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ORIGINAL ARTICLE

Prospective Study

Serum proinflammatory cytokines and nutritional status in pediatric chronic liver disease

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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-1β (IL-1β), IL-6 and tumor necrosis factor-α 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^{th}-75^{th} 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

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[1]. It is the most common cause of chronic liver disease in children and can progress to cirrhosis[2]. The etiology of this disease is still unknown[3]. Late referral to specialized centers is still a problem that can affect patient survival[4]. Alpha-1 antitrypsin deficiency, Alagille syndrome and progressive familial intrahepatic cholestasis (PFIC) are other causes of liver disease in the pediatric population[5]. Complications related to chronic liver disease and cirrhosis include portal hypertension, variceal bleeding, ascites and failure to thrive[6-8].

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

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[14-16]. 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[17]. This clinical issue remains common, especially in end stage liver disease[18,19].

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

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

Many studies have evaluated the cytokine profiles of children with chronic liver disease[25,26], 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-1β, IL-6 and TNF-α.

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[27].

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[28]; model for end-stage liver disease (MELD) score[29] for adolescents older than 12 years of age and pediatric end stage liver disease (PELD) score[30] 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[31,32]. 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[33] 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-1β, IL-6 and TNF-α), serum (2.0 mL) was immediately separated by centrifugation for 15 min at 3000 rpm and stored at -80 ℃, 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-1β), 0.7 pg/mL (IL-6) and 5.5 pg/mL (TNF-α).

Statistical analysis

Continuous variables were expressed as mean ± SD or median and interquartile range (25^{th}-75^{th} 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 $P \leqslant 0.05$.

RESULTS

Subjects

The study population's median (25^{th}-75^{th} centile)

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

Variables	Patients (*n* = 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[1]	
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)

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

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

Cytokine	Nutritional risk	Well-nourished	*P* value[1]
Interleukin-1β (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-α (pg/mL)	10.74 (8.17-12.35)	6.66 (4.28-11.26)	0.880

[1]Mann-Whitney *U* test. Data are expressed as median (25^{th}-75^{th} centile). TNF-α: Tumor necrosis factor-α.

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

Liver function tests	Median (25^{th}-75^{th})	r_s	*P* 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_s = Spearman correlation test.

Cytokine assessment

The overall median (25^{th}-75^{th} centile) levels detected for IL-1β, IL-6 and TNF-α 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-α 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-1β only correlated inversely with TSF/A (r_s = -0.41; P = 0.006). There was no correlation between the serum TNF-α 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-α 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-1β levels were not associated with liver disease severity assessed through Child-Pugh, PELD and MELD scores in our study population. The TNF-α 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

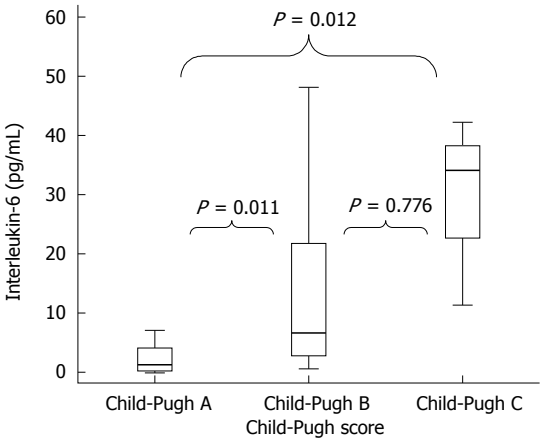

Figure 1 Interleukin-6 levels in children and adolescents with chronic liver disease according to Child-Pugh score.

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[34]. 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[20]. 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[35]. This hypermetabolic state could be due to inflammation by the presence of ascending cholangitis, ascites and disordered substrate and energy uptake[15]. 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[1]	β	*P* value
Child-Pugh score[2]	0.581	< 0.001
PELD/MELD score[3]	0.535	0.001

[1]Logarithmic transformation was applied; [2]Adjusted for nutritional status. R^2 = 37.8%; [3]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[36], 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[37]. 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[38]. It is well established that the presence of inflammatory activity induces peripheral loss of lean body mass[24]. 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-1β and TNF-α, which is in agreement with a study on cystic fibrosis patients[39]. 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[40].

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[41]. 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[42].

Recent studies have suggested that IL-6 plays an important role in the pathogenesis of several diseases[43,44]. 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[45]. 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-α[46]. In our study, the TNF-α levels were also associated with liver disease severity, but they were not associated with the nutritional status assessed by anthropometric parameters. The IL-1β 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[47]. We can speculate that this may have occurred in our study, because IL-1β could be somehow stimulating IL-6 and TNF-α 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.

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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-1β (IL-1β), IL-6 and tumor necrosis factor-α, 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.

