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# Autoregressive cross-lagged models of IMPACT-III and Pediatric Crohn's Disease Activity indexes during one year infliximab therapy in pediatric patients with Crohn's disease

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## KEYWORDS

Crohn's disease;  
Pediatric;  
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IMPACT-III;  
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cross-lagged analysis

## Abstract

**Background:** Quality of life (QoL) is an important outcome measure in the evaluation of therapies for inflammatory bowel disease. The primary aim of this study was to determine the effect of one year infliximab treatment on QoL and clinical parameters in pediatric patients with Crohn's diseases (CD).

**Methods:** Our prospective study involved 51 children with conventional therapy resistant, severe CD (mean age: 15.25 years, range: 11–18 years). Infliximab was given according to the protocol (5 mg/kg, at weeks 0, 2, 6 and every 8 weeks). During the infliximab courses QoL of patients was evaluated by IMPACT-III questionnaire at weeks 0, 6, 30 and 53. At the same time, the Pediatric Crohn's Disease Activity Index (PCDAI) score was calculated. Moreover, serum C-reactive protein (CRP), serum platelets and serum albumin were followed up. Auto-regressive, cross-lagged models were used to assess relation between QoL and the clinical parameters.

**Results:** The initial IMPACT-III scores [median, percentile 25–75 (pc 25–75) at week 0: 115, 102.5–130.25] increased significantly ( $p < 0.001$ ) following infliximab therapy at week 54 (median: 141.5,

**Abbreviations:** QoL, quality of life; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; PCDAI, Pediatric Crohn's Disease Activity Index; IFX, infliximab; CRP, C-reactive protein; ARCL, autoregressive cross-lagged model;  $\chi^2$ , Chi-square; df, degree of freedom; CFI, Comparative Fit Index; TLI, Tucker–Lewis Index; NNFI, non-normed fit index; RMSEA, Root Mean Square Error of Approximation; SEM, structural equation modeling; MLR, maximum likelihood estimation robust

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124.5–153.75). Clinical and laboratory parameters also improved significantly ( $p < 0.001$ ). Auto-regressive regression coefficients ( $\beta$  value) were significant between each variable over time. The strongest cross-lagged relations were observed between IMPACT-III and serum albumin, IMPACT-III and platelets. Reliability test of IMPACT-III revealed an excellent level of internal consistency (Cronbach's alpha = 0.931).

**Conclusion:** Infliximab treatment has beneficial clinical effect which is confirmed by decrease of PCDAI and increase of IMPACT-III. Autoregressive regression analysis showed regression relation between IMPACT-III and PCDAI and laboratory parameters.

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## 1. Introduction

Crohn's disease (CD), referred as a part of inflammatory bowel disease (IBD), is a chronic inflammatory condition of the gastrointestinal tract with strong impact on quality of life (QoL). CD is induced by multi-factorial causes such as genetic, environmental factors and pathological immune response.<sup>1</sup>

IBD can occur at any age, but most typically presents in the second or third decade. However, recent international studies reported permanent increase of IBD frequency in childhood too. Based on Hungarian data, the incidence of IBD in childhood (under 18 years) is  $7.5/10^5$  (CD:  $4.7/10^5$ , UC:  $2.3/10^5$ ), which corresponds with the internationally published data.<sup>2–5</sup>

QoL is not well known in children and adolescent patients with CD. Some studies have reported worse QoL in this population than healthy ones.<sup>6,7</sup> Moreover, cross-sectional studies show an association of active CD with a poor QoL.<sup>8</sup> The psychological health of children with CD may be closely related to the somatic symptoms of CD. CD may issue in lack of social integration and poor social functioning.<sup>9,10</sup> To examine this correspondence the IMPACT questionnaire was specifically developed and validated to measure the disease specific health related QoL of children with IBD by Griffiths and Otley et al.<sup>11</sup> The questionnaire consists of 6 domains: bowel symptoms, body image, functional/social impairment, emotional impairment, tests/treatments and systemic impairment which gives an overview of the patient's psychological status.<sup>12</sup> As it has been noted in the original validation study, mean IMPACT score varies significantly depending on the disease severity. Otley et al. found that patients had significantly better QoL half a year, then one year following the diagnosis compared to the time at diagnosis.<sup>13</sup>

Over the last decade the introduction of anti-tumor necrosis factor-alpha (TNF- $\alpha$ ) drugs has dramatically changed the treatment of IBD, especially in patients who are refractory or intolerant to the conventional medication. One of these biological agents is the infliximab (IFX) which is a new therapeutic opportunity for patients with CD, including pediatric population, refractory to conventional therapy. IFX is a human–murine chimera monoclonal immunoglobulin G1 antibody which can block the soluble and membrane-attached TNF- $\alpha$ , the most important pro-inflammatory cytokine in IBD.<sup>14–16</sup> Recent studies have reported the beneficial effect of IFX in pediatric patients with CD. However, long term effect and relation to QoL have not been well established.<sup>15,17–20</sup>

Therefore, the primary aim of our study was to analyze the impact of IFX on QoL following one-year treatment. Our secondary aim was to apply a new statistical methodology in

this field to determine the interaction between QoL and clinical parameters. Autoregressive cross-lagged association permitted a complex analysis, wherein the QoL was in the focus.

