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# C-Reactive Protein/Albumin Ratio at Diagnosis of Pediatric Inflammatory Bowel Disease: A Retrospective Multi-Center Study

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**Conflict of interest:** None declared

**Background:** This study aimed to evaluate the C-reactive protein-to-albumin (CRP/albumin) ratio at diagnosis of pediatric inflammatory bowel disease (IBD).





**Material/Methods:** Serum CRP/albumin ratio was calculated for patients with Crohn's disease (CD; n=186) and ulcerative colitis (UC; n=159) aged 3-18 years.

**Results:** Patients with CD differed in CRP/albumin ratio at diagnosis in groups with quiescent, mild, moderate, and severe disease ( $P=0.011$ ). CRP/albumin ratio at diagnosis was significant in differentiating patients with severe CD from quiescent disease at diagnosis (area under the curve (AUC)=0.94, odds ratio (OR)=63.4, 95% confidence interval (CI) 7.1-569.1,  $P<0.0001$ ). CRP/albumin ratio at diagnosis could moderately differentiate penetrating from non-penetrating disease behavior in CD at diagnosis (AUC=0.73, OR=6.3, 95% CI 2.0-19.3,  $P<0.001$ ). Furthermore, CRP/albumin ratio at diagnosis weakly differentiated IBD patients in need of biological treatment in a step-up procedure (AUC=0.58, OR=2.1, 95% CI 1.3-3.4,  $P=0.022$ ) and in need of surgery (AUC=0.63, OR=3.1, 95% CI 1.4-7.2,  $P=0.006$ ). For the IBD, CRP/albumin ratio at diagnosis was weakly correlated with age at first immunosuppressive treatment ( $\rho=0.20$ ,  $P=0.018$ ), time from diagnosis to first biological treatment ( $\rho=-0.37$ ,  $P<0.001$ ), days spent in hospital ( $\rho=0.26$ ,  $P=0.007$ ), number of severe relapses ( $\rho=0.31$ ,  $P=0.001$ ), and Pediatric Crohn's Disease Activity Index ( $\rho=0.38$ ,  $P=0.002$ ).

**Conclusions:** The present findings add to previous studies carried out in adult patients and show that the CRP/albumin ratio at diagnosis was not significantly associated with the course of either CD or UC in children. However, CRP/albumin ratio could differentiate patients with severe CD from those with quiescent disease.

**Keywords:** **Albumins • Colitis, Ulcerative • Crohn Disease • CRP Protein, Human • Hospitalization**

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## Background

Inflammatory bowel diseases (IBD) are chronic conditions with globally rising burden and complex, still unknown etiology [1,2]. The 2 main pathophysiological entities – Crohn's disease (CD) and ulcerative colitis (UC) – are conditions with variable clinical course, including frequent flares, requiring surgery and hospitalizations, and generating psychological problems [3]. The accurate diagnosis of IBD requires a combination of disease history, physical and laboratory examination, imaging procedures such as enterography, and histology [4]. Although several diagnostic indicators have been developed to date, the search for inexpensive and quick markers of disease outcomes in IBD is ongoing.

Despite multiple advantages of calprotectin, this marker still has some limitations (eg, costs and sample availability) [5-7]. Combined measurements of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and albumin, along with fecal calprotectin, have been shown to have diagnostic utility for CD [8]. Other inflammatory markers in adults include neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and lymphocyte/monocyte ratio (LMR) [9]. Of these, combined NLR and PLR can predict active endoscopic disease in adults with UC [10] and differentiate adults with CD from non-CD controls [11]. Some promising results for this group of markers were also found in children [12,13].

