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Evolução do estado nutricional de crianças submetidas ao transplante hepático: uma análise longitudinal das medidas antropométricas.

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Este Trabalho de Conclusão de Curso foi julgado adequado para obtenção do título de Bacharel em Medicina e aprovado em sua forma final pelo Curso de Graduação em Medicina do Centro de Ciências, Tecnologias e Saúde da Universidade Federal de Santa Catarina

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RESUMO

Introdução: O transplante hepático é uma opção terapêutica para crianças com doenças hepáticas graves, mas o estado nutricional comprometido, comum nesses pacientes, pode afetar significativamente os desfechos do transplante. A avaliação nutricional pré e pós-transplante, utilizando medidas antropométricas, é essencial para otimizar os resultados clínicos e garantir a recuperação adequada. **Objetivo**: Avaliar a evolução nutricional de crianças e adolescentes entre 0 e 18 anos submetidos ao transplante hepático, comparando os períodos pré e pós-operatório, e determinar o tempo médio para que pacientes desnutridos atinjam a eutrofia. **Método**: Estudo longitudinal retrospectivo com 66 crianças e adolescentes que realizaram transplante hepático no Hospital da Criança Santo Antônio. Dados antropométricos (peso, altura e IMC) foram coletados e expressos em escores Z. Análise estatística com teste t de Student para amostras pareadas e curva de Kaplan-Meier. **Resultados**: No pré-transplante, 43,94% estavam desnutridos. Após o transplante, houve aumento significativo nas médias de peso (12,47 kg para 16,63 kg; $p < 0,0001$), estatura (80,09 cm para 91,51 cm; $p < 0,0001$) e IMC (16,60 kg/m² para 18,29 kg/m²; $p < 0,0001$). Os escores Z de peso para idade (-1,16 para 0,23; $p < 0,0001$), estatura para idade (-1,55 para -1,28; $p = 0,024$) e IMC para idade (-0,29 para 1,61; $p < 0,0001$) também melhoraram. O tempo médio para atingir a eutrofia foi de 228 dias. **Conclusão**: O transplante hepático melhorou o estado nutricional das crianças e adolescentes, refletido pelo aumento nos parâmetros antropométricos. Verificou-se que o tempo médio para atingir a eutrofia foi aproximadamente 7,5 meses.

Palavras-chave: Transplante de Fígado; Criança; Antropometria; Estado Nutricional.

ABSTRACT

Background & Aims: Liver transplantation is a therapeutic option for children with severe liver disease, but compromised nutritional status can impact outcomes. Pre- and post-transplant nutritional assessments using anthropometric measures are essential to optimize outcomes and ensure proper recovery. **Objective**: To evaluate the nutritional outcomes of children and adolescents (ages 0 to 18) undergoing liver transplantation, comparing preoperative and postoperative periods, and to determine the average time required for malnourished patients to reach eutrophy. **Method**: This retrospective longitudinal study utilized a non-probabilistic convenience sample of 66 children and adolescents who underwent liver transplantation at hospital in a Brazilian capital. Anthropometric data (weight, height, and Body Mass Index (BMI)-for-age) were extracted from medical records and expressed as Z-scores according to the World Health Organization (WHO) growth charts for sex and age. Statistical analyses were performed using the paired Student's T-test and the Kaplan-Meier survival curve. **Results**: Before the transplant, 43.94% of the patients were malnourished. Following the procedure, significant increases were observed in mean weight (from 12.47 kg to 16.63 kg; $p < 0.0001$), height (from 80.09 cm to 91.51 cm; $p < 0.0001$), and BMI (from 16.60 kg/m² to 18.29 kg/m²; $p < 0.0001$). The Z-scores for weight-for-age (-1.16 to 0.23; $p < 0.0001$), height-for-age (-1.55 to -1.28; $p = 0.024$), and BMI-for-age (-0.29 to 1.61; $p < 0.0001$) also improved. The average time to reach eutrophy: was 228 days. **Conclusions**: Liver transplantation significantly improved the nutritional outcomes of children and adolescents, as evidenced by improvements in anthropometric parameters. The mean time to reach eutrophy was approximately 7.5 months.

Keywords: Liver Transplantation; Pediatric; Anthropometry; Nutritional Status.

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LISTA DE SIGLAS E ABREVIATURAS

AASLD	American Association for the Study of Liver Disease
AST	American Society of Transplantation
BMI	Body Mass Index
ICD	International Classification of Diseases
IGF	Insulin-Like Growth Facto
ISCMPA	Irmandade Santa Casa de Misericórdia de Porto Alegre
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
SD	Standard Deviation
WHO	World Health Organization

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ARTIGO CIENTÍFICO

Nutritional Outcomes in Pediatric Liver Transplantation: A Longitudinal Analysis of Anthropometric Measures

Running title: **Post-Transplant Nutritional Outcomes in Pediatrics**

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Author contributions: Guilherme de Araujo Baptistello designed the research study, wrote the manuscript, collected and evaluated the data, performed the statistical analysis and performed comparisons to ensure accuracy; Thais Oliveira de Sousa wrote the manuscript and critically evaluated the final version; Melina Utz Melere designed the research study, collected anthropometric measurements, collected the data, and critically evaluated the final version; Caroline da Silva Beskow evaluated the data, performed comparisons to ensure accuracy and critically evaluated the final version; Cristina Targa Ferreira, Carolina Soares da Silva, Luiza Salgado Nader, Flávia Heinz Feier, and Antônio Nocchi Kalil critically evaluated the final version; Simone Farias-Antúnez wrote the manuscript, verified the interpretation of the results and critically evaluated the final version; All authors have read and approve the final manuscript.