## 2. Patients and methods

### 2.1. Patients

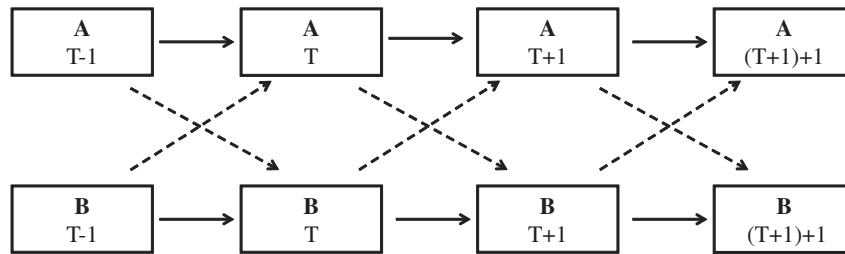
In our prospective study, performed at the 1st Department of Pediatrics of Semmelweis University in Budapest, Hungary, 51 children with severe CD resistant for conventional therapy (azathioprine, steroid) were involved. Of the 51 children 30 (58.8%) were girls, the mean age was 15.25 years (ranged: 11–18 years). The mean time since diagnosis was made 2.29 years (range: 0.1–10 years) (Table 1). The results of IMPACT-III, the analysis of clinical indicators, like Pediatric Crohn's Disease Activity Index (PCDAI)<sup>21</sup> and laboratory parameters were registered at every visits in 40 cases.

## 3. Procedure and measures

IFX at a dose of 5 mg/kg intravenous infusion was applied as induction therapy at weeks 0, 2 and 6, and as maintenance therapy at every following 8 weeks, as it has been accepted by the outcomes of the REACH study considered as the guideline

**Table 1** Characteristics of the study population. 5-ASA: 5-aminosalicylic acid, IFX: infliximab.

Gender	21 male; 30 female
Mean age (year) [range]	15.25 [11–18]
Mean disease duration (year) [range]	2.29 [0.1–10]
Medical treatment when IFX therapy was introduced (N)	
Azathioprine + 5-ASA + steroid + antibiotic	4
Azathioprine + 5-ASA + steroid	11
Azathioprine + 5-ASA + antibiotic	4
Azathioprine + 5-ASA	24
5-ASA + antibiotic	3
5-ASA + steroid	1
Azathioprine	3
5-ASA	1



**Figure 1** Standard presentation of the autoregressive cross-lagged model. —>: autoregressive association between parameters; - ->: cross-lagged association between parameters; A, B: measured parameters.

for IFX treatment in pediatric CD.<sup>22</sup> During infliximab therapy course the QoL of the patients was assessed by IMPACT-III questionnaire at weeks 0, 6, 30 as well as 53. At the same time PCDAI score was also determined to assess the disease severity. Moreover, some of the laboratory parameters like serum C-reactive protein (CRP), serum platelet and serum albumin were registered and followed.

### 3.1. IMPACT-III

To measure health-related QoL for the first time in Hungary (validated in 2008), the Canadian IMPACT-III questionnaire – developed by Otley et al. has been applied at the 1st Department of Pediatrics, Semmelweis University since February, 2009. This specific self-report questionnaire was developed for youth with IBD at the age between 8 and 17 years. It consists of 35 queries covering 6 domains: bowel symptoms, systemic symptoms, emotional functioning, social functioning, body image and treatment/interventions which allow us to analyze each domain separately. Children indicated the extent on a 5 point Likert scale to which they are belonging by specific aspects of their health condition. Possible scores range from 35 to 175, the higher score indicates better QoL.<sup>11</sup>

In addition, PCDAI was registered and followed.<sup>21</sup>

## 4. Ethics

Written, informed consent was obtained from parents prior to the procedure and the study was approved by the Semmelweis University Regional and Institutional Committee and Research Ethics.

## 5. Statistical analysis

Based on results of Kolmogorov–Smirnov and Shapiro–Wilk normality tests, data were non-normal distribution. Therefore, Friedman test and Wilcoxon single rank test with Bonferroni analysis as post-hoc test were applied to follow up the changes of each variable through the treatment period (IBM® SPSS® 20, Chicago, IL). p values lower than 0.05 were accepted as statistically significant. In case of post-hoc analysis p values lower than 0.008 were regarded as significant change. Correlation between IMPACT-III and PCDAI was assessed by Spearman's rank-order correlations (IBM® SPSS® 20, Chicago, IL).