Serum CRP and albumin measurements are relatively cheap and available. CRP is an acute-phase protein and is more frequently elevated in children with CD than in those with UC [14]. Serum CRP response seem to differ individually, sometimes with unexpectedly low concentrations despite clinical history [15]. This may be caused by differences in CRP genotypes and other extraintestinal inflammatory processes. Three single-nucleotide polymorphisms (rs1205, rs1130864, and rs1417938) are associated with higher CRP concentrations at diagnosis, but the genotype was not linked with CD phenotype and remission after anti-tumor necrosis factor-alpha (anti-TNF) therapy [14]. In adults, lower CRP concentrations at diagnosis (in approximately 30% of patients with CD) led to milder disease phenotype [3], which suggests these patients require only basic therapy. This in turn would avoid overtreatment and unnecessary costs and risks [3]. In adults with UC, CRP above 45 mg/L and more than 8 stools a day at the third day of intensive treatment is an indicator for colectomy [16]. Similarly, in pediatric IBD, high inflammatory burden at diagnosis suggests poor prognosis, and high CRP is linked with higher risk of immunosuppression intake and surgery [14].

Albumin concentrations can also reflect systemic inflammatory burden, nutritional status, and poor prognosis in multiple disease entities. Hypoalbuminemia is associated with infliximab

failure in adult UC [17-19], whereas higher concentrations of albumin predicts remission 8 weeks after infliximab induction [20]. Together, low albumin and high CRP concentrations are linked with disease severity [21,22].

CRP/albumin ratio has shown high value in acute pancreatitis [23], colorectal cancer [24], and sepsis [25]. In IBD, CRP/albumin ratio has high discriminative power for active disease in adults [26,27] and correlates with moderate and severe endoscopic activity in UC [28]. CRP/albumin ratio measured after infliximab salvage can potentially predict colectomy in acute severe UC [29], but this depends on timing of the test [17]. Serum CRP/albumin ratio measured on the third day after infliximab intake can reach 79% sensitivity and 80% specificity to predict colectomy, with more efficiency than that of Mayo scores [17]. Predicting unresponsiveness to anti-TNF therapies is an important aspect of modern precision medicine and can help avoid unnecessary costs and risks [17,30].

Available reports on CRP/albumin ratio in IBD concern adult patients [26-28]. Therefore, this retrospective study aimed to evaluate the CRP/albumin ratio at diagnosis of IBD in 345 pediatric patients aged between 3 and 18 years in relation with IBD severity described with different clinical parameters. The measurement of disease severity is notoriously difficult to define, which has been reported previously [31]. It is based on clinical data, endoscopic picture, and extraintestinal features. In our study these included: Paris classification in terms of extent and behavior, past surgeries, disease activity assessment, and patient's nutritional status, which can also inform about disease severity to some extent [31]. The severity is also described by number of exacerbations per year, days spent in hospital, and necessary treatment, because it suggests no response to previous therapy.

## Material and Methods

### Patients

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Bioethical Committee from the Poznań University of Medical Sciences on 5 November 2015 (protocol number 960/15). All parents/legal guardians consented to participation of their children in the study. Dual consent of the patient and parent was collected in case of children over 16 years old. A retrospective multicenter cohort study (the Polish Pediatric Crohn's and Colitis Cohort, POCOCO) was conducted between April 2016 and March 2019 in 7 centers in Poland (Poznań, Warsaw (2 centers), Wrocław, Zabrze, Katowice and Bydgoszcz) [32,33]. The inclusion criteria were diagnosis of UC or CD and age 3-18 years. We excluded patients with life-threatening and severe general

conditions. The diagnosis of IBD was based on European diagnostic criteria and confirmed by experienced gastroenterologists [4,34,35]. The histologic examination were according to European criteria [36].

The data on CRP [mg/L] and albumin concentrations [g/dl] at diagnosis were collected retrospectively. The ratio for 345 patients aged 3-18 years was calculated (CD n=186 and UC n=159; F=149, M=196). The lowest and highest concentrations of CRP/albumin ratio at diagnosis were defined with 1<sup>st</sup> and 3<sup>rd</sup> quartiles, respectively, independently for UC and CD.

