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Original research article

The combination of fecal calprotectin with ESR, CRP and albumin discriminates more accurately children with Crohn's disease

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ABSTRACT

Purpose: Increased fecal calprotectin is a sensitive marker of various types of intestinal inflammation. We investigated correlations between high fecal calprotectin concentration and serum inflammatory markers in children with different intestinal diseases with diarrhea with/without blood and/or abdominal pain, to test whether the combination of these markers can differentiate potential patients with inflammatory bowel disease.
Materials/methods: The study included 128 children with high fecal calprotectin concentration (> 150ug/g) and symptoms suggesting bowel disorders, hospitalized in the years 2013– 2015. Twenty-six (20%) patients were diagnosed with Crohn's disease, 55 (43%) with ulcerative colitis, 32 (25%) with intestinal infection and 15 (12%) with food protein induced proctocolitis.
Results: Significantly increased inflammatory markers were detected in children with inflammatory bowel disease, with a correlation between calprotectin and erythrocyte sedimentation rate – ESR (R = 0.53), mean corpuscular volume – MCV (R = -0.64), red blood cell distribution width (R = 0.56), albumin (R = −0.52), hemoglobin (R = −0.53) only in Crohn's disease patients. To discriminate Crohn's disease patients from patients with intestinal infection and patients with food protein induced proctocolitis, AUC analysis was performed. It revealed that considering ESR, CRP and albumin as additional markers to fecal calprotectin significantly improved diagnostic performance (AUC 0.917, p = 0.038).
Conclusions: In children with abdominal pain and/or diarrhea, increased ESR, CRP and decreased albumin combined with a high fecal calprotectin level yields additional diagnostic value in screening potential patients with Crohn's disease. As far as differentiation of ulcerative colitis is concerned, low additional diagnostic value was found when high fecal calprotectin was combined with albumin.

1. Introduction

In pediatric population, symptoms of inflammatory bowel disease (IBD) do not differentiate this disease from other intestinal disorders. The gold standard in diagnosing IBD is colonoscopy [1]. However, this procedure is expensive and invasive. On the other hand, serum markers of inflammation are insufficient for discriminating between IBD and other intestinal inflammatory diseases [1]. It has been demonstrated that a high level of fecal calprotectin (FC) is very sensitive (97%) but moderately specific (71%) in diagnosing inflammatory bowel diseases (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC) [2–6]. Moreover, according to literature reports, a high FC level has also been reported in other diseases such as infectious diarrhea, necrotizing enterocolitis, cow's milk protein allergy, colorectal cancer, colonic polyps, a non-steroidal anti-inflammatory drug induced enteropathy, cystic fibrosis, juvenile idiopathic arthritis, and even untreated celiac disease [2,7–9]. However, combining FC with serum markers of inflammation might prove valuable in distinguishing patients with IBD from individuals with other intestinal disorders in whom high FC was detected. It has already been shown that an increased FC level is a good predictor of intestinal inflammation, particularly when combined with an elevated C-reactive protein serum concentration, observed in adults and not-naïve IBD patients [10,11]. There are no published data concerning the association of FC with other commonly tested blood inflammatory

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markers, whose values are abnormal in IBD but not typically in other intestinal diseases. The combination of these markers and FC might increase the predictive value of the test to screen patients with IBD before requesting endoscopic procedures.

Therefore, the aim of the study was to determine the correlation between high FC concentration and serum inflammatory markers (C-reactive protein - CRP, erythrocyte sedimentation rate – ESR, white blood count - WBC, platelet count - PLT, red blood cell distribution width - RDW, mean platelet volume – MPV, albumin) and complete blood count (hemoglobin – Hb, mean corpuscular volume – MCV) in children with different intestinal diseases manifested with diarrhea with or without blood and/or abdominal pain, in order to examine whether the combination of these markers can differentiate potential patients with IBD.