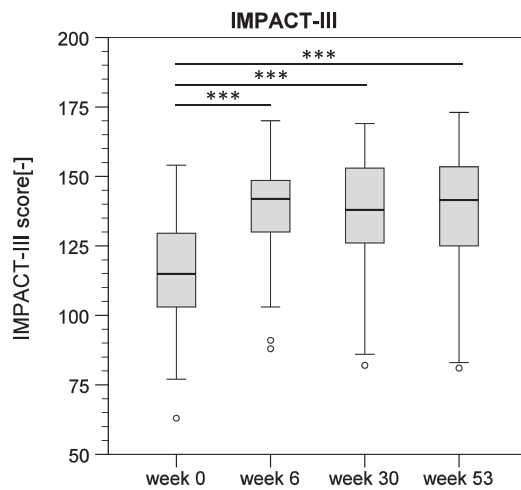
To test the reliability of IMPACT-III Cronbach's alpha was determined (IBM® SPSS® 20, Chicago, IL).

To examine the relationships between QoL (IMPACT-III) and clinical- and laboratory parameters an autoregressive cross-lagged model (ARCL) was applied (Mplus 6.01). The concept of the ARCL model is the following; the value at the time of T is predicted by the value at the time of the previous time, T – 1. The autoregressive pathways estimate the association between IMPACT-III at four different times (week 0, week 6, week 30, week 53). We can analyze the association between week 0 and week 6; week 6 and week 30, as well as week 30 and week 53. Moreover, the cross-lagged pathways allow us to measure the relation between IMPACT-III and clinical factors (Fig. 1). Due to deviation from normal distribution, in all structural equation modeling (SEM) analysis maximum likelihood estimation robust to non-normality (MLR) was used.<sup>23</sup>

To evaluate the overall model fit, absolute fit index (chi-square value), comparative fit index (CFI), Tucker–Lewis Fit Index or non-normed fit index (TLI or NNFI), and root mean

**Table 2** The median scores for total IMPACT-III and the scores for all 6 IMPACT-III domain separately. pc 25,75 = percentile 25 and percentile 75.

	Week 0	Week 6	Week 30	Week 53
	Median (pc25,75)	Median (pc25,75)	Median (pc25,75)	Median (pc25,75)
Total IMPACT-III	115.0 (102.5, 130.25)	142.0 (130, 148.75)	138.0 (126, 153)	141.50 (124.5, 153.75)
IMPACT-III bowel symptoms	3.571 (2.785, 4.25)	4.428 (4.035, 4.571)	4.428 (3.928, 4.571)	4.428 (3.892, 4.857)
IMPACT-III systemic symptoms	2.833 (2.0, 3.333)	4.0 (3.333, 4.583)	4.0 (3.333, 4.666)	4.0 (3.333, 4.333)
IMPACT-III emotional functioning	3.142 (2.285, 3.571)	4.0 (3.178, 4.285)	3.785 (3.178, 4.285)	3.857 (3.178, 4.428)
IMPACT-III social functioning	3.583 (3.187, 3.972)	4.083 (3.75, 4.333)	4.208 (3.687, 4.562)	4.083 (3.75, 4.562)
IMPACT-III body image	3.0 (2.416, 3.666)	3.50 (3.0, 3.666)	3.333 (3.0, 4.0)	3.666 (3.0, 4.0)
IMPACT-III treatment/interventions	3.0 (2.333, 3.666)	3.666 (2.666, 4.333)	3.666 (2.666, 4.333)	3.666 (3.0, 4.25)



**Figure 2** Development of IMPACT-III scores with significance at the definite times during one year IFX period. \*\*\* =  $p < 0.008$ .

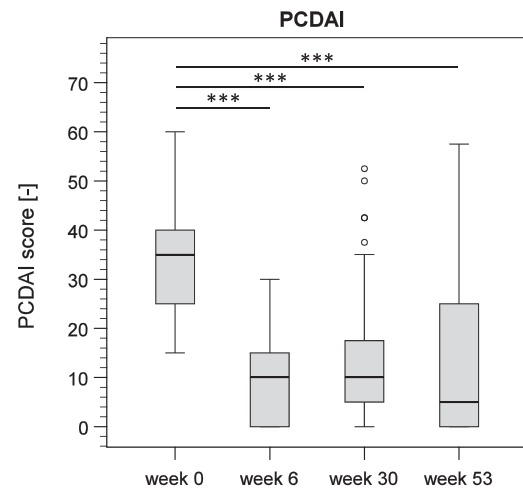
square error approximation (RMSEA) were calculated. CFI and TLI reflect the total variance accounted for by the model and indicate a fit relative to a null model. Values greater than 0.90 are desired, values greater than 0.95 indicate good fit, and values greater than 0.90 indicate satisfactory fit. RMSEA reflects the variance of residuals, values smaller than 0.08 indicate adequate fit while values smaller than 0.05 signify excellent fit.<sup>24,25</sup>