REFERENCES

1 **Hartley JL**, Davenport M, Kelly DA. Biliary atresia. *Lancet* 2009; **374**: 1704-1713 [PMID: 19914515 DOI: 10.1016/S0140-6736(09)60946-6]

2 **Jimenez-Rivera C**, Jolin-Dahel KS, Fortinsky KJ, Gozdyra P, Benchimol EI. International incidence and outcomes of biliary atresia. *J Pediatr Gastroenterol Nutr* 2013; **56**: 344-354 [PMID: 23263590 DOI: 10.1097/MPG.0b013e318282a913]

3 **Santos JL**, Carvalho E, Bezerra JA. Advances in biliary atresia: from patient care to research. *Braz J Med Biol Res* 2010; **43**: 522-527 [PMID: 20464347]

4 **Carvalho Ed**, Santos JL, Silveira TR, Kieling CO, Silva LR, Porta G, Miura IK, De Tommaso AM, Brandão MÂ, Ferreira AR, Macêdo JR, Almeida Neto JT. Biliary atresia: the Brazilian experience. *J Pediatr* (Rio J) 2010; **86**: 473-479 [PMID: 21140036 DOI: 10.2223/jped.2054]

5 **Suchy FJ**. Neonatal cholestasis. *Pediatr Rev* 2004; **25**: 388-396 [PMID: 15520084 DOI: 10.1542/pir.25-11-388]

6 **Davenport M**. Biliary atresia: clinical aspects. *Semin Pediatr Surg* 2012; **21**: 175-184 [PMID: 22800970 DOI: 10.1053/j.sempedsurg.2012.05.010]

7 **Kelly DA**, Davenport M. Current management of biliary atresia. *Arch Dis Child* 2007; **92**: 1132-1135 [PMID: 17878208 DOI: 10.1136/adc.2006.101451]

8 **Shneider BL**, Abel B, Haber B, Karpen SJ, Magee JC, Romero R, Schwarz K, Bass LM, Kerkar N, Miethke AG, Rosenthal P,

Turmelle Y, Robuck PR, Sokol RJ. Portal hypertension in children and young adults with biliary atresia. *J Pediatr Gastroenterol Nutr* 2012; **55**: 567-573 [PMID: 22903006 DOI: 10.1097/MPG.0b013e31826eb0cf]

9 **Tsouka A**, McLin VA. Complications of chronic liver disease. *Clin Res Hepatol Gastroenterol* 2012; **36**: 262-267 [PMID: 22521556 DOI: 10.1016/j.clinre.2012.03.015]

10 **Utterson EC**, Shepherd RW, Sokol RJ, Bucuvalas J, Magee JC, McDiarmid SV, Anand R. Biliary atresia: clinical profiles, risk factors, and outcomes of 755 patients listed for liver transplantation. *J Pediatr* 2005; **147**: 180-185 [PMID: 16126046 DOI: 10.1016/j.jpeds.2005.04.073]

11 **DeRusso PA**, Ye W, Shepherd R, Haber BA, Shneider BL, Whitington PF, Schwarz KB, Bezerra JA, Rosenthal P, Karpen S, Squires RH, Magee JC, Robuck PR, Sokol RJ. Growth failure and outcomes in infants with biliary atresia: a report from the Biliary Atresia Research Consortium. *Hepatology* 2007; **46**: 1632-1638 [PMID: 17929308 DOI: 10.1002/hep.21923]

12 **Barshes NR**, Chang IF, Karpen SJ, Carter BA, Goss JA. Impact of pretransplant growth retardation in pediatric liver transplantation. *J Pediatr Gastroenterol Nutr* 2006; **43**: 89-94 [PMID: 16819383]

13 **Hartman C**, Shamir R, Hecht C, Koletzko B. Malnutrition screening tools for hospitalized children. *Curr Opin Clin Nutr Metab Care* 2012; **15**: 303-309 [PMID: 22588189 DOI: 10.1097/MCO.0b013e328352dcd4]

14 **Merli M**, Giusto M, Gentili F, Novelli G, Ferretti G, Riggio O, Corradini SG, Siciliano M, Farcomeni A, Attili AF, Berloco P, Rossi M. Nutritional status: its influence on the outcome of patients undergoing liver transplantation. *Liver Int* 2010; **30**: 208-214 [PMID: 19840246 DOI: 10.1111/j.1478-3231.2009.02135]

15 **Nightingale S**, Ng VL. Optimizing nutritional management in children with chronic liver disease. *Pediatr Clin North Am* 2009; **56**: 1161-1183 [PMID: 19931069 DOI: 10.1016/j.pcl.2009.06.005]

16 **Sanchez AJ**, Aranda-Michel J. Nutrition for the liver transplant patient. *Liver Transpl* 2006; **12**: 1310-1316 [PMID: 16933224 DOI: 10.1002/lt.20894]