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Keywords: Pediatric anthropometry, Nutritional recovery, Nutritional deficiency, Pediatric liver transplantation, Risk of complications, post-transplant growth

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ABSTRACT

Objective: To evaluate the nutritional outcomes of children and adolescents (ages 0 to 18) undergoing liver transplantation, comparing preoperative and postoperative periods, and to determine the average time required for malnourished patients to reach eutrophy. **Method**: This retrospective longitudinal study utilized a non-probabilistic convenience sample of 66 children and adolescents who underwent liver transplantation at hospital in a Brazilian capital. Anthropometric data (weight, height, and Body Mass Index (BMI)-for-age) were extracted from medical records and expressed as Z-scores according to the World Health Organization (WHO) growth charts for sex and age. Statistical analyses were performed using the paired Student's T-test and the Kaplan-Meier survival curve**. Results**: Before the transplant, 43.94% of the patients were malnourished. Following the procedure, significant increases were observed in mean weight (from 12.47 kg to 16.63 kg; $p < 0.0001$), height (from 80.09 cm to 91.51 cm; $p < 0.0001$), and BMI (from 16.60 kg/m² to 18.29 kg/m²; $p < 0.0001$). The Z-scores for weight-for-age (-1.16 to 0.23; $p < 0.0001$), height-for-age (-1.55 to -1.28; $p = 0.024$), and BMI-for-age (-0.29 to 1.61; $p < 0.0001$) also improved. The average time to reach eutrophy: was 228 days. **Conclusions**: Liver transplantation significantly improved the nutritional outcomes of children and adolescents, as evidenced by improvements in anthropometric parameters. The mean time to reach eutrophy was approximately 7.5 months.

Keywords: Liver Transplantation; Pediatric; Anthropometry; Nutritional Status.

INTRODUCTION

The liver is essential for managing energy and nutrient metabolism. Liver diseases lead to complex pathophysiological disturbances affecting nutrient digestion, absorption, distribution, storage, and utilization. In pediatric patients, chronic liver diseases are predominantly characterized by cholestatic.[1] Research indicates that malnutrition affects between 65% and 100% of patients with chronic liver diseases.[2]

Malnutrition, a multifactorial condition prevalent in children with liver disease, significantly increases the risks of morbidity and mortality. Therefore, maintaining an adequate nutritional status in children with chronic liver disease can prevent severe hepatic complications.[3]

Moukarzel et al.'s research established a strong correlation between nutritional status and liver transplant outcomes in pediatric patients. The findings suggest that children with poor nutrition are more prone to infections after transplant, surgical complications, and a higher chance of mortality.[4] In addition, malnutrition in kids with end-stage liver disease can lead to long-term challenges after the transplant, including delayed cognitive development and slower growth.[3,1]

Thus, it is evident that malnutrition is a critical modifiable factor both before and after liver transplantation.[3] For this reason, assessing nutritional status is crucial, with anthropometric evaluation being highlighted as a simple, convenient, cost-effective, efficient, quick, and non-invasive approach.[5] Longitudinal assessment of nutritional status, primarily using height-for-age, but also weight-for-age and Body Mass Index (BMI)-for-age indicators, has proven to be an effective method for monitoring the nutritional condition of liver transplant patients over the long term and is already routinely collected in clinical practice. These measures provide a precise and comprehensive evaluation of nutritional status, aiding in more accurate clinical

management.[6]

Liver transplantation often becomes a child's only chance of survival in case of severe liver pathology, and the consideration of the nutritional aspect is an integral component of its success. Liver transplantation represents a vital intervention for children with advanced liver disease, where comprehensive nutritional assessment is key to supporting successful outcomes. This study contributes meaningfully by analyzing changes in anthropometric measures and nutritional status among these patients, while also providing an average timeline for malnourished individuals to reach a healthy nutritional state. The findings offer valuable insights to enhance post-transplant care and improve our understanding of the nutritional and anthropometric adjustments experienced by this patient group.The objective of this study was to follow pediatric patients undergoing liver transplantation at the Pediatric Liver Transplantation Service of Hospital Criança Santo Antônio, Santa Casa da Misericórdia, Porto Alegre, Brazil, and to evaluate the impact of nutritional status evolution using anthropometric measures (weight, height, and BMI) in children and adolescents aged 0 to 18 years, before and after transplantation.

