.3%) had proctitis, whereas 1 (1.3%) was diagnosed with both pancolitis and backwash ileitis.

TABLE 1. Patient demographics

Demographic information	N (%)
Number of patients (N)	75
Female	43 (57.3%)
Male	32 (43.2%)
Age	
Median age, y	14.4 (±3.12)
Disease category	
Crohn disease	56 (75.6%)
Ulcerative colitis	15 (20.2%)
Symptoms (being investigated)	4 (5.3%)
Disease location (Crohn disease)	
Ileal	7 (9.3%)
Ileocolonic	26 (34.6%)
Colonic	11 (14.6%)
Disease location (ulcerative colitis)	
Left-sided	1 (1.3%)
Pancolitis	9 (12%)
Proctitis	1 (1.3%)
Pancolitis and backwash-ileitis	1 (1.3%)
Surgical history	
Prior surgery	19 (22.9%)
Therapy	
Yes	19 (25.3%)
No	56 (74.6%)

Values are shown as N with respective percentages.

Accuracy of Ultrasound Compared With Endoscopy

The accuracy of US in predicting disease severity was compared to endoscopy by anatomical segment (for ileal, colonic, and ileocolonic). Sensitivity and specificity values were calculated for each segment of the bowel. Ileal disease was detected via US with a sensitivity of 100% (95% confidence interval [CI] 84.5–100) and specificity of 100% (95% CI 83.8–100). The sensitivity of US for detecting disease of the colon was 86.6% (95% CI 59.5–98.3) with a specificity of 100% (95% CI 75.2–100). The overall sensitivity and specificity of US in predicting disease severity in comparison to endoscopy was 100% (95% CI 90–100) and 95% (95% CI 83–99.3), respectively, indicating that US was most sensitive in detecting disease in the ileum and equally specific for detecting disease in the ileum and colon (Table 2). The positive predictive value and negative predictive value of US combining colonic and ileal disease were 94.5% (CI 81.1%–99.3%) and 100% (CI 90.7%–100%), respectively (Table 3). There was substantial agreement between US and endoscopy for all disease locations (weight kappa = 0.85, 95% CI 0.76–0.95) and substantial agreement for identifying ileocolonic disease (weighted kappa = 0.96, 95% CI = 0.89–1.00).

Development of the Score

Four US parameters were analyzed in the development of the Simple Pediatric Activity Ultrasound Score (SPAUSS) to determine which parameters significantly predicted disease severity on US: mesenteric inflammatory fat, mesenteric lymph nodes, hyperemia, or color flow as seen on Doppler and BWT. Of the 4 parameters analyzed, BWT (graded as absent, mild, moderate, or severe) and presence or absence of mesenteric inflammatory fat were found to significantly predict disease severity ($P = 0.0182$ and $P = 0.0003$, respectively) with increasing BWT and inflammatory fat predicting the most severe disease. Increasing BWT was an accurate predictor of disease severity with an odds ratio (OR) of 3.79 (95% CI 1.28–11.2) for BWT 4 to 6 mm and an OR of 6.00 (95% CI 1.57–22.95) for BWT 7 to 8 mm compared to normal BWT. Presence of mesenteric inflammatory fat accurately predicted disease severity with an OR 5.70 (95% CI 1.52–21.32) (Table 4). A predictive score was developed using these 2 significant US parameters and hyperemia. For BWT, 1.0 to 3.9, 4.0 to 6.9, and ≥7.0 mm corresponded with scores of 1, 4, and 6, respectively. Absent, mild, and moderate/severe hyperemia corresponded to scores of 0, 1, and 2, respectively. For inflammatory fat, absent, mild, and moderate/severe were assigned scores of 0, 1, and 6, respectively. A total score was then generated from these 3 parameters, with a score of >7 being the most sensitive and specific for predicting active disease. The plotted receiver operating characteristic curve demonstrated good

TABLE 2. Sensitivity, specificity, and accuracy analysis for ultrasound in comparison to criterion standard ileocolonoscopy

Population	Segment of analysis	Sensitivity, (95% CI)	Specificity, (95% CI)	Accuracy, (95% CI)
(N = 75)	Colon + ileum (n = 75)	100% (90–100)	95% (83–99.3)	97.3% (90.7–99.6)
	Colon (n = 24)	86.6% (59.5–98.3)	100% (75.2–100)	91.6% (73–98.9)
	Ileum (n = 43)	100% (84.5–100)	100% (83.8–100)	100% (91.7–100)

Values are percentages with respective confidence intervals.
CI = confidence interval.