## 6. Results

### 6.1. Results of Friedman test and Wilcoxon single rank test with Bonferroni analysis

QoL of patients improved significantly due to IFX treatment ( $\chi^2 = 58.101$ ;  $p < 0.001$ ). The IMPACT-III median scores at week 0 (initial of infliximab treatment) and week 6 were 115 [pc 25,75: 102.5, 130.25] and 142 (pc 25,75: 130, 148.75), respectively. After two infliximab infusion therapies the QoL was significantly better than the initial score ( $Z = -5.846$ ;  $p < 0.001$ ). Along the maintenance treatment the IMPACT-III median was also higher at week 30 and week 53 than at week 0, 138 (pc 25,75: 126, 153) and 141.5 (pc 25,75: 124.5, 153.75), respectively, which indicated significant improvement in the QoL during IFX therapy compared to initial status (Table 2, Fig. 2).

The IMPACT-III questionnaire allows us to evaluate the 6 domains separately. Table 2 contains the calculated median



**Figure 3** Development of PCDAI scores with significance at the definite times during one year IFX period. \*\*\* =  $p < 0.008$ , PCDAI = Pediatric Crohn's Disease Activity Index.

scores for each domain at the examined weeks. Each domain noticed better median score during the examined period than at the time of initial. The systemic symptom domain improved the most and the body image domain the least by week 6 and week 53. Statistically, all domains improved significantly during IFX course ( $p < 0.01$ ).

The development of PCDAI was also assessed to monitor the effect of the infliximab induction and maintenance therapy. Results showed significant decrease in PCDAI ( $\chi^2 = 59.492$ ,  $p < 0.001$ ) during the period of one year infliximab treatment compared to the initial scores. The median PCDAI score was 35.0 (pc 25,75: 25, 40.625) at week 0 and decreased by 10.0 (pc 25,75: 0, 15.625) by week 6 ( $Z = -6.028$ ;  $p < 0.001$ ). During maintenance therapy the PCDAI median scores were 10.0 (pc 25,75: 5, 18.125) and 5.0 (pc 25,75: 0, 25) at week 30 and week 53, respectively, which were significant changes with respect to the initials (Table 3, Fig. 3).

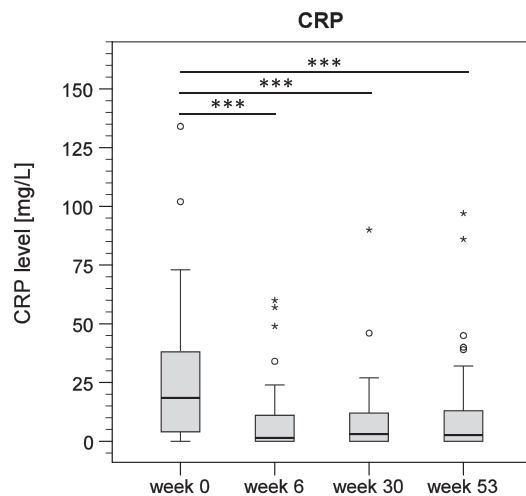
Based on PCDAI scores, more than half of the patients were in remission at every monitoring time: 58.8%, 65.1% and 61.9% at week 6, week 30 and week 53, respectively. PCDAI  $< 12.5$  was regarded as a limit of remission.

Favorable changes in laboratory parameters were also noticed. The serum CRP and platelets remarkably decreased, and serum albumin significantly increased. The data are depicted in Table 3 and Figs. 4–6 in detail.

Previous normality test showed that the data were not-normal distribution, so Spearman's correlation tests were run to assess the relationship between IMPACT III and PCDAI.

**Table 3** Median scores of PCDAI and laboratory parameters. pc25,75 = percentile 25 and percentile 75, PCDAI = Pediatric Crohn's Disease Activity Index, CRP = C-reactive protein.