MATERIALS AND METHODS

This study was a retrospective longitudinal analysis. The participants included children and adolescents (ages 0-18) treated at the hepatology outpatient clinic of Hospital Criança Santo Antônio, Santa Casa da Misericórdia, Porto Alegre, Brazil, who underwent liver transplantation between 2013 and 2024. Participants were selected according to their liver transplant diagnosis, categorized under the International Classification of Diseases (ICD) code Z94.4. This was a non-probabilistic convenience sample, including all children who underwent liver transplantation at the hospital, with parental authorization obtained through signed Informed Consent Forms.This project was approved by the Ethics Committee of the Irmandade da Santa Casa de Misericórdia de Porto Alegre (ISCMPA) under CAEE number 19926219.4.0000.5683 and approval number 3.900.764. This study is part of an umbrella project approved under the aforementioned ethical approval number, whose primary objective is to evaluate the profile of human leukocyte antigen (HLA) and the presence of donor-specific antibodies (DSA) in liver transplant recipients, correlating these factors with the clinical evolution of the patients. In this context, the parent project includes clinical parameters that may directly impact the functionality and metabolism of individuals. Within this scope, the analysis of nutritional status progression and anthropometric measurements stands out, providing valuable insights into the systemic implications related to transplantation and its associated complications.

Eligibility criteria

Children and adolescents (ages 0-18) who underwent liver transplantation at the hospital between 2013 and 2024, with parental or legal guardian consent for participation. Participants who lacked anthropometric data for the pre- or post-transplant periods, with an average interval of one year, or those who had deceased, were excluded.

Study variables - Primary Outcome

Nutritional status evolution was assessed through anthropometric measurements in children and adolescents aged 0 to 18 years. The status was determined using weight, height, and BMI measurements, applying weight-for-age, height-for-age, and BMI-for-age indices. Weight was measured as follows: Children under 2 years were weighed either naked or wearing a clean, dry diaper, using a pediatric scale. A P15 Welmy 15 kg digital pediatric scale was used. Children aged 2 years or older were weighed individually, in a private setting, barefoot, wearing light clothing, and standing unassisted in the center of the electronic scale platform. The Welmy W200A electronic scale was used. All measurements were recorded in kilograms. Height was measured as follows: Children under 3 years had their height measured using an aluminum and plastic infantometer with 1 mm precision. For children aged 3 years or older, height was measured using a stadiometer equipped with a movable block, also made of aluminum and plastic, with 1 mm precision. This measurement was recorded in centimeters. BMI was calculated using the formula BMI = weight / (height)² and recorded in kg/m². The measurements were taken by a trained data collector, strictly following the techniques and guidelines established by the World Health Organization (WHO). These measurements were standardized according to the WHO growth curves by sex and age and expressed as Z-scores, using the WHO Anthro software (version 3.1) /2010 and WHO Anthro Plus/2007. The Z-score cutoff of -2 was used to classify the nutritional status of children in relation to underweight, stunting, and malnutrition. Children with Z-scores between -1 and -2 were classified as at risk of malnutrition, while those with Z-scores between -1 and +1 were considered eutrophic. Children with Z-scores between +1 and +2 were classified as overweight, and those with Z-scores above +2 were categorized as obese. The change in nutritional status was assessed by comparing the difference in pre-transplant anthropometric parameters with the same parameters after an average of 12 months post-transplant. The average time to reach eutrophy was calculated as the

number of days between the transplant date and the date when eutrophic status was reached. For children under 5 years, weight-for-age and/or height-for-age were used to assess nutritional status, while for children over 5 years, BMI-for-age, weight-for-age (up to 10 years), and/or height-for-age were used. Reaching eutrophy was defined as the normalization of initially inadequate anthropometric parameters. For cases with two or more inadequate parameters, eutrophy was achieved through the correction of at least one of them. For individuals with only one inadequate parameter, eutrophy was achieved by normalizing that specific parameter. Malnutrition was defined as the presence of at least one inadequate anthropometric parameter as mentioned above.[7]

Independent Variables

In this study, the independent variables considered were sex (male and female) and age (in years and months). Both sex and age were obtained from the information available in the medical records. The age at which eutrophic status was reached was calculated as the difference between the date of birth and the date when eutrophy was reached.

Data source and execution protocol

Data were collected from hospital medical records over the research period. All data from 2013 to May 2024 were extracted from the medical records. Data extraction was performed by two researchers to ensure accuracy through subsequent comparison. The data were meticulously recorded and organized in an Excel spreadsheet for analysis.

Data analysis

Data analysis was performed using Minitab Statistical Software, version 21.4.2. The data were described statistically in terms of mean ± standard deviation (SD), median (for

quantitative variables), minimum, maximum (for both quantitative and qualitative variables), and percentages (for qualitative variables), where applicable. The analysis included a paired Student's t-test to assess statistically significant differences between the means of the variables before and approximately 12 months after transplantation. Additionally, the average time for malnourished patients to reach eutrophic status was calculated using a Kaplan-Meier curve. The level of significance was set at $p < 0.05$.

RESULTS

Population Characteristics

The sample studied was made up of 66 children and adolescents who had undergone liver transplantation, of whom 54.55% were male and 45.45% were female. The average age at transplantation was 2.59 years, with a standard deviation of 3.7 years. Of the patients, 29 were malnourished before the transplant, representing 43.94% of the total. Table 1 presents the basic demographic data.

Table