

## Prospective Study

## Serum proinflammatory cytokines and nutritional status in pediatric chronic liver disease

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**Author contributions:** Santetti D, Dornelles CTL and Goldani HAS designed the study, analyzed the data and wrote the manuscript; Santetti D collected the data; de Albuquerque Wilasco MI was involved in editing the manuscript; Fontella FU and Werlang ICR performed the laboratory assays; Kieling CO, dos Santos JL and Vieira SMG analyzed the data and edited the manuscript.

**Supported by** Fundo de Incentivo a Pesquisa (FIPE), Hospital de Clínicas de Porto Alegre, Post-Graduate Program of Child and Adolescent Health-UFRGS and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brazil.

**Institutional review board statement:** This study was reviewed and approved by the Research and Ethics Committee of Hospital de Clínicas de Porto Alegre (protocol n°.11/0078).

**Clinical trial registration:** The authors of the manuscript entitled “Serum proinflammatory cytokines and nutritional status in pediatric chronic liver disease” declare that this study is registered at the Research and Ethics Committee of Hospital de Clínicas de Porto Alegre, Brazil (IRB00000921). The registration identification number is 11-0078.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** The authors declare that they have no conflicts of interest.

**Data sharing statement:** No additional data are available.

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**Received:** October 20, 2014

**Peer-review started:** October 20, 2014

**First decision:** December 11, 2014

**Revised:** January 6, 2015

**Accepted:** February 13, 2015

**Article in press:** February 13, 2015

**Published online:** August 7, 2015

## Abstract

**AIM:** To evaluate the nutritional status and its association with proinflammatory cytokines in children with chronic liver disease.

**METHODS:** We performed a cross-sectional study with 43 children and adolescents, aged 0 to 17 years, diagnosed with chronic liver disease. All patients regularly attended the Pediatric Hepatology Unit and were under nutritional follow up. The exclusion criteria were fever from any etiology at the time of enrollment, inborn errors of the metabolism and any chronic illness. The severity of liver disease was assessed by Child-Pugh, Model for End-stage Liver Disease (MELD) and Pediatric End Stage Liver Disease (PELD) scores. Anthropometric parameters were height/age, body mass index/age and triceps skinfold/age according to World Health Organization standards. The cutoff points for nutritional status were risk of malnutrition (Z-score < -1.00) and malnutrition (Z-score < -2.00). Interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-6 and tumor necrosis factor- $\alpha$  levels were assessed by commercial ELISA kits. For multivariate analysis, linear regression was applied to assess the association between cytokine levels, disease severity and nutritional status.

**RESULTS:** The median (25<sup>th</sup>-75<sup>th</sup> centile) age of the study population was 60 (17-116)-mo-old, and 53.5% were female. Biliary atresia was the main cause of chronic liver disease (72%). With respect to Child-Pugh score, cirrhotic patients were distributed as follows: 57.1% Child-Pugh A, a mild presentation of the disease, 34.3% Child-Pugh B, a moderate stage of cirrhosis and 8.6% Child-Pugh C, were considered severe cases. PELD and MELD scores were only above the cutoff point in 5 cases. IL-6 values were increased in patients at nutritional risk (34.9%) compared with those who were well-nourished [7.12 (0.58-34.23) pg/mL *vs* 1.63 (0.53-3.43) pg/mL;  $P = 0.02$ ], correlating inversely with triceps skinfold-for-age z-score ( $r_s = -0.61$ ;  $P < 0.001$ ). IL-6 levels were associated with liver disease severity assessed by Child-Pugh score ( $P = 0.001$ ). This association remained significant after adjusting for nutritional status in a linear regression model.

**CONCLUSION:** High IL-6 levels were found in children with chronic liver disease at nutritional risk. Inflammatory activity may be related to nutritional status deterioration in these patients.