### Disease Severity

Pediatric Ulcerative Colitis Activity Index (PUCAI) or Pediatric Crohn's Disease Activity Index (PCDAI) were used to define disease activity at diagnosis and the worst flare [37]. In CD, quiescence was defined as PCDAI  $\leq 10$ . A PCDAI score of 11-30 points was considered as a mild activity, 31-49 as moderate, and  $\geq 50$  as severe [38-40]. In UC, PUCAI  $\leq 10$  was defined as quiescent, 10-34 as a mild activity, 35-64 as moderate activity, and  $\geq 65$  as severe disease [37,41]. The worst flare was defined when PUCAI/PCDAI was the highest in the medical history. Approximately 30.1% of patients had their worst flare at diagnosis, while 64 patients (18.5%) received their first immunosuppressive drug at diagnosis (CD n=47; UC n=17). Patients were treated with azathioprine, methotrexate, mercaptopurine, cyclosporine, mycophenolate mofetil, or tacrolimus according to standard guidelines [42,43].

Localization and behavior of disease was defined using the Paris classification [44]. The criteria to initiate the biological treatment were as per the regulations of the drug programs specified by the Polish Ministry of Health, uniform for all centers [45]. Corticosteroids were administered according to contemporary European guidelines [43]. Serum albumin concentration was determined by the spectrophotometric bromocresol green method (Abbott Alinity, Santa Clara, USA). Serum CRP concentration was measured with the Alinity CRP Vario Reagent Kit 7P5620 (Abbott Alinity, Santa Clara, USA).

### Statistical Analysis

Two-tailed Fisher's exact test was used for the comparison of categorical parameters. The normality of data was determined with Shapiro-Wilk test. Continuous variables were presented as medians and 1<sup>st</sup>-3<sup>rd</sup> quartiles. The comparisons between 2 groups were performed with the Mann-Whitney U test and comparisons among multiple groups were performed with the Kruskal-Wallis test. To determine the relationships between CRP/albumin ratio and other parameters associated with disease severity, Spearman's correlation analysis was used. Receiver operating characteristic (ROC) curve analysis was used

to obtain the optimal cut-off values of the CRP/albumin ratio by Youden index with standard errors (SE). Maximum sensitivity and specificity were calculated. Statistical significance was set at  $P < 0.05$ . Statistical analyses were performed with the use of JASP 0.10.2 (University of Amsterdam, Amsterdam, The Netherlands) and Statistica 13.1 (TBICO Software, Palo Alto, CA, USA).

### Results

CRP was elevated ( $> 5$  mg/L) in 65.9% of patients with CD and in 39.6% of patients with UC. CRP/albumin ratio at diagnosis and at worst flare were higher in patients with CD compared to those of patients with UC (Table 1). In 25.3% of patients with CD, the first dose of immunosuppressant drug was taken directly after diagnosis. CRP/albumin ratio at diagnosis did not differ between patients with CD with and without immunosuppressive medications ( $P = 0.994$ ). In patients with UC, 10.7% had immunosuppressive medication at diagnosis and CRP/albumin ratio differed from those without immunosuppressive treatment (0.02 (0.01-0.06) vs 0.08 (0.01-0.32),  $P = 0.0424$ ).

We found that 6.3% of patients with CD had quiescent disease at the date of diagnosis, 42.5% had mild activity, 27.0% had moderate activity, and 24.1% had severe activity, whereas 2.7% of patients with UC had quiescent disease at diagnosis, 25.7% had mild activity, 52.0% had moderate activity, and 19.6% were severe.

CRP/albumin ratio at diagnosis differed depending on PCDAI severity groups at diagnosis ( $P = 0.011$ ), but not as defined by the PUCAI severity groups ( $P = 0.353$ ) (Table 2).

At worst flare, CRP/albumin ratio concentrations differed significantly across PCDAI severity groups ( $P < 0.002$ ) and PUCAI severity groups ( $P < 0.002$ ).