2. Materials and methods

2.1. Patient selection

The retrospective investigation included 138 children treated in the Department of Pediatrics, Gastroenterology and Allergology and the Gastroenterology Outpatient Clinic in the years 2013–2015 due to gastrointestinal (GI) tract symptoms such as abdominal pain, diarrhea with or without blood in the stool combined with high FC concentration (> 150 µg/g). This level of FC (exceeding the upper reference limit threefold) had previously been reported as a good predictor of IBD offering the highest sensitivity [12,13]. Despite elevated FC levels, 10 children were not included in the study since they were diagnosed with juvenile polyps or the etiology of symptoms was unknown.

Based on the final diagnosis the participants were categorized into 4 groups:

1 26 children with newly diagnosed CD, aged 5–17 years (17 male / 9 female). Diagnosis was based on ESPGHAN guidelines, including radiological, endoscopic and histological criteria [1]. Disease location, according to the Paris classification, was described as L1 (distal 1/3 ileum) in 12 patients (46%), L3- (ileocolonic) in 6 (23%), L4 (upper GI tract) in 1 (4%), L1 + L4 in 4 (15%) and L3 + L4 in 3 (12%) [14]. Disease activity, according to the pediatric CD activity index (PCDAI) [15], was scored as: severe (> 50pts) in 1 patient (4%), moderate (30–50 pt s) in 8 (31%) and mild (< 30pts) in 17 children (65%). None of the patients was being treated at the time of diagnosis and collection of samples for tests.
2 55 children with newly diagnosed UC, aged 1–17 years (27 male / 28 female). Diagnosis was based on ESPGHAN guidelines including radiological, endoscopic and histological criteria [1]. Disease location, based on the Paris classification, was described as E1 (ulcerative proctitis) in 8 patients (15%), E2 (left-sided UC) in 16 (29%), E3 (extensive, hepatic flexure distally) in 4 (7%) and E4 (pancolitis) in 27 children (49%) [14]. Disease activity, according to the pediatric UC activity index (PUCAI) [16], was scored as: severe (> 65pts) in 5 patients (9%), moderate (35–64 pt s) in 26 (47%) and mild (10–34 pt s) in 24 children (44%). None of the patients was being treated at the time of diagnosis and collection of samples for tests.
3 15 children with newly diagnosed FPIP, a non-IgE mediated food allergy, aged 2 months-17 years (7 male / 8 female). Diagnosis was determined based on ESPGHAN guidelines [17]. Endoscopic management of the lower digestive tract was performed in 7 (44%) children, revealing nonspecific mild inflammatory lesions in the colon (erythema, small erosions or nodular hyperplasia).
4 32 children with newly diagnosed intestinal infection/infestation (InIn), aged 7 months-17 years (20 male / 12 female). Among them, 6 patients had viral infections, 16 bacterial infections and 1 enterobiasis. Diagnosis was based on stool examination.

2.2. Measurement of serum inflammatory markers

Serum CRP (mg/L) and albumin (g/dL) levels were determined by immunoturbidimetry (Abbott Diagnostics, Japan). The ESR was evaluated according to the Westergren method (mm/h). The complete blood count was measured using a Hematology Analyzer (Beckman Coulter). The cut-off values of the biomarkers (ESR > 10 mm/h, CRP > 5 mg/L, WBC $> 10 \times 10^3$/uL, PLT $> 350 \times 10^3$/uL, Hb < 11 g/dL, MCV < 75 fL, RDW $> 15\%$, MPV < 7 fL, Albumin < 3.5 g/dL) were based on the laboratory reference ranges of the Medical University of Bialystok Children's Hospital (Poland).

2.3. Measurement of fecal calprotectin

A parent of each child and the older children were provided with a plastic container and were instructed on how to collect stool samples. All fecal samples were collected during hospitalization, frozen and stored at - 80 °C immediately following receipt until analysis. FC concentration was determined by ELISA kit (IDK Calprotectin, Immundiagnostik, Bensheim, Germany) according to the manufacturer's instructions. The upper normal limit is determined as 50 µg of calprotectin per 1 g of feces.