	Week 0	Week 6	Week 30	Week 53
	Median (pc25,75)	Median (pc25,75)	Median (pc25,75)	Median (pc25,75)
PCDAI [-]	35 (25.0, 40.625)	10 (0, 15.625)	10 (5.0, 18.125)	5 (0, 25.0)
Serum CRP [mg/L]	18.5 (3.750, 38.50)	1.5 (0, 11.250)	3 (0, 12.250)	2.5 (0, 14.250)
Serum platelets [g/L]	516 (418, 684)	372 (310, 498)	368 (308, 475)	375 (310, 521)
Serum albumin [g/L]	41 (36, 43)	44 (40, 46)	45 (41, 47)	44 (37, 47)

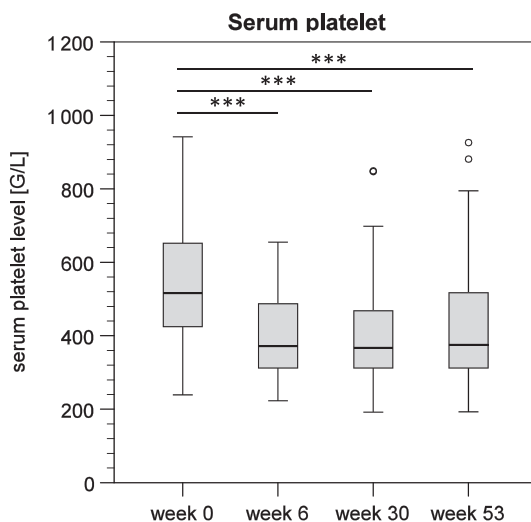


**Figure 4** Development of CRP levels with significance at the definite times during one year IFX period. \*\*\* =  $p < 0.008$ , CRP = C-reactive protein.

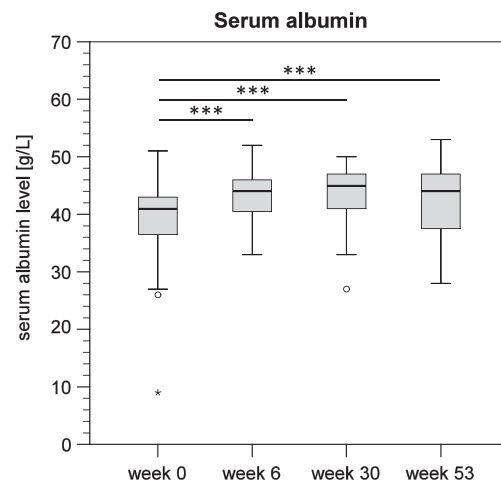
Preliminary analysis showed the relationship not to be monotonic in every case, as assessed by visual inspection of a scatter plot. There was a negative correlation between IMPACT-III and PCDAI (Table 4.). The strongest relation was observed at week 53 (Spearman's correlation coefficient =  $-0.661$ ).

## 6.2. Analysis of reliability

Cronbach's alpha is 0.931, which indicates an excellent level of internal consistency for our IMPACT-III scale with this specific sample. Cronbach's alpha was also calculated if particular item was deleted from the scale. Corrected item total correlation was checked, 3 of the 35 questions were lower than 0.25. However Cronbach's alpha did not change considerably, the advance is not remarkable (Table 5).



**Figure 5** Development of platelet levels with significance at the definite times during one year IFX period. \*\*\* =  $p < 0.008$ .



**Figure 6** Development of serum albumin levels with significance at the definite times during one year IFX period. \*\*\* =  $p < 0.008$ .

## 6.3. Results of autoregressive cross-lagged analysis

To analyze the relation between QoL and other clinical parameters four ARCL models were studied:

*Model 1:* ARCL model of IMPACT-III and PCDAI

*Model 2:* ARCL model of IMPACT-III and CRP levels

*Model 3:* ARCL model of IMPACT-III and serum albumin levels

*Model 4:* ARCL model of IMPACT-III and platelets levels.

Result of the nesting analysis showed that *Model 1* was a well-specified model, fitted the data the best:  $\chi^2 = 11.53$ , CFI = 1.0, RMSEA = 0.0. CFI and RMSEA of the other 3 models indicated poor fit (Table 6).

Excluding the regression of PCDAI between *week 0* and *week 6* in *Model 1*, all autoregressive pathways between the regular visits were significant within each model. These findings were supported by autoregressive regression coefficients ( $\beta$  value) (Figs. 7–10). Moreover, the highest relation was observed between *week 30* and *week 53* in every grade.  $\beta$  values and related critical ratios (CR) of the ARCL model of IMPACT-III and PCDAI are summarized in detail in Table 7.

Cross-lagged association was observed between serum level of CRP and IMPACT-III; serum level of albumin and IMPACT-III; and level of platelet and IMPACT-III, however these models did not fit well (Table 6, Figs. 8–10).

**Table 4** Results of correlation analysis between IMPACT-III and PCDAI.  $\rho$  = Spearman's Rank Order Correlation Coefficient, Sig. (2-tailed) = two-tailed significance level (p-value) of the correlation coefficient.