**Key words:** Cytokines; Interleukin-6; Malnutrition; Cirrhosis; Child

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**Core tip:** Inflammatory activity has been suggested as a component of the pathogenesis of illness-related malnutrition. Several studies have evaluated proinflammatory cytokines in pediatric chronic liver

disease, but none have addressed the possible association between these biomarkers and nutritional status. This study showed that the interleukin-6 levels were significantly increased in children and adolescents at nutritional risk. To the best of our knowledge, this is the first study to analyze the relationship between the cytokine levels and nutritional status in children and adolescents with chronic liver disease.

Santetti D, de Albuquerque Wilasco MI, Dornelles CTL, Werlang ICR, Fontella FU, Kieling CO, dos Santos JL, Vieira SMG, Goldani HAS. Serum proinflammatory cytokines and nutritional status in pediatric chronic liver disease. *World J Gastroenterol* 2015; 21(29): 8927-8934 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i29/8927.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i29.8927>

## INTRODUCTION

Biliary atresia (BA) is an obstructive cholangiopathy that is present at birth or developed during the first two weeks of life<sup>[1]</sup>. It is the most common cause of chronic liver disease in children and can progress to cirrhosis<sup>[2]</sup>. The etiology of this disease is still unknown<sup>[3]</sup>. Late referral to specialized centers is still a problem that can affect patient survival<sup>[4]</sup>. Alpha-1 antitrypsin deficiency, Alagille syndrome and progressive familial intrahepatic cholestasis (PFIC) are other causes of liver disease in the pediatric population<sup>[5]</sup>. Complications related to chronic liver disease and cirrhosis include portal hypertension, variceal bleeding, ascites and failure to thrive<sup>[6-8]</sup>.

It is well established that nutritional status is an important factor in the prognosis of chronic liver disease<sup>[9]</sup>. Growth deficits may influence pre- and post-transplantation mortality<sup>[10,11]</sup>. The presence of pre-transplant stunting seems to be associated with longer hospital stays and increased costs with hospitalization at the time of transplantation<sup>[12]</sup>. Early identification of nutritional risk is important so that a multidisciplinary team can implement individualized dietary interventions<sup>[13]</sup>.

Malnutrition in liver disease is related to several conditions, such as reduced caloric intake, anorexia, early satiety, abnormalities in the metabolism of macronutrients, hypermetabolism and increased proinflammatory cytokines<sup>[14-16]</sup>. In cholestatic patients, there is a significant decrease in the bile acids concentrations in the intestine with consequent malabsorption of lipids and fat-soluble vitamins<sup>[17]</sup>. This clinical issue remains common, especially in end stage liver disease<sup>[18,19]</sup>.

Recently, inflammatory activity is suggested as a component of the pathogenesis of illness-related malnutrition<sup>[20,21]</sup>. Moreover, it is possible that proinflammatory cytokines could impair growth and

muscle breakdown through several pathways<sup>[20,22]</sup>. The inclusion of the assessment of proinflammatory cytokines, such as the concentrations of interleukin-1 beta (IL-1 $\beta$ ), IL-6, tumor necrosis factor-alpha (TNF- $\alpha$ ) and C-reactive protein (CRP), is currently recommended in routine clinical care<sup>[20,23,24]</sup>.

Many studies have evaluated the cytokine profiles of children with chronic liver disease<sup>[25,26]</sup>, but none have explored the possible association between these biomarkers of inflammation and nutritional status. Given the lack of studies on this relationship, the present study aimed to evaluate the nutritional status of children and adolescents with chronic liver disease, and its association with inflammatory activity, by measuring the proinflammatory cytokines IL-1 $\beta$ , IL-6 and TNF- $\alpha$ .

## MATERIALS AND METHODS

### **Subjects and design**

The present cross-sectional study evaluated a total of 43 children and adolescents from 3 mo to 17 years of age with a clinical diagnosis of chronic liver disease. All patients regularly attended the Pediatric Hepatology Unit, Hospital de Clinicas de Porto Alegre, a tertiary reference center for pediatric liver disease and liver transplantation in Southern Brazil. All patients were under regular nutritional follow up and their dietary intake was evaluated as a systematic approach of the multidisciplinary team at our institution.