2.4. Statistical analysis

Data analysis was performed using the Statistica software. The results are presented as median (min-max). Markers with a skewed distribution (calprotectin, ESR, CRP and RDW) were log transformed. The significance of difference in the data was evaluated with the Mann-Whitney non-parametric U test Based on Spearman analysis, correlations between the FC concentration and the selected parameters of complete blood count (Hb, MCV) and inflammatory markers (ESR, CRP, albumin, PLT, RDW, MPV) were tested.

The diagnostic value of the markers combined with FC concentration was estimated using multivariate regression and ROC curves analyses. Some variables deviated significantly from normal distribution (Shapiro-Wilk test) and therefore they were log-transformed to decrease skewness. Log-transformed variables were: FC, ESR, CRP, MCV, albumin and RDW. To determine the combined diagnostic usefulness of sets of clinical covariates, synthetic indicators were developed. These indicators are linear combinations of selected variables. Coefficients of these combinations were obtained using the multivariate binary logistic regression model. These synthetic indicators were used to construct receiver operating characteristic curves and calculate AUCs. The diagnostic value of synthetic indicators was compared to the diagnostic value of single FC (log-transformed) using a test for comparing to AUC values [18]. An increase in the diagnostic value of additional variables compared to single FC was also estimated by comparing nested binary logistic models. To calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of synthetic indicators, cut-off values were selected, based on the Youden index maximisation criterion.

Biomarker analyses for CD patients were compared to the food protein induced proctocolitis (FPIP) and intestinal infection (InIn) groups. Biomarker analyses for UC patients were compared to the FPIP and InIn groups. $P < 0.05$ was considered statistically significant.

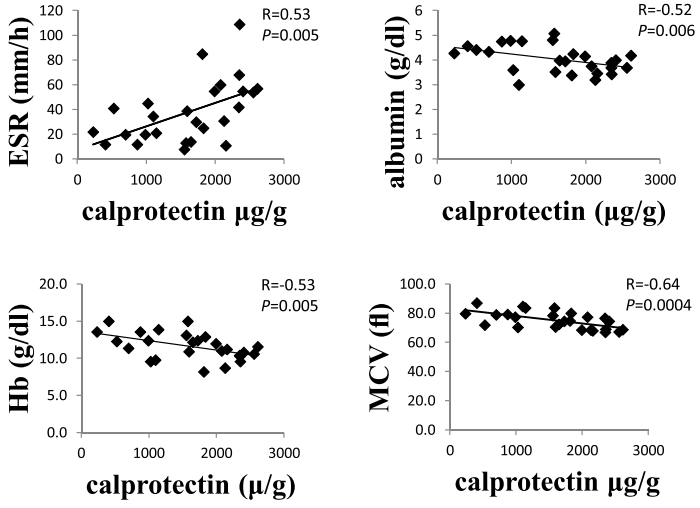
2.5. Ethical issues

The study protocol was approved by the Ethics Committee of the Medical University of Bialystok (approval number R-I-002/308/2014). Written informed consent was obtained from the parents of all the study participants.

Table 1
Background data, median (min-max) values of markers and percentage of patients with abnormal result of inflammatory marker in study groups. Significance is accepted at $p < 0.05$. †indicates p < 0.05 CD vs InIn; ‡indicates p < 0.05 CD vs FPIP, § indicates p < 0.05 UC vs InIn, ¶ indicates p < 0.05 UC vs FPIP.