CRP/albumin ratio at diagnosis in patients with CD was correlated weakly with age at first immunosuppressive drug, time from diagnosis to first biological treatment, days spent in hospital, number of severe relapses, and PCDAI (Table 3). No such correlations were found in patients with UC. CRP/albumin ratio at diagnosis was poorly correlated with PUCAI at diagnosis ( $\rho = 0.16$ ;  $P = 0.047$ ), but not at worst flare ( $\rho = 0.10$ ;  $P = 0.264$ ). In patients who were taking immunosuppressant agents at diagnosis, the correlation between CRP/albumin ratio and PCDAI was stronger, but still moderate ( $\rho = 0.46$ ).

Patients with lowest ( $< 1^{\text{st}}$  quartile) values of CRP/albumin ratio at diagnosis were significantly younger at induction of first biological treatment than those with highest CRP/albumin ratio – age 11 (7-13) vs 13 (10-15) ( $P = 0.036$ ). Further, patients with

**Table 1.** Basic characteristics of subjects (n=345).

| Variables<br>Median (IQR) or n (%)                  | CD                      | UC                   | p value |
|---|-------------------------|----------------------|---------|
| <b>Age [years]</b>                                  |                         |                      |         |
| At inclusion  | 15 (13-17)              | 15 (11-16)           | 0.012   |
| At diagnosis  | 12 (10-14)              | 12 (8-15)            | 0.237   |
| <b>Disease duration [years]</b>                     | 1.7 (0.6-3.9)           | 1.5 (0.2-3.5)        | 0.166   |
| <b>Nutritional status</b>                           |                         |                      |         |
| Weight at diagnosis [z score]                       | -0.81 ([-1.39]-[-0.00]) | -0.54 ([-1.23]-0.17) | 0.025   |
| Height at diagnosis [z score]                       | -0.37 ([-1.33]-0.48)    | 0.02 ([-0.75]-0.75)  | 0.005   |
| Body mass index at diagnosis [z score]              | -0.77 ([-1.46]-[-0.06]) | -0.54 ([-1.08]-0.15) | 0.043   |
| <b>Serum biomarkers</b>                             |                         |                      |         |
| Albumin at diagnosis [g/dl]                         | 3.9 (3.5-4.3)           | 4.1 (3.7-4.4)        | 0.003   |
| Albumin at worst flare [g/dl]                       | 3.9 (3.5-4.3)           | 4.2 (3.8-4.4)        | <0.001  |
| CRP at diagnosis [mg/L]                             | 13.0 (2.1-30.3)         | 2.4 (0.5-11.5)       | <0.001  |
| CRP at worst flare [mg/L]                           | 14.3 (3.3-39.1)         | 2.7 (0.6-15.0)       | <0.001  |
| CRP/albumin ratio at diagnosis [mg/g]               | 0.34 (0.05-0.90)        | 0.06 (0.01-0.28)     | <0.001  |
| CRP/albumin ratio at worst flare [mg/g]             | 0.38 (0.08-1.03)        | 0.07 (0.01-0.34)     | <0.001  |
| <b>Disease activity scales</b>                      |                         |                      |         |
| PUCAI at diagnosis                                  |                         | 45 (30-60)           |         |
| PUCAI at worst flare                                |                         | 50 (35-65)           |         |
| PCDAI at diagnosis                                  | 32 (23-48)              |                      |         |
| PCDAI at worst flare                                | 39 (30-53)              |                      |         |
| <b>Treatment</b>                                    |                         |                      |         |
| Systemic corticosteroids*                           | 94 (50.5)               | 113 (71.1)           | <0.001  |
| Immunosuppressive and anti-inflammatory treatment** | 144 (77.4)              | 89 (56.3)            | <0.001  |
| Biological therapy***                               | 90 (48.4)               | 39 (24.5)            | <0.001  |
| Operative treatment                                 | 23 (12.4)               | 3 (1.9)              | <0.001  |
| Colectomy   | 2 (1.1)                 | 3 (1.9)              | 0.666   |
| Resection   | 9 (4.8)                 | 0 (0.0)              | 0.004   |
| Fistula   | 4 (2.2)                 | 0 (0.0)              | 0.127   |
| Perforation   | 2 (1.1)                 | 0 (0.0)              | 0.501   |
| Abscess   | 6 (3.2)                 | 0 (0.0)              | 0.033   |