In our study, cirrhosis was diagnosed by histological and/or standard ultrasonographic and clinical criteria in patients with chronic liver disease. The histological criteria were the presence of nodular formation and fibrosis on liver biopsy. Ultrasonographic findings were the presence of esophageal varices on endoscopy and/or ultrasound, showing heterogeneous echogenicity of the liver and signs of portal hypertension. The clinical criteria were hepatosplenomegaly, ascites, hypoalbuminemia and coagulopathy<sup>[27]</sup>.

The exclusion criteria were as follows: fever of any etiology at the time of enrollment, inborn errors of the metabolism and any chronic illness besides cirrhosis.

### **Disease severity**

The severity of liver disease was assessed according to Child-Pugh score<sup>[28]</sup>; model for end-stage liver disease (MELD) score<sup>[29]</sup> for adolescents older than 12 years of age and pediatric end stage liver disease (PELD) score<sup>[30]</sup> for participants younger than 12 years of age. Scores higher than 15 were considered the cut-off point for liver disease severity.

### **Anthropometric parameters**

The anthropometric parameters used in this study included the following: body mass index-for-age (BMI/A), height-for-age (H/A), mid upper arm circumference-for-age (MUAC/A) and triceps skinfold-for-age (TSF/

A), according to World Health Organization (WHO) reference techniques<sup>[31,32]</sup>. The same trained researcher performed all measurements. The variables were presented as Z-scores. For children under 5 years of age, the WHO Anthro (version 3.2.2) software was applied. Children older than 5 years of age were evaluated using WHO Anthro Plus and anthropometric standards proposed by Frisancho<sup>[33]</sup> to calculate the MUAC/A and TSF/A. The risk of malnutrition was defined based on Z-score < -1.00 for BMI/A or TSF/A and malnutrition as Z-score < -2.00. For statistical purposes, the two categories, risk of malnutrition and malnutrition, were assembled in a single group called nutritional risk. In patients with ascites, we did not consider values of BMI/A, because this parameter may underestimate the diagnosis of malnutrition due to fluid retention.

### **Biochemical assays**

Blood samples were collected from all patients during the performance of routine tests such as: serum albumin, creatinine, conjugated bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), prothrombin time, international normalized ratio (INR) and CRP. All laboratory tests were executed according to standard operating protocols from the Biochemistry Laboratory of the local institution.

For cytokine assessment (IL-1 $\beta$ , IL-6 and TNF- $\alpha$ ), serum (2.0 mL) was immediately separated by centrifugation for 15 min at 3000 rpm and stored at -80 °C, until analysis. The cytokine concentrations were measured in duplicate using commercial ELISA kits (RD Systems, Inc., Minneapolis, MN, United States) according to the manufacturer's protocol. The minimum detectable levels for cytokines were as follows: 1.0 pg/mL (IL-1 $\beta$ ), 0.7 pg/mL (IL-6) and 5.5 pg/mL (TNF- $\alpha$ ).

### **Statistical analysis**

Continuous variables were expressed as mean  $\pm$  SD or median and interquartile range (25<sup>th</sup>-75<sup>th</sup> centile). To evaluate the association between categorical variables chi-square test was used. Regarding the correlation between quantitative variables Spearman correlation rank was applied. To compare two groups of quantitative variables we used Mann-Whitney *U* test, and to compare more than two groups, we used Kruskal-Wallis test. The linearity was tested and logarithm adjustment was performed. For multivariate analysis, linear regression was applied to assess the association between the cytokine levels, disease severity and nutritional status. Data were considered statistically significant at  $P \leq 0.05$ .