	CD	UC	InIn	FPIP
Demographics				
Number (%)	26 (20)	55 (43)	32 (25)	15 (12)
female, n (%)	9 (35)	28 (51)	12 (37)	8 (53)
male, n (%)	17 (65)	27 (49)	20 (63)	7 (47)
Mean age yrs (range)	13.3 (5–17)	12.8 (1–17)	8.9 (0.16–17)	3.6 (0.16–17)
Laboratory tests: median (min-max)				
FC (μg/g)	1683.5† (227.6–2609.9)	1691§ (178.2–3103.4)	511.4 (199–3093.1)	1211.5 (211–2756.9)
CRP (mg/L)	24.5 (0.9–156) † ‡	3.9 (0–44) ¶	4.6 (0.2–194)	0.6 (0–7)
> 5 mg/dL n (%)	20 (77%) † ‡	26 (47%) ¶	12 (40%)	1 (8%)
ESR (mm/h)	35 (8–109) †	16 (2–120)	12 (2-92)	11 (10–22)
> 10 mm/h n (%)	25 (96%)† ‡	34 (67%) ¶	10 (56%)	2 (15%)
WBC (10^3/μL)	8.11 (4–15.3)	8.29 (3.07–20)	7.55 (3.8–18.2)	8.85 (4.64–14.1)
> 10 × 10^3/μL n (%)	6 (23%)	18 (32%)	8 (25%)	5 (33%)
Hb (g/dL)	11.5 (8.2–15)	12.4 (8.8-15.8)	12.5 (8.8–16.3)	11.5 (9.8–14)
< 11 g/dL n (%)	15 (58%)	21 (38%)	10 (31%)	5 (33%)
MCV (fL)	74.7 (66.9–87) †	80.2 (62.7–94.8)	78.9 (72.2–88.8)	78.8 (62.7–87.9)
< 75 fL n (%)	14 (54%)	9 (16%)	9 (28%)	5 (33%)
PLT (10^3/μL)	352.5 (160–625)	327 (151–676)	277.5 (156–655)	326 (164–486)
> 350 × 10^3/μL n (%)	14 (54%)†	25 (46%)	8 (25%)	5 (33%)
MPV (fL)	9.9 (8.6–12.5) ‡	10 (7.7–12.6)	10.1 (8–12.7)	10.6 (9.9–11.7)
< 7 fL n (%)	0	0	0	0
RDW (%)	14.6 (12–19.3) † ‡	13.5 (11.9–25.9)	13.7 (11.8–20)	13.2 (11.8–23.2)
> 15% n (%)	11 (42%)†	10 (18%)	1 (3%)	3 (21%)
Albumin (g/dL)	3.9 (3.01–5.07) †	4.5 (2.17–5.36) §	4.6 (4.17–5.24)	4.5 (3.79–5.29)
< 3.5 g/dL n (%)	5 (19%)	4 (7%)	0	0

CD - Crohn's disease, UC - ulcerative colitis, InIn - intestinal infections, FPIP - food protein-induced proctocolitis, FC- fecal calprotectin, ESR – erythrocyte sedimentation rate, CRP – C-reactive protein, WBC – white blood count, PLT – platelets, Hb – hemoglobin, MCV – mean corpuscular volume, RDW – red blood cell distribution width, MPV – mean platelet volume, n – number.



ESR – erythrocyte sedimentation rate, Hb – hemoglobin, MCV – mean corpuscular volume

Fig. 1. The correlations between fecal calprotectin concentration and levels of inflammatory markers in children with Crohn's disease (Spearman's rank correlation coefficient).

3. Results

3.1. Comparison of fecal calprotectin levels and inflammatory markers between study groups

We analyzed inflammatory marker levels in patients with high FC concentration in order to find the best non-invasive indicator of CD or UC, but the results of patients with CD and UC were not compared. The background data of study groups, median values of FC concentration and selected serum markers of inflammation and parameters of complete blood count are presented in Table 1. The lowest median value of FC was demonstrated by children with InIn compared with the CD and UC groups (511.4 vs 1683.6 vs 1691, respectively; $P < 0.05$). Despite the fact that the group of patients with UC was the most numerous (43%), abnormal results of the tested markers were mainly observed in children with CD. As shown in Table 1, CD patients demonstrated significantly elevated CRP (24.5 mg/L vs 4.6 mg/L), ESR (35 mm/h vs 12 mm/h), RDW (14.6% vs 13.7%) and a decreased albumin level

(3.9 g/dL vs 4.6 g/dL), MCV (74.7 fL vs 78.9 fL) in comparison to patients with InIn. Moreover, significantly elevated levels of ESR, CRP, RDW and PLT were detected more frequently in CD patients than in the InIn or FPIP groups (Table 1). Similar differences were observed when CD patients were compared with children with FPIP who displayed higher CRP (24.5 mg/L vs 0.6 mg/L, respectively) and RDW (14.6% vs 13.2%), and decreased MPV (9.9 fL vs 10.6 fL).