	Week 0	Week 6	Week 53
$\rho$	$-0.333$	$-0.39$	$-0.661$
Sig. (2-tailed)	0.017	$<0.005$	$<0.001$



**Table 5** Questions which result in better reliability if item was deleted.

	Scale mean if item deleted	Scale variance if item deleted	Corrected item-total correlation	Squared multiple correlation	Cronbach's alpha if item deleted
Question 30	110.700	521.194	0.109	0.624	0.933
Question 31	111.740	519.290	0.209	0.764	0.932
Question 33	111.460	515.876	0.245	0.644	0.931

## 7. Discussion

This study has several important implications. Our results support the reliability of IMPACT-III, the disease specific health related QoL measure. Our findings also support the effectiveness of IFX both on QoL and on PCDAI. To the best of our knowledge this study is the first to report ARCL analysis to evaluate the relation between QoL and IFX treatment course. Though, we did not find a prospective relation between QoL and PCDAI, one may argue that the direction of the cross lagged regression coefficients between IMPACT-III and PCDAI suggests that children who evaluate their QoL being better will have lower values on PCDAI prospectively, but having good PCDAI values do not guarantee high QoL prospectively.

Previously, several studies reported successful usage of ARCL model, particularly in psychological topic.<sup>26–28</sup> In the present study ARCL analysis was applied to measure the prospective relationship between QoL and clinical parameters. Out of the 4 examined models the model of IMPACT-III and PCDAI (*Model 1*) fits well. However, the characterization of other three models indicated poor fit. Thus, the results of ARCL in these three cases have to be evaluated cautiously. Necessarily, the QoL has been affected by several factors, which effect lower model fit index. Presumably, more data may reduce the effect of such external factors. In our trial autoregression was seen in every model, except between *weeks 0* and *6* in the first model. The strongest relationship between examined parameters developed between the time at the last two data recording (*weeks 30* and *53*). This effect may be explicated that after a half year treatment period there were no remarkable changes in patient's condition anymore.

Result of reliability test shows distinguished internal consistency of IMPACT-III questionnaire. Otley et al. had

similar result in the value of reliability of the original IMPACT questionnaire ( $\alpha = 0.96$ ).<sup>11</sup> Kilroy and her colleagues had also observed a high internal reliability ( $\alpha = 0.90$ ) of IMPACT-III, similarly to a Croatian study ( $\alpha = 0.92$ ).<sup>7,29</sup> The areas on which participants indicated the most effect on QoL appeared to be social functioning followed by bowel symptoms, emotional functioning, treatment interventions, body image and systemic symptoms. In contrast, results of our analysis represented the higher improvement in systemic symptoms followed by bowel symptoms, emotional functioning, body image, treatment interventions and social functioning. Only 3 questions had low inter-item correlation suggesting a need for confirmatory factor analysis to test the proposed factor structure of the instrument.

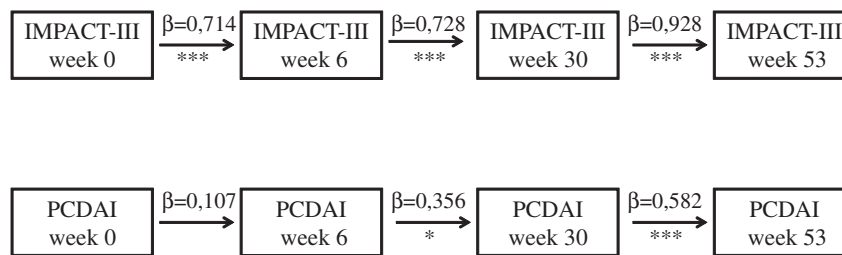
The results of this prospective study covering one year IFX treatment period, suggest that treatment with IFX indicated better QoL compared to initial status in children with severe CD. Improvement of QoL during IFX treatment in CD has been reported only in a few studies. One of the most important clinical trials about the efficacy of IFX therapy in childhood was the REACH study. In a part of this trial QoL was also measured by IMPACT-III and the results indicated significantly higher QoL during induction and maintenance IFX treatment compared to the baseline values.<sup>22</sup> De Boer and his colleges examined the effect of IFX during on-going therapy in children population. They assessed the changes in quality of life with IMPACT-III and disease severity. During on-going therapy a single dose of IFX resulted in decreased CRP and improvement in QoL in patients who were symptomatic at the time of treatment. After a single dose of IFX initial IMPACT-III (day 0) score increased by day 14.<sup>30</sup> A Spanish trial assessed the influence of the extended biological treatments, like IFX and adalimumab, on IBD. Results of this study demonstrated that most of the patients with sustained response to adalimumab or IFX normalized their perception of health. However, a group of patients, mainly affected by CD, does not restore their health related QoL to normal.<sup>31</sup> A recent study from New Zealand suggested moderate to strong negative correlation between the PCDAI and Health Related QoL in pediatric patients with CD ( $\rho = -0.596$ ,  $p < 0.05$ ), so did another research indicating the higher disease activity the more diminished QoL in each area.<sup>12,32</sup>