\* e.g. methylprednisolone, prednisone, hydrocortisone; \*\* e.g. azathioprine, methotrexate, mercaptopurine, cyclosporine, mycophenolate mofetil, tacrolimus; \*\*\* e.g. infliximab, adalimumab, golimumab, vedolizumab. CD – Crohn’s disease; CRP – C-reactive protein (reference values 0-5 mg/L); IQR – interquartile range; PUCAI – Pediatric Ulcerative Colitis Activity Index; PCDAI – Pediatric Crohn’s Disease Activity Index; UC – ulcerative colitis.

**Table 2.** CRP/albumin ratio, C-reactive protein (CRP), and albumin concentrations depending on disease activity.

| Parameter median<br>(1 <sup>st</sup> -3 <sup>rd</sup> quartile) | PCDAI                     |                  |                      |                  | p value |
|---|---------------------------|------------------|----------------------|------------------|---------|
|   | Quiescent<br>n=11         | Mild<br>n=74     | Moderate<br>n=47     | Severe<br>n=42   |         |
| CRP/albumin ratio at diagnosis                                  | 0.02 (0.01-0.05)          | 0.33 (0.05-0.79) | 0.38 (0.12-0.91)     | 0.60 (0.31-1.80) | 0.011   |
| CRP at diagnosis [mg/l]   | 0.8 (0.5-2.3)             | 12.0 (2.0-28.3)  | 14.4 (4.6-26.8)      | 24.2 (12.9-49.5) | 0.007   |
| Albumin at diagnosis [g/dl]                                     | 4.5 (4.2-4.7)             | 4.0 (3.8-4.3)    | 3.8 (3.4-4.2)        | 3.7 (3.1-3.8)    | 0.003   |
| Parameter median<br>(1 <sup>st</sup> -3 <sup>rd</sup> quartile) | PCDAI<br>non-severe n=132 |                  | PCDAI<br>Severe n=42 |                  | p value |
|   | 0.29 (0.05-0.71)          |                  | 0.60 (0.31-1.80)     |                  |         |
| CRP/albumin ratio at diagnosis                                  | 0.29 (0.05-0.71)          |                  | 0.60 (0.31-1.80)     |                  | <0.001  |
| CRP at diagnosis [mg/l]   | 11.8 (2.0-24.9)           |                  | 24.2 (12.9-49.5)     |                  | 0.041   |
| Albumin at diagnosis [g/dl]                                     | 4.0 (3.7-4.3)             |                  | 3.7 (3.1-3.8)        |                  | 0.028   |
| Parameter median<br>(1 <sup>st</sup> -3 <sup>rd</sup> quartile) | PUCAI                     |                  |                      |                  | p value |
|   | Quiescent<br>n=4          | Mild<br>n=38     | Moderate<br>n=77     | Severe<br>n=29   |         |
| CRP/albumin ratio at diagnosis                                  | 0.11 (0.02-0.21)          | 0.03 (0.01-0.09) | 0.09 (0.01-0.32)     | 0.09 (0.00-0.36) | 0.353   |
| CRP at diagnosis [mg/l]   | 4.6 (1.0-8.9)             | 1.4 (0.5-3.8)    | 3.8 (0.5-11.6)       | 2.8 (0.2-14.2)   | 0.429   |
| Albumin at diagnosis [g/dl]                                     | 4.2 (4.1-4.3)             | 4.4 (4.0-4.5)    | 4.1 (3.7-4.3)        | 4.0 (3.2-4.4)    | 0.011   |
| Parameter median<br>(1 <sup>st</sup> -3 <sup>rd</sup> quartile) | PUCAI<br>non-severe n=119 |                  | PUCAI<br>severe n=29 |                  | p value |
|   | 0.05 (0.01-0.25)          |                  | 0.09 (0.01-0.36)     |                  |         |
| CRP/albumin ratio at diagnosis                                  | 0.05 (0.01-0.25)          |                  | 0.09 (0.01-0.36)     |                  | 0.906   |
| CRP at diagnosis [mg/l]   | 2.2 (0.5-10.7)            |                  | 2.8 (0.2-14.2)       |                  | 0.856   |
| Albumin at diagnosis [g/dl]                                     | 4.2 (3.8-4.4)             |                  | 4.0 (3.2-4.4)        |                  | 0.049   |