Interestingly, patients with UC demonstrated only significantly higher CRP in comparison to the FPIP group (3.9 mg/L vs 0.6 mg/dL) and lower albumin concentration than patients with InIn (4.5 g/dL vs 4.6 g/dL). No differences in biomarker values between patients with FPIP and those with InIn were found.

3.2. Correlation analysis between fecal calprotectin concentrations and levels of selected inflammatory markers

Significant correlations between FC and selected serum inflammatory markers were observed only in the CD group. As shown in Fig. 1, FC concentrations were positively correlated with ESR (R = 0.53, $P = 0.005$) and RDW levels (R = 0.56, $P = 0.003$), and negatively correlated with MCV (R = -0.64, p = 0.0004), albumin (R = -0.52, $P = 0.006$) and Hb levels (R = -0.53, $P = 0.005$). In UC patients, the correlation, at the limit of statistical significance (R = 0.26, P = 0.044), was detected between FC and CRP, however no more correlations between the tested markers were found in the UC, FPIP and InIn groups. Among CD/UC children, only the PCDAI correlated with FC (R = 0.61; $P < 0.05$).

3.3. Multivariate analysis

In order to select the best markers for the discrimination of CD patients univariate analysis was performed. Out of the 10 examined markers, 6 markers (FC, ESR, CRP, MCV, RDW, albumin) with $P < 0.05$ were included in the multivariate logistic regression analysis (Tables 2 and 3). FC alone had the lowest AUC (0.77) and PPV (71%), but the addition of any of the tested markers to FC increased the AUC, as shown in Table 3. However, combining FC with ESR, CRP and albumin resulted in a significant increase in AUC (0.917), PPV (82.1%) and accuracy (85.7%). Adding RDW and MCV to this model did not improve AUC or influence the other variables compared to the model with FC, ESR, CRP and albumin (Table 3). It is worth noting, that the model combining biomarkers without CRP,MCV and RDW also resulted in significant increase in AUC (0.906) with concomitant improvement of values of other variables compared to the measurement of single FC (Table 3).

For UC patients, a univariate analysis showed $p < 0.05$ only for 2 markers (FC and albumin). AUC for FC was low (0.63; 95%CI 0.52-0.74) and adding albumin changed slightly its value (0.7, 95%CI 0.59-0.8) (data not shown).

4. Discussion

FC is a highly sensitive but not a very specific marker of IBD since an enhanced level of FC has also been reported in patients with InIn (viral or bacterial) and food allergy [2,7]. Moreover, this protein has been identified as a useful marker in the evaluation of treatment response to protein hydrolysate formula [7]. Our study confirmed previous reports demonstrating enhanced FC levels in various intestinal diseases. However, our results for the first time revealed a significantly higher FC level in children with CD and UC in comparison to subjects with InIn but not with food allergy. Despite the fact that increased FC indicates the inflammatory process in lower digestive tract, the serum markers differed significantly between the study groups. The majority of abnormal results of the tested markers were mainly observed in children with CD. Furthermore, the significant correlation of ESR, MCV, albumin, RDW with FC was found only in the CD group. In the clinical practice the values of ESR and albumin are used to estimate the activity of CD based on the PCDAI [15]. Interestingly, our results showed a correlation between CRP and FC in the UC group, but not in the CD group, which is in opposition to the report by Vieira et al. [19]. However, in this study, only adult patients were analyzed, so other variables such as age or coexisting disorders could influence the results [19]. We also did not find any correlation between CRP and FC in patients with InIn, confirming the results of Chen et al. [2]. Among the remaining tested markers, low albumin concentration proved to be a strong marker for both CD and UC patients in comparison to children with InIn, which is in line with published reports [20,21]. Other inflammatory markers, already identified as the predictors of active IBD, such as decreased MCV and high RDW were also detected in our CD group but not in children with InIn and FPIP [22–24]. No difference in median Hb levels and white blood count was found between the groups, although the decreasing concentration of Hb in parallel with the increasing severity of infection or inflammation such as IBD has been previously reported [19,22,24,25]. Also, decreased MPV and platelet count have been presumed to be a potential inflammatory markers and disease activity indicators in several studies, in our study group none of the patients presented these markers below the normal range [25–27].