TABLE 3. Positive and negative predictive value analysis for ultrasound in comparison to criterion standard ileocolonoscopy

Population	Segment of analysis	PPV (95% CI)	NPV (95% CI)
(N = 75)	Colon + ileum (n = 75)	94.5% (81.8–99.3)	100% (90.7–100)
	Colon (n = 24)	100% (75.2–100)	81.8% (48.2–97.7)
	Ileum (n = 43)	100% (84.5–100)	100% (83.8–100)

Values are percentages with respective confidence intervals.
CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value.

predictive capacity to distinguish between normal and active disease with an area under the curve was 82.1% (95% CI 0.72–0.92) (Fig. 1).

DISCUSSION

Ileocolonoscopy is currently the criterion standard for IBD diagnosis; however, it has limitations regarding repeated use as a disease monitoring tool. The use of cross-sectional imaging is increasing, demonstrating accuracy compared to endoscopy, and a valuable noninvasive modality for assessing not only disease activity, but also presence of complications and response to therapy (9). To date, cross-sectional imaging in Canadian children with IBD is typically limited to MR. Several systemic reviews have shown transabdominal intestinal US to be an accurate and even superior modality for the detection and monitoring of disease activity in IBD. Studies are, however, primarily from adults and data in the pediatric population are lacking. In addition, there is no standardized scoring system for bowel US (10). In adult populations, sensitivity and specificity of US ranges from 85% to 97% and 83% to 95%, respectively (11). In children, sensitivity and specificity for detecting small intestinal disease is reported as 75% and 100%, respectively. Pallotta et al (12) reported a sensitivity and specificity of 100% for small intestine contrast ultrasonography in undiagnosed patients. Our data demonstrate similar sensitivity and specificity.

Variation in sensitivity and specificity may be due to several factors. Firstly, mild, mucosal disease characterized by small aphthous ulcers is difficult to detect with US and duodenal, proximal small bowel and rectal disease is challenging to accurately identify. Several severe cases of CD were noted to have disease in the proximal small bowel (on esophagogastroduodenoscopy) and rectum, which could not be well visualized on US. This may account for the discrepancies observed in the assessment of mild versus moderate to severe disease. Another important consideration is the inclusion of patients with both UC and CD in the analysis. Although BWT and hyperemia are established sequelae of both diseases, the pathophysiology underlying these conditions is different in that CD presents with transmural involvement while UC is limited to the mucosa and submucosa (1). Moreover, UC is continuous from the rectum, whereas CD presents with skip distribution in the small and/or large intestine. Hyperemia was included in the score given it's established importance in reflecting disease activity, similarly demonstrated as enhancement by other imaging modalities such as CT and MR. These differences warrant separation of those patients with UC and CD in future analysis. Of note, infectious colitis is particularly difficult to differentiate from IBD on US (or other imaging modality) as both may present with increased BWT and mesenteric inflammation. However, the use of high-resolution probes to delineate a mural echo pattern of inflammation

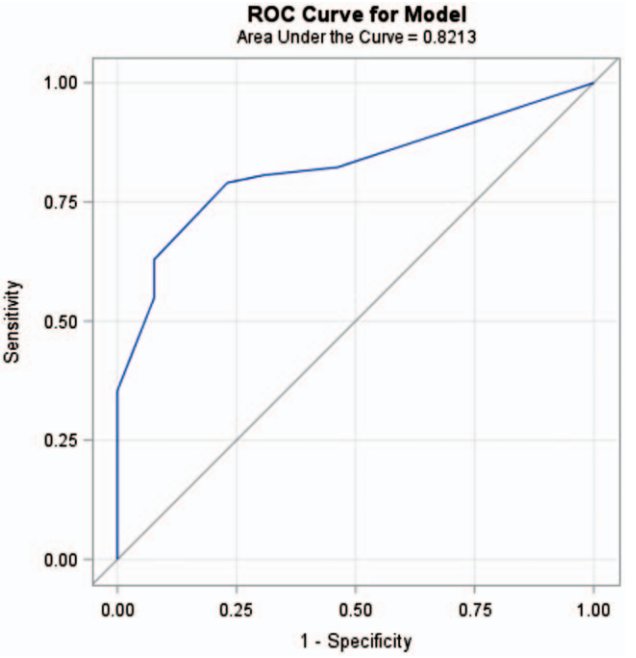

FIGURE 1. Receiver operating characteristics (ROC) curve demonstrating the prediction of disease activity using the derived Simple Pediatric Activity Ultrasound Score (SPAUSS) applied to the retrospective cohort. Disease activity is categorized as ''inactive'' (normal or mild) and active (including both moderate and severe).