## RESULTS

### **Subjects**

The study population's median (25<sup>th</sup>-75<sup>th</sup> centile)

**Table 1** Demographic and clinical data of the study population *n* (%)

Variables	Patients ( <i>n</i> = 43)
Age (yr)	
< 2	13 (30.2)
2-5	9 (20.9)
5-10	11 (25.6)
> 10	10 (23.3)
Female	23 (53.5)
Nutritional status <sup>1</sup>	
Well-nourished	28 (65.1)
Risk of malnutrition	10 (23.3)
Malnutrition	5 (11.6)
Causes of chronic liver disease	
Biliary atresia	31 (72)
Alpha-1 antitrypsin deficiency	6 (14)
Sinusoidal obstruction syndrome	1 (2.3)
Idiopathic chronic liver disease	1 (2.3)
Cirrhosis by cytomegalovirus	1 (2.3)
Cryptogenic cirrhosis	3 (7)
Cholestasis (CB ≥ 2.0 mg/dL)	12 (27.9)
Albumin (< 3.5 g/L)	12 (27.9)
Portal hypertension	24 (55.8)
Ascites	3 (7)
Hepatomegaly	25 (58.1)
Splenomegaly	32 (74.4)
Cirrhosis	35 (81.4)
Child-Pugh score	
A	20/35 (57.1)
B	12/35 (34.3)
C	3/35 (8.6)
PELD score (> 15)	4/27 (14.8)
MELD score (> 15)	1/8 (12.5)

<sup>1</sup>Parameters for nutritional assessment: triceps skinfold-for-age and body mass index-for-age. CB: Conjugated bilirubin; PELD: Pediatric end stage liver disease; MELD: Model for end stage liver disease.

age was 60 (17-116) mo. BA was the main cause of chronic liver disease (72%). Eight patients had no cirrhosis criteria at the time of enrollment. Of all 35 cirrhotic patients, 24 were diagnosed by liver biopsy. From the remaining 11 without liver biopsy, all had ultrasonographic alterations that were compatible with cirrhosis and portal hypertension (splenomegaly and/or esophageal varices) without portal vein thrombosis.

Regarding Child-Pugh score, cirrhotic patients were distributed as follows: 57.1% Child-Pugh A with a mild presentation of the disease, 34.3% Child-Pugh with a moderate stage of cirrhosis and 8.6% Child-Pugh C were considered severe cases. PELD and MELD scores were only higher than the cutoff point of 15 in 5 cases. Complete demographic and clinical data are shown in Table 1.

### Nutritional status

Malnutrition was detected among 11.6% of the children and adolescents with chronic liver disease and 23.3% were considered at risk of malnutrition. The frequency of nutritional risk (risk of malnutrition plus malnutrition) was higher in children younger than 2 years of age, corresponding to 61.5% in this age group ( $P = 0.037$ ). With respect to linear growth, a

**Table 2** Cytokine levels in children with chronic liver disease at nutritional risk *vs* well-nourished

Cytokine	Nutritional risk	Well-nourished	<i>P</i> value <sup>1</sup>
Interleukin-1 $\beta$ (pg/mL)	0.10 (0-0.66)	0.05 (0-0.28)	0.144
Interleukin-6 (pg/mL)	7.12 (0.58-34.23)	1.63 (0.53-3.43)	0.020
TNF- $\alpha$ (pg/mL)	10.74 (8.17-12.35)	6.66 (4.28-11.26)	0.880

<sup>1</sup>Mann-Whitney *U* test. Data are expressed as median (25<sup>th</sup>-75<sup>th</sup> centile). TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ .

**Table 3** Correlations between the interleukin-6 levels and routine liver function tests

Liver function tests	Median (25 <sup>th</sup> -75 <sup>th</sup> )	<i>r<sub>s</sub></i>	<i>P</i> value
Aspartate aminotransferase (U/L)	73.50 (49.25-177.00)	0.70	< 0.001
Alanine aminotransferase (U/L)	60.00 (33.75-115.75)	0.49	0.001
Conjugated Bilirubin (mg/dL)	0.7 (0.2-2.57)	0.72	< 0.001

*r<sub>s</sub>* = Spearman correlation test.

frequency of 23.3% of low height-for-age was found.

### Cytokine assessment

The overall median (25<sup>th</sup>-75<sup>th</sup> centile) levels detected for IL-1 $\beta$ , IL-6 and TNF- $\alpha$  were, respectively, 0.07 (0-0.30) pg/mL, 2.2 (0.58-6.8) pg/mL and 8.3 (4.6-11.9) pg/mL. Both IL-6 and TNF- $\alpha$  levels were different between age groups ( $P = 0.004$ ;  $P = 0.003$ ).

We found an inverse correlation between IL-6 and TSF/A ( $r_s = -0.61$ ;  $P < 0.001$ ), IL-6 and MUAC/A ( $r_s = -0.51$ ;  $P = 0.001$ ), and IL-6 and H/A ( $r_s = -0.34$ ;  $P = 0.023$ ). IL-1 $\beta$  only correlated inversely with TSF/A ( $r_s = -0.41$ ;  $P = 0.006$ ). There was no correlation between the serum TNF- $\alpha$  and TSF/A.

The IL-6 values were significantly increased in patients at nutritional risk ( $P = 0.02$ ). The cytokine levels in well-nourished children with chronic liver disease compared with those at nutritional risk are presented in Table 2.

### Relationship between cytokines and disease severity

A strong correlation was verified between IL-6 and PELD score ( $r_s = 0.79$ ;  $P < 0.001$ ) as well as between TNF- $\alpha$  and MELD score ( $r_s = 0.76$ ;  $P = 0.017$ ). The IL-6 levels and routine liver function test correlations are shown in Table 3. With respect to albumin, the serum levels correlated inversely with IL-6 levels ( $r_s = -0.80$ ;  $P < 0.001$ ) as CRP had a strong positive correlation to this cytokine ( $r_s = 0.76$ ;  $P < 0.001$ ).

The IL-1 $\beta$  levels were not associated with liver disease severity assessed through Child-Pugh, PELD and MELD scores in our study population. The TNF- $\alpha$  levels were associated with PELD ( $P = 0.026$ ) and Child-Pugh scores ( $P = 0.050$ ).

The IL-6 levels also had a significant association with liver disease severity, which was evaluated by both PELD score ( $P = 0.014$ ) and Child-Pugh score ( $P = 0.001$ ). The distribution of this cytokine among



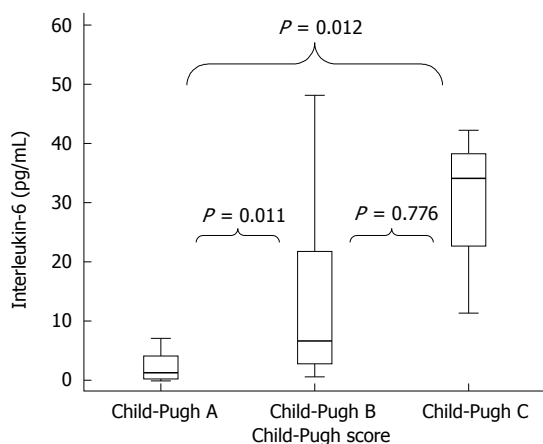


Figure 1 Interleukin-6 levels in children and adolescents with chronic liver disease according to Child-Pugh score.

Child-Pugh's categories A, B and C is shown in Figure 1. In the multivariate model, IL-6 remained associated with the disease severity that was measured by Child-Pugh score and PELD/MELD scores after adjusting for nutritional status (Table 4).

## DISCUSSION

This study assessed the relationship between the serum proinflammatory cytokines and nutritional status in children and adolescents with chronic liver disease. We demonstrated that the IL-6 levels were significantly increased in children and adolescents at nutritional risk enrolled in our study. To the best of our knowledge, this is the first study to analyze the relationship between the cytokine levels and nutritional status in children and adolescents with chronic liver disease.

Our results agreed with previous findings that suggested that the serum concentrations of IL-6 could be used to identify patients at risk of nutritional deterioration<sup>[34]</sup>. Illness-related malnutrition appears to display an association with inflammatory components through increased resting energy expenditure, decreased calorie consumption, anorexia, nutrient loss, altered nutrient utilization and malabsorption<sup>[20]</sup>. This concept seems to be appropriate for children and adolescents with chronic liver disease who have an intense protein catabolism, changes in body composition and muscle loss.

Increased resting energy expenditure could be related to weight and growth impairment in pediatric chronic liver disease, which may be approximately 30% higher compared with a healthy child<sup>[35]</sup>. This hypermetabolic state could be due to inflammation by the presence of ascending cholangitis, ascites and disordered substrate and energy uptake<sup>[15]</sup>. Additionally, altered intestinal permeability with consequent endotoxemia is directly linked to increased cytokine production observed in cirrhosis. It is suggested

Table 4 Multiple linear regression models for interleukin-6 levels adjusted for liver disease severity and nutritional status

Models <sup>1</sup>	$\beta$	P value
Child-Pugh score <sup>2</sup>	0.581	< 0.001
PELD/MELD score <sup>3</sup>	0.535	0.001

<sup>1</sup>Logarithmic transformation was applied; <sup>2</sup>Adjusted for nutritional status.  $R^2 = 37.8\%$ ; <sup>3</sup>Adjusted for nutritional status.  $R^2 = 30.6\%$ . PELD: Pediatric end stage liver disease; MELD: Model for end stage liver disease.

that malnourished cirrhotic patients have increased intestinal permeability compared with those who are well-nourished<sup>[36]</sup>, which could explain the higher levels of IL-6 found in our patients at nutritional risk. However, in cirrhotic adults, increased systemic levels of IL-6 did not correlate with body mass index<sup>[37]</sup>. We can assume that there are still conflicting data related to the possible relationship between malnutrition and proinflammatory cytokines production, especially in chronic liver disease.

The pathophysiology of malnutrition is thought to be the combined influence of undernutrition and inflammatory activity in the body composition<sup>[38]</sup>. It is well established that the presence of inflammatory activity induces peripheral loss of lean body mass<sup>[24]</sup>. In our study, we found a strong inverse correlation between the IL-6 levels and TSF/A Z-score, a parameter of body composition. This finding agrees with a possible link between the loss of lean body mass and inflammatory activity. However, these associations were not confirmed for IL-1 $\beta$  and TNF- $\alpha$ , which is in agreement with a study on cystic fibrosis patients<sup>[39]</sup>. Anthropometric parameters, such as TSF/A, are important tools for the nutritional assessment of cirrhotic patients, especially at advanced stages of the disease. It has been reported that there is a correlation between the liver disease severity, estimated by liver function tests, and impaired nutritional status, measured by anthropometric markers<sup>[40]</sup>.

Concerning nutritional assessment tools, it is well known that serum albumin shows low sensitivity and specificity as a marker of nutritional status, especially in patients with liver disease. Furthermore, it is assumed that albumin could be indicative of the presence of inflammation<sup>[41]</sup>. In agreement with this theoretical assumption, we found a strong inverse correlation between the IL-6 levels and albumin. With respect to the relationship between CRP and IL-6, there was a positive correlation in our study once this cytokine stimulates the release of CRP by the liver during the acute phase of inflammation. A recent study reported that this acute-phase protein could also be used as a tool to predict short-term mortality in severely hospitalized cirrhotic patients<sup>[42]</sup>.

Recent studies have suggested that IL-6 plays an important role in the pathogenesis of several diseases<sup>[43,44]</sup>. Focusing on liver disease patients, there seems to be an imbalance between proinflammatory

and anti-inflammatory cytokines in cirrhosis. The activated Kupffer cells of the liver are involved in cytokine secretion. A study comparing children with BA and intra-hepatic cholestatic diseases have reported higher values of IL-6 in the BA group, indicating the presence of chronic inflammation. Nevertheless, there was no mention of the patient's nutritional status. The authors concluded that IL-6 could contribute to determining the disease severity<sup>[45]</sup>. As for these studies, we found an association between the liver disease severity, assessed by Child-Pugh score, and increased IL-6 levels. Moreover, we also found a positive correlation between IL-6 and routine liver function tests, such as AST, ALT and CB.

Increased lipid oxidation and decreased glucose uptake were demonstrated by indirect calorimetry in cirrhotic patients, and this metabolic abnormality is correlated with the disease severity and circulating levels of TNF- $\alpha$ <sup>[46]</sup>. In our study, the TNF- $\alpha$  levels were also associated with liver disease severity, but they were not associated with the nutritional status assessed by anthropometric parameters. The IL-1 $\beta$  levels were not significantly related to the outcomes in our study. However, it is well established that proinflammatory cytokines can act through stimulating one another's production<sup>[47]</sup>. We can speculate that this may have occurred in our study, because IL-1 $\beta$  could be somehow stimulating IL-6 and TNF- $\alpha$  production.

The limitation of the study may be due to the small number of severe liver disease patients (Child-Pugh C) because all patients were enrolled in the outpatient clinic. Moreover, the study design (cross sectional) did not allow for medium or long-term follow up to assess the nutritional and clinical outcomes. The strength of this study is that we found the relationship between high IL-6 levels in children and adolescents with chronic liver disease at nutritional risk. However, we could not determine the exact cause of increased IL-6 levels, which could be from either malnutrition or chronic liver disease or both.

We reported a relationship between high IL-6 levels and nutritional status in children and adolescents with chronic liver disease. Our findings suggest that inflammatory activity appears to be part of the evolution of pediatric chronic liver disease. Extensive knowledge of this inflammatory panorama is of main importance in our field, enabling the creation of new approaches to nutritional support. Further research is required to evaluate the effect of dietary intervention on inflammatory response, in children and adolescents with chronic liver disease.

## ACKNOWLEDGMENTS

We thank the Unit of Biostatistics, Grupo de Pesquisa e Pós Graduação, Hospital de Clínicas de Porto Alegre, Brazil.

## COMMENTS

### Background

Malnutrition in liver disease is frequently related to decreased caloric intake, early satiety, and abnormalities in the metabolism of macronutrients. Additionally, it has also been hypothesized that malnutrition might be related to inflammatory activity in patients with chronic diseases.

### Research frontiers

This is essentially a clinical study that assessed the relationship between the cytokine levels and nutritional status in children and adolescents with chronic liver disease.

### Innovations and breakthroughs

Several studies evaluated the cytokine profiles of children with chronic liver diseases, but none addressed the possible association between these biomarkers of inflammation and nutritional status. This is the first study to analyze the relationship between the cytokine levels and nutritional status in children and adolescents with chronic liver disease.

### Applications

Understanding the role of proinflammatory cytokines, such as IL-6, in pediatric chronic liver disease, might be a helpful tool for assessing the illness-related malnutrition presented by these patients.

### Terminology

Cytokines are inflammatory mediators produced by T cells. The circulating levels of these biomarkers are identified in the presence of overproduction with consequent impact on homeostasis. Proinflammatory cytokines, such as Interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-6 and tumor necrosis factor- $\alpha$ , may be associated with illness-related malnutrition.

### Peer-review

This manuscript highlights the association between the IL-6 levels and nutritional status deterioration. Their findings suggest that inflammatory activity appears to be part of the evolution of pediatric chronic liver disease. Extensive knowledge of this inflammatory panorama is of primary importance in their field, enabling the creation of new approaches to nutritional support.

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