Finally, we demonstrated that increased FC combined with particular serum inflammatory markers might indicate more specifically children who require endoscopy due to suspected IBD. To the best of our knowledge, there are no available studies concerning such an analysis. Based on multivariate analysis, the best combination of markers to detect CD was FC, ESR, CRP and albumin compared to FC as a single marker. Adding the remaining biomarkers like MCV and RDW, also provided diagnostic value, however did not increase the significance of AUC and other variables. For patients with UC the most

Table 2
Linear combination of selected variables used to determine their combined diagnostic usefulness.

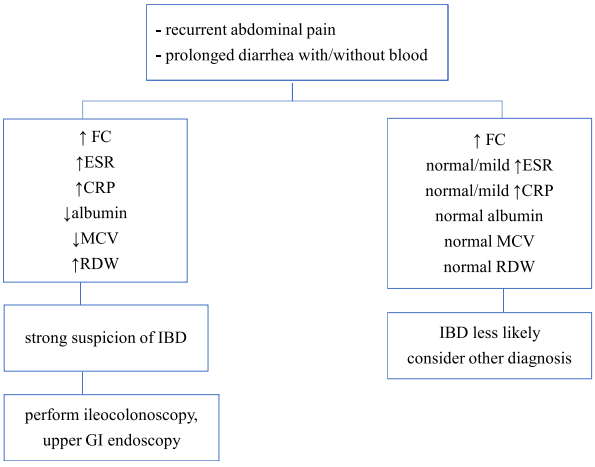
Indicator	Linear combination of variables
FC + ESR	1,10*ln(FC) + 146*ln(ESR)
FC + CRP	0,94*ln(FC) + 055*ln(CRP)
FC + MCV	0,92*ln(FC)-0,10*MCV
FC + albumin	0,79*ln(FC)-2,29*Albumin
FC + RDW	1,08*ln(FC) + 376*ln(RDW)
FC + ESR + CRP	1,11*ln(FC) + 112*ln(ESR) + 036*ln(CRP)
FC + ESR + albumin	1,10*ln(FC) + 121*ln(ESR)-1,31*Albumin
FC + CRP + albumin	0,62*ln(FC) + 042*ln(CRP)-2,03*Albumin
FC + ESR + CRP + albumin	1,05*ln(FC) + 100*ln(ESR) + 019*ln(CRP)-1,34*Albumin
FC + ESR + CRP + MCV + albumin	1,07*ln(FC) + 116*ln(ESR) + 016*ln(CRP) + 006*MCV-1,65*Albumin
FC + ESR + CRP + MCV + albumin + RDW	1,07*ln(FC) + 116*ln(ESR) + 016*ln(CRP) + 006*MCV-1,65*Albumin
FC + CRP + MCV + albumin + RDW	0,79*ln(FC) + 046*ln(CRP) + 003*MCV-1,43*Albumin + 379*ln(RDW)

FC - fecal calprotectin, ESR – erythrocyte sedimentation rate, CRP – C-reactive protein, WBC – white blood count, PLT – platelets, Hb – hemoglobin, MCV – mean corpuscular volume, RDW – red blood cell distribution width, MPV – mean platelet volume.