17 **McKiernan P**. Neonatal jaundice. *Clin Res Hepatol Gastroenterol* 2012; **36**: 253-256 [PMID: 22609294 DOI: 10.1016/j.clinre.2012.03.018]

18 **Dornelles CT**, Goldani HA, Wilasco MI, Maurer RL, Kieling CO, Porowski M, Ferreira CT, Santos JL, Vieira SM, Silveira TR. Ghrelin, leptin and insulin in cirrhotic children and adolescents: relationship with cirrhosis severity and nutritional status. *Regul Pept* 2013; **180**: 26-32 [PMID: 23142314 DOI: 10.1016/j.regpep.2012.10.004]

19 **Neto JS**, Pugliese R, Fonseca EA, Vincenzi R, Pugliese V, Candido H, Stein AB, Benavides M, Ketzer B, Teng H, Porta G, Miura IK, Baggio V, Guimaraes T, Porta A, Rodrigues CA, Carnevale FC, Carone E, Kondo M, Chapchap P. Four hundred thirty consecutive pediatric living donor liver transplants: variables associated with posttransplant patient and graft survival. *Liver Transpl* 2012; **18**: 577-584 [PMID: 22271646 DOI: 10.1002/lt.23393]

20 **Mehta NM**, Corkins MR, Lyman B, Malone A, Goday PS, Carney LN, Monczka JL, Plogsted SW, Schwenk WF. Defining pediatric malnutrition: a paradigm shift toward etiology-related definitions. *JPEN J Parenter Enteral Nutr* 2013; **37**: 460-481 [PMID: 23528324 DOI: 10.1177/0148607113479972]

21 **White JV**, Guenter P, Jensen G, Malone A, Schofield M. Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *JPEN J Parenter Enteral Nutr* 2012; **36**: 275-283 [PMID: 22535923 DOI: 10.1177/0148607112440285]

22 **Zoico E**, Roubenoff R. The role of cytokines in regulating protein metabolism and muscle function. *Nutr Rev* 2002; **60**: 39-51 [PMID: 11852969 DOI: 10.1301/00296640260085949]

23 **Soeters PB**, Reijven PL, van Bokhorst-de van der Schueren MA, Schols JM, Halfens RJ, Meijers JM, van Gemert WG. A rational approach to nutritional assessment. *Clin Nutr* 2008; **27**: 706-716 [PMID: 18783855 DOI: 10.1016/j.clnu.2008.07.009]

24 **Soeters PB**, Schols AM. Advances in understanding and assessing malnutrition. *Curr Opin Clin Nutr Metab Care* 2009; **12**: 487-494 [PMID: 19512916 DOI: 10.1097/MCO.0b013e32832da243]

25 **Kobayashi H**, Yamataka A, Lane GJ, Miyano T. Levels of circulating antiinflammatory cytokine interleukin-1 receptor antagonist and proinflammatory cytokines at different stages of biliary atresia. *J Pediatr Surg* 2002; **37**: 1038-1041 [PMID: 12077767 DOI: 10.1053/jpsu.2002.33840]

26 **Narayanaswamy B**, Gonde C, Tredger JM, Hussain M, Vergani D, Davenport M. Serial circulating markers of inflammation in biliary atresia--evolution of the post-operative inflammatory process. *Hepatology* 2007; **46**: 180-187 [PMID: 17596879 DOI: 10.1002/hep.21701]

27 **Schuppan D**, Afdhal NH. Liver cirrhosis. *Lancet* 2008; **371**: 838-851 [PMID: 18328931 DOI: 10.1016/S0140-6736(08)60383-9]

28 **Pugh RN**, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646-649 [PMID: 4541913 DOI: 10.1002/bjs.1800600817]

29 **Kamath PS**, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**: 464-470 [PMID: 11172350 DOI: 10.1053/jhep.2001.22172]

30 **McDiarmid SV**, Anand R, Lindblad AS. Development of a pediatric end-stage liver disease score to predict poor outcome in children awaiting liver transplantation. *Transplantation* 2002; **74**: 173-181 [PMID: 12151728 DOI: 10.1097/00007890-200207270-00006]

31 **World Health Organization**. WHO Child Growth Standards: Methods and development: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age. Geneva: World Health Organization, 2006

32 **World Health Organization**. WHO Child Growth Standards: Methods and development: Head circumference-for-age, arm circumference-for-age, triceps skinfold-for-age and subscapular skinfold-for-age. Geneva: World Health Organization, 2007

33 **Frisancho A**. Anthropometric Standards An Interactive Nutritional Reference of Body Size and Body Composition for Children and Adults. 2nd ed. Michigan: University of Michigan Press, 2008