TABLE 4. Odds ratios for ultrasound parameters predicting active disease, compared to criterion standard ileocolonoscopy

	Odds ratios (OR)				
	Effect	Point estimate	95% Wald confidence limits	*P*	Score
Bowel wall thickness (BWT)*	Mild (4–6.9 mm)	3.79	1.2–11.2	0.0182	4
	Moderate/severe (≥7 mm)	6.00	1.57–22.95	0.0066	6
Color Doppler (hyperemia)†	Mild	1.25	0.33–4.74	0.7486	1
	Moderate/severe	1.51	0.3–5.9	0.5326	2
Inflammatory fat‡	Mild	1.42	0.39–5.13	0.6924	1
	Moderate/severe	5.7	1.5–21.3	0.0003	6

*0 = BWT 1–3.9 mm (reference), 1 = BWT 4 to 6.9 mm, 2 = BWT ≥7 mm.
†0 = Absent/ no color Doppler, 1 = mild activity on color Doppler, 2 = moderate or severe activity on color Doppler.
‡0 = Absent, 1 = mild inflammatory fat, 2 = moderate/severe inflammatory fat.

has been found to be specific for CD, although differentiating UC and infectious colitis is more challenging as they present with similar echo patterns (13). As such, it is vital that future studies include cohorts for CD, UC, and infectious colitis for comparison.

Endoscopy was selected for comparison because it is considered criterion standard for IBD assessment. There are, however, inherent limitations when comparing these modalities. US is unique in the ability to transmurally depict the bowel wall, evaluating thickness, and extramural features. Endoscopy is limited to direct visualization of the mucosa. Advancement of the endoscope to ensure adequate visualization of all bowel segments can be significantly limited by stenosis, in addition to pain, and severe disease. Despite these considerations, US has demonstrated accuracy in comparison to endoscopy both in the retrospective pediatric analysis and in retrospective and prospective adult cohorts (14,15).

There is immense need for standardization of US evaluation to reduce inter-rater variability and to ensure consistency in measurement, so evaluators speak the same language. Like MR and endoscopy, US assessment can be limited by operator expertise and technique. Several scores exist with the aim of standardizing assessment of disease activity. Calabrese et al (11) developed a numerical index to quantify intestinal damage as detected by small intestine contrast ultrasonography named the sonographic lesion index for CD. The score incorporates BWT, lumen diameter, and number and length of mucosal lesions. Similar to the current study, presence of mesenteric adipose tissue, lymph nodes, and fibrostenotic disease were also considered as important variables (11). Although valuable, this score is for adults, is complex, and thus not widely used. In addition, the variables were not identified statistically. The variables identified in this study have been shown to be significant in other scores (16): the magnetic resonance index of activity, Crohn disease MRI Index, and Nancy scoring systems currently exist for assessing CD with magnetic resonance enterography, and all 3 identify BWT and hyperemia as significant predictors of disease severity. The most widely used score is the magnetic resonance index of activity score, which incorporates BWT, contrast enhancement, edema, and ulceration into a combined, segment-by-segment index that shows significant correlation with CDEIS (17). None of these parameters were generated statistically.

One of the advantages of US and cross-sectional imaging is the ability to evaluate small bowel disease not accessible by routine endoscopy. None of the current MR scores include length, mesenteric fat, or lymph nodes. There is subjectivity in these measures and thus potential variability in measurement (15). Although they are not included as parameters in this study, the importance of length of disease and penetrating complications cannot be overlooked. Ultimately, the SPAUSS was developed with the aim of providing a simple, reproducible scoring system for activity through which to accurately monitor disease in the pediatric population and further analysis should aim to prospectively validate the score and determine whether the addition of other variables would improve accuracy.

Endoscopy is the criterion standard for diagnosis of IBD because mucosal biopsies can be obtained to accurately differentiate UC from CD (18). Although US has proven accuracy with regard to assessment of disease severity, it is still an indirect measure limited to transmural assessment of the bowel. US has demonstrated higher sensitivity and specificity for the identification of moderate to severe disease versus milder disease. More superficial mucosal aphthous ulceration observed in milder disease may be missed with US. Therefore, US is a valuable complement to ileocolonoscopy and the aim of the SPAUSS is to provide a tool for monitoring disease activity, response to therapy, and assessment of complications. It may also be used to triage of patients and expedite endoscopic diagnosis, avoiding potentially unnecessary invasive assessments and repeated general anesthetics in children.

There are limitations with the current study. Firstly, the sample size is small and retrospective in nature. The lack of criterion standard for cross-sectional imaging may underestimate the accuracy of US and prevent the inclusion of several important variables in the analysis and scoring system that may aid in assessment of disease severity such as length of disease and presence of penetrating disease. The SPAUSS was developed using multiple logistic regression analysis to identify significant parameters that best predict disease severity in a retrospective cohort; further analysis in a prospective, point of care cohort would be beneficial for further validation of the scoring system. Of note, we have developed a similar score in the adult population that has been both retrospectively and prospectively validated and shows great promise as an accurate index for the standardization of US assessments (19). The SPAUSS may facilitate noninvasive, broader use at the bedside for monitoring inflammation and is vital in the effort to standardize measurement in children.

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