Table 3
Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy (ACC) and area under the curve (AUC) of FC and combination of FC with ESR, CRP, MCV, RDW or albumin to identify Crohn's disease (CD) patients among study group (FPIP and InIn).

Marker	Sensitivity	Specificity	PPV	NPV	ACC	AUC (95%Cl)	P*	P**
FC	84.6%	70.0%	71.0%	84.0%	76.8%	0.777 (0.652–0.902)		
FC and ESR	92.3%	76.7%	77.4%	92.0%	83.9%	0.895 (0.814–0.976)	0.06	0.0001
FC and CRP	73.1%	86.7%	82.6%	78.8%	80.4%	0.851 (0.749–0.954)	0.3	0.0001
FC and MCV	88.5%	66.7%	69.7%	87.0%	76.8%	0.817 (0.700–0.935)	0.6	0.047
FC and albumin	65.4%	96.7%	94.4%	76.3%	82.1%	0.821 (0.710–0.932)	0.5	0.0001
FC and RDW	84.6%	66.7%	68.8%	83.3%	75.0%	0.801 (0.680–0.922)	0.77	0.07
FC and ESR, CRP	96.2%	80.0%	80.6%	96.0%	87.5%	0.899 (0.813–0.984)	0.09	0.0001
FC and ESR, albumin	80.8%	83.3%	80.8%	83.3%	82.1%	0.906 (0.833–0.979)	0.04	0.0001
FC and CRP, albumin	84.6%	83.3%	81.5%	86.2%	83.9%	0.881 (0.792–0.970)	0.13	0.0001
FC and ESR, CRP, albumin	88.5%	83.3%	82.1%	89.3%	85.7%	0.917 (0.849–0.985)	0.038	0.0001
FC and ESR, CRP, MCV and albumin	88.5%	83.3%	82.1%	89.3%	85.7%	0.917 (0.849–0.986)	0.044	0.0001
FC and ESR, CRP, MCV and albumin, RDW	88.5%	83.3%	82.1%	89.3%	85.7%	0.917 (0.849–0.986)	0.028	0.0001
FC and CRP, MCV and albumin, RDW	69.2%	93.3%	90.0%	77.8%	82.1%	0.870 (0.778–0.962)	0.15	0.0001

FC - fecal calprotectin, ESR – erythrocyte sedimentation rate, MCV – mean corpuscular volume, RDW – red blood cell distribution width, CI – confidence interval. All biomarkers were log transformed before analysis due to skewed distribution.
p* test for comparing AUC value of merged indicators against AUC of FC alone.
p ** tests for comparing nested binary regression models (multivariate models against univariate model with FC).



FC – fecal calprotectin, ESR – erythrocyte sedimentation rate, CRP – C-reactive protein, MCV – mean corpuscular volume, RDW – red blood cell distribution width

Fig. 2. Proposed preliminary diagnostic algorithm in the management of children suspected to have IBD.

specific was the combination of only two biomarkers: FC with albumin. Based on our results we propose a preliminary diagnostic algorithm in the management of children suspected to have IBD, which is presented on Fig. 2.

The limitation of the present study was the small number of participants and the fact that the population was selected on the basis of high FC levels and therefore the results may not be relevant to the general population. However, these promising findings should be validated in a multicenter study.

5. Conclusions

In the pediatric population, reliable, non-invasive markers are needed to properly select patients who require endoscopic procedures. A high FC concentration is a sensitive, but a non-specific marker of intestinal inflammation. Moreover, symptoms of IBD do not differentiate this disease from other intestinal disorders. Our results show that the increased FC level combined with high ESR, CRP and low albumin level may serve as a predictive indicator identifying patients with potential CD among individuals with enhanced FC and symptoms suggesting IBD. Other biomarkers (MCV, RDW) also provided additional value to the FC measurement in the CD group. Low additional diagnostic value was obtained when high FC was combined with albumin as far as the differentiation of UC is concerned.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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