In line with QoL clinical indexes, PCDAI and laboratory parameters were also significantly improved. As the results of the REACH study showed, 56% of the patients who received IFX maintenance treatment every 8 weeks were in remission at week 54. In our study similar remission rate was observed, 62% of the patients were in remission (defined as PCDAI  $\leq 12.5$ ) after one year IFX therapy.<sup>22</sup> The long-term outcome of IFX therapy was also investigated in several studies.<sup>15,20,33,34</sup> One of them reported that more than half of the initial responders

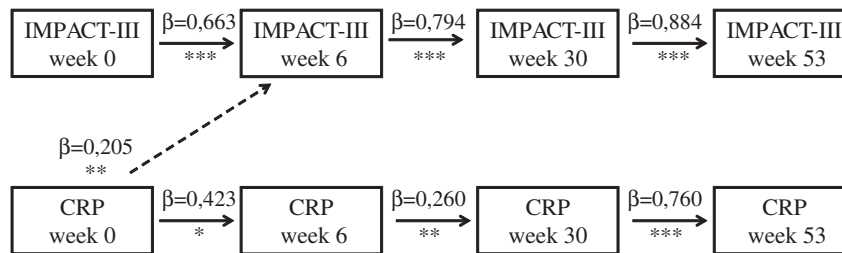
**Table 6** Global fit of the autoregressive cross-lagged models.

$\chi^2$ : Chi-square, df: degree of freedom, CFI: Comparative Fit Index; TLI: Tucker–Lewis Index; RMSEA: Root Mean Square Error of Approximation, PCDAI: Pediatric Crohn's Disease Activity Index. *Model 1*: ARCL model of IMPACT-III and PCDAI; *Model 2*: ARCL model of IMPACT-III and CRP levels; *Model 3*: ARCL model of IMPACT-III and serum albumin levels; *Model 4*: ARCL model of IMPACT-III and platelet levels.

	$\chi^2$	df	CFI	TLI	RMSEA
<i>Model 1</i>	11.525	12	1.000	1.005	0.000
<i>Model 2</i>	23.139	12	0.949	0.884	0.135
<i>Model 3</i>	24.283	12	0.940	0.865	0.143
<i>Model 4</i>	34.716	12	0.902	0.779	0.199



**Figure 7** Autoregressive cross-lagged association between IMPACT-III and PCDAI. \*\*\*:  $p < 0.001$ ; \*\*:  $p < 0.01$ ; \*:  $p < 0.05$ ; +:  $p < 0.1$ ; PCDAI: Pediatric Crohn's Disease Activity Index.



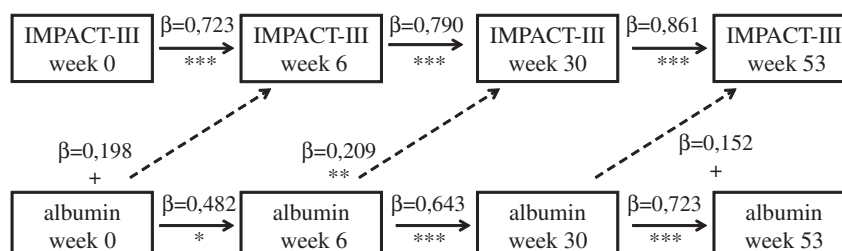
**Figure 8** Autoregressive cross-lagged association between IMPACT-III and CRP. \*\*\*:  $p < 0.001$ ; \*\*:  $p < 0.01$ ; \*:  $p < 0.05$ ; +:  $p < 0.1$ ; CRP: C-reactive protein.

to IFX (55%) maintained benefits 3 years after IFX initiation indicating a favorable result.<sup>18</sup> Regarding the induction, the mentioned studies had similar findings as our previous research had; IFX initial therapy had good clinical efficacy in most of the patients.<sup>35</sup> Nevertheless, several previous trials revealed the loss of this beneficial response. Primary and secondary failures of IFX were observed in 10–30%, and 30–40% of the patient, respectively.<sup>36,37</sup> Our results showed lower rate of primary and secondary loss of response at 6% and 20% of the patients, respectively. However, the predictors of loss of response were not examined in this study. Based on previous observations concomitant immunosuppressive treatment positively correlated with response to IFX.<sup>38</sup> Episodic therapy was associated with an increased likelihood for secondary non-response. Interestingly, trials in the UK described that male gender had a significantly lower chance for both primary and secondary loss of response. The proposed explanation for that finding reflects the fact that functional disorders, such as irritable bowel syndrome, which may mimic the symptoms of IBD, are more prevalent in the female population. However, this assumption was uncertified.<sup>39</sup>

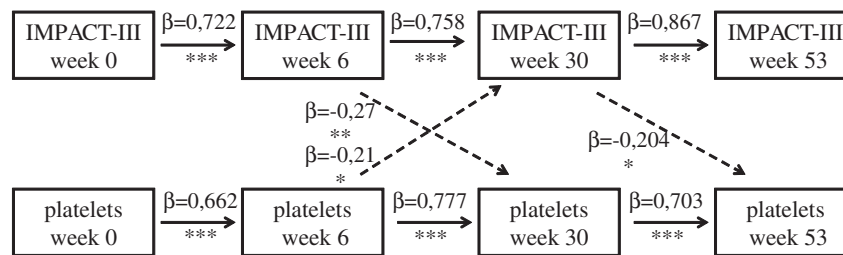
Correlation analysis revealed strong negative correlation between IMPACT-III and PCDAI at week 53. However, the association between these parameters at week 0 was very low. Possible explanations for these findings may be that the psychological status of these children was affected by several factors. In case of relapse some patients may get used to the alteration in their health status easier; moreover some patient resigned their physical status.

In the present study efficacy of IFX was followed by laboratory parameters. CRP has been used as a biomarker of luminal inflammation and a predictor of the course of Crohn's disease, as the present study also demonstrated it.<sup>40–46</sup> Amount of platelets and serum albumin levels are known as further standard markers of gut inflammation. According to our findings, these markers improved significantly during IFX course, which has confirmed the efficacy and anti-inflammatory effect of IFX.

In conclusion, our study confirmed that one year IFX treatment provided remission with sustained response in more than half of the young patients with pediatric-onset CD. Our findings well represent the efficacy of IFX treatment



**Figure 9** Autoregressive cross-lagged association between IMPACT-III and albumin. \*\*\*:  $p < 0.001$ ; \*\*:  $p < 0.01$ ; \*:  $p < 0.05$ ; +:  $p < 0.1$ .



**Figure 10** Autoregressive cross-lagged association between IMPACT-III and platelets. \*\*\*:  $p < 0.001$ ; \*\*:  $p < 0.01$ ; \*:  $p < 0.05$ ; +:  $p < 0.1$ .

**Table 7** Parameter estimates of the base autoregressive cross-lagged Model 1.

Paths	Standardized coefficients ( $\beta$ )	Critical ratio
IMPACT (week 0) $\rightarrow$ IMPACT (week 6)	0.714	8.622 ***
IMPACT (week 6) $\rightarrow$ IMPACT (week 30)	0.728	6.312 ***
IMPACT (week 30) $\rightarrow$ IMPACT (week 53)	0.928	12.904 ***
PCDAI (week 0) $\rightarrow$ PCDAI (week 6)	0.107	0.752 (ns)
PCDAI (week 6) $\rightarrow$ PCDAI (week 30)	0.356	1.899 <sup>+</sup>
PCDAI (week 30) $\rightarrow$ PCDAI (week 53)	0.582	3.455 ***
IMPACT (week 0) $\rightarrow$ PCDAI (week 6)	-0.203	-1.564 (ns)
IMPACT (week 6) $\rightarrow$ PCDAI (week 30)	-0.212	-1.236 (ns)
IMPACT (week 30) $\rightarrow$ PCDAI (week 53)	-0.265	-1.533 (ns)
PCDAI (week 0) $\rightarrow$ IMPACT (week 6)	0.120	1.332 (ns)
PCDAI (week 6) $\rightarrow$ IMPACT (week 30)	-0.094	-0.580 (ns)
PCDAI (week 30) $\rightarrow$ IMPACT (week 53)	0.000	-0.003 (ns)

\*\*\*  $p < 0.001$ ; +  $p < 0.1$ ; ns = non-significant; PCDAI: Pediatric Crohn's Disease Activity Index.

in pediatric patients with CD. Moreover, they proved the fact that QoL improves due to TNF-alpha antagonist therapy. Autoregressive cross-lagged analysis showed autoregression and cross-lagged association between QoL and clinical parameters.

## Conflict of interest

The authors declare no conflict of interest.

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**Statement of authorship:** DSz carried out the studies and data analyses and drafted the manuscript. GyK participated in the statistical analysis. AA participated in the design of the study. AD participated the samples collection and analyses. KM, KEM participated in the sample collection and writing of the manuscript. PLL, MP participated in the design of the study. BL, PG, ÁCs participated the samples collection and statistical analysis. GV conceived of the study, and participated in design and coordination and helped to draft the manuscript. All authors approved the submitted version.

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