CRP – C-reactive protein (reference values 0-5 mg/L); PUCAI– Pediatric Ulcerative Colitis Activity Index; PCDAI – Pediatric Crohn's Disease Activity Index.

**Table 3.** Significant correlations with CRP/albumin ratio at diagnosis in children with Crohn's disease.

| Parameter  | n   | Median (IQR)     | rho   | p value |
|--|-----|------------------|-------|---------|
| Age at first immunosuppressive treatment [years] | 143 | 13.1 (10.8-15.2) | 0.20  | 0.018   |
| Time-to-first biological treatment [months]      | 86  | 12.1 (4.7-26.0)  | -0.37 | <0.001  |
| Time-to-first surgery [months]                   | 19  | 11.5 (0.0-29.1)  | 0.56  | 0.012   |
| Days of hospitalization for relapse/year         | 109 | 4.4 (1.4-7.2)    | 0.26  | 0.007   |
| Severe relapses from diagnosis/year              | 106 | 0.2 (0.0-0.5)    | 0.31  | 0.001   |
| PCDAI at diagnosis                               | 172 | 32 (23-48)       | 0.38  | 0.002   |
| PCDAI at worst flare                             | 150 | 39 (30-53)       | 0.19  | 0.023   |

IQR – interquartile range; PCDAI – Pediatric Crohn's Disease Activity Index.

lowest CRP/albumin ratio at diagnosis had earlier induction of immunosuppressive treatment than those with highest CRP/albumin ratio – months 0.7 (0-8.1) vs 3.0 (0.2-9.2) ( $P=0.036$ ).

CRP/albumin ratio was not useful in identifying the need for biological treatment or surgery (area under the ROC curve (AUC) for both  $<0.65$ ). In patients with IBD who took immunosuppressive agents at diagnosis ( $n=64$ ), CRP/albumin ratio poorly differentiated patients in need of biological treatment, with an AUC=0.664 (SE 0.068,  $P=0.015$ ). The cut-off was 0.31 (OR=3.6 (1.2-11.1), sensitivity was 79%, and specificity was 49%. Serum CRP/albumin ratio did not define the need for surgery in patients with IBD who had immunosuppressive treatment introduced at diagnosis.

Serum CRP/albumin ratio at diagnosis showed clinical utility in differentiating patients with CD who have severe disease from those with quiescent disease AUC=0.94 (SE=0.041, OR=63.4, 95% CI 7.1-569.1,  $P<0.001$ ). The cut-off point for CRP/albumin ratio to differentiate severe from quiescent disease was 0.15. The sensitivity and specificity for this cut-off point were 92.3% and 84.1%, respectively.

Serum CRP/albumin ratio at diagnosis was poor/moderate in differentiating patients with various disease localizations and behaviors defined by the Paris classification. The highest sensitivity and AUC value for CRP/albumin ratio at diagnosis were obtained for differentiating penetrating from non-penetrating disease behavior in CD at diagnosis (AUC=0.73, OR=6.3, 95% CI 2.0-19.3,  $P<0.001$ , sensitivity 98.1%, specificity 10.9%).

## Discussion

Finding a reliable and inexpensive indicator and predictor of IBD severity remains a challenge. This retrospective study is the first report on the relationships of CRP/albumin ratio with IBD characteristics in children. When patients were grouped into quiescent, mild, moderate, and severe disease according to the PCDAI, there was a difference in CRP/albumin ratio at diagnosis. However, the indicator seems to be useful only in discriminating between severe CD vs quiescent disease at diagnosis, showing 92.3% sensitivity and 84.1% specificity (AUC 0.94), whereas CRP/albumin ratio at diagnosis weakly differentiated patients with IBD in need of treatment escalation (biologics and surgery). In CD, CRP/albumin ratio at diagnosis was correlated weakly with age at first immunosuppressive treatment, time from diagnosis to first biological treatment, days spent in hospital, number of severe relapses, and PCDAI. Although these results were statistically significant, their clinical utility is limited. Serum CRP/albumin ratio at diagnosis was poor/moderate in differentiating patients with various disease localizations and behaviors, with the highest

AUC for differentiating penetrating from non-penetrating disease behavior in CD.

Biomarkers that are easily available, simple to calculate, and objective are needed to rapidly describe the changing nature of pediatric IBD. Serum CRP/albumin ratio has been proposed as such a marker, but available reports come from adult cohorts. Previous studies conducted in adult patients cannot be directly compared with the results of the present study. In a single-center study from China (601 adults) [26], disease activity in CD was strongly correlated ( $\rho=0.76$ ) with CRP/albumin ratio, whereas in the present study, CRP/albumin ratio at diagnosis was only weakly ( $\rho=0.38$ ) correlated with the PCDAI at diagnosis. In patients who took immunosuppressants at diagnosis, this relationship was stronger but still moderate ( $\rho=0.46$ ). Sayar et al reported that AUC values of 0.941 (cut-off 0.6 and sensitivity 88.9%, specificity 90.3%) determined severe disease in adults [21]. In our study, the AUC for CRP/albumin ratio to differentiate severe disease from less severe at diagnosis was 0.697 (cut-off 0.3 and sensitivity 50%, specificity 76%) and this significant, but weak relationship was found only for patients with CD. This could be explained by disease duration. In a recent study of adults with UC from Japan, CRP/albumin ratio was a useful serum marker for disease activity only in patients who had the disease for more than 7 years [28]. Disease duration in our cohort was approximately 2 years (range 0-14 years).

Recent reports in adult UC showed promising results for using routinely obtained CRP/albumin ratio marker in therapy optimization and hence precision medicine in IBD. A CRP/albumin ratio cut-off of 0.37 after infliximab has accurately predicted need for colectomy, with AUC of 0.73, but the optimal timing of the test requires further research [27,29]. In adults, CRP/albumin ratio measurements are useful particularly in UC, but high CRP alone is associated with the disease phenotype and better response to biological treatment [46-49]. In children, CRP response can differ between individuals even in overt clinical disease. Further research is needed to determine whether this is dependent on CRP genotype.

One of the study limitations is the retrospective data collection. One must always consider the bias caused during data collection and by different approaches of attending clinicians. The measurement of high-sensitivity CRP would also increase the precision of analyses [50]. Calprotectin measurement would further help defining the severity of disease. Nevertheless, this is the first large study to show relationships between CRP/albumin ratio and IBD phenotype in children. We also included analysis for patients who used immunosuppressive agents at diagnosis, a fact rarely considered previously, which may affect the level of inflammatory markers. Despite robustness of the sample, prospective studies are required to confirm the role of this biomarker in children.

## Conclusions

These findings add to previous studies carried out in adult patients and show that the CRP/albumin ratio at diagnosis was not significantly associated with the course of either CD or UC in children. However, CRP/albumin ratio could help to differentiate patients with severe CD from those with quiescent disease.

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