34 **Mehta NM**, Duggan CP. Nutritional deficiencies during critical illness. *Pediatr Clin North Am* 2009; **56**: 1143-1160 [PMID: 19931068 DOI: 10.1016/j.pcl.2009.06.007]

35 **Greer R**, Lehnert M, Lewindon P, Cleghorn GJ, Shepherd RW. Body composition and components of energy expenditure in children with end-stage liver disease. *J Pediatr Gastroenterol Nutr* 2003; **36**: 358-363 [PMID: 12604974 DOI: 10.1097/00005176-200303000-00010]

36 **Norman K**, Pirlich M. Gastrointestinal tract in liver disease: which organ is sick? *Curr Opin Clin Nutr Metab Care* 2008; **11**: 613-619 [PMID: 18685458 DOI: 10.1097/MCO.0b013e32830a70bc]

37 **Wiest R**, Weigert J, Wanninger J, Neumeier M, Bauer S, Schmidhofer S, Farkas S, Scherer MN, Schäffler A, Schölmerich J, Buechler C. Impaired hepatic removal of interleukin-6 in patients with liver cirrhosis. *Cytokine* 2011; **53**: 178-183 [PMID: 20637651 DOI: 10.1016/j.cyto.2010.06.013]

38 **Meijers JM**, van Bokhorst-de van der Schueren MA, Schols JM, Soeters PB, Halfens RJ. Defining malnutrition: mission or mission impossible? *Nutrition* 2010; **26**: 432-440 [PMID: 19954929 DOI: 10.1016/j.nut.2009.06.012]

39 **King SJ**, Nyulasi IB, Bailey M, Kotsimbos T, Wilson JW. Loss of fat-free mass over four years in adult cystic fibrosis is associated with high serum interleukin-6 levels but not tumour necrosis factor-alpha. *Clin Nutr* 2014; **33**: 150-155 [PMID: 23664115 DOI: 10.1016/j.clnu.2013.04.012]

40 **Hurtado-López EF**, Larrosa-Haro A, Vásquez-Garibay EM, Macías-Rosales R, Troyo-Sanromán R, Bojórquez-Ramos MC. Liver function test results predict nutritional status evaluated by arm anthropometric indicators. *J Pediatr Gastroenterol Nutr* 2007; **45**: 451-457 [PMID: 18030212 DOI: 10.1097/

mpg.0b013e3180f60b9e]
41 **Jensen GL**. Inflammation as the key interface of the medical and nutrition universes: a provocative examination of the future of clinical nutrition and medicine. *JPEN J Parenter Enteral Nutr* 2006; **30**: 453-463 [PMID: 16931617 DOI: 10.1177/0148607106030005453]
42 **Cervoni JP**, Thévenot T, Weil D, Muel E, Barbot O, Sheppard F, Monnet E, Di Martino V. C-reactive protein predicts short-term mortality in patients with cirrhosis. *J Hepatol* 2012; **56**: 1299-1304 [PMID: 22314431 DOI: 10.1016/j.jhep.2011.12.030]
43 **Beberashvili I**, Sinuani I, Azar A, Yasur H, Shapiro G, Feldman L, Averbukh Z, Weissgarten J. IL-6 levels, nutritional status, and mortality in prevalent hemodialysis patients. *Clin J Am Soc Nephrol* 2011; **6**: 2253-2263 [PMID: 21852667 DOI: 10.2215/CJN.01770211]
44 **Jang JW**, Oh BS, Kwon JH, You CR, Chung KW, Kay CS, Jung HS. Serum interleukin-6 and C-reactive protein as a prognostic indicator in hepatocellular carcinoma. *Cytokine* 2012; **60**: 686-693 [PMID: 22906998 DOI: 10.1016/j.cyto.2012.07.017]
45 **El-Faramawy AA**, El-Shazly LB, Abbass AA, Ismail HA. Serum IL-6 and IL-8 in infants with biliary atresia in comparison to intrahepatic cholestasis. *Trop Gastroenterol* 2011; **32**: 50-55 [PMID: 21922857]
46 **Shiraki M**, Terakura Y, Iwasa J, Shimizu M, Miwa Y, Murakami N, Nagaki M, Moriwaki H. Elevated serum tumor necrosis factor-alpha and soluble tumor necrosis factor receptors correlate with aberrant energy metabolism in liver cirrhosis. *Nutrition* 2010; **26**: 269-275 [PMID: 19695831 DOI: 10.1016/j.nut.2009.04.016]
47 **Schuett H**, Luchtefeld M, Grothusen C, Grote K, Schieffer B. How much is too much? Interleukin-6 and its signalling in atherosclerosis. *Thromb Haemost* 2009; **102**: 215-222 [PMID: 19652871 DOI: 10.1160/TH09-05-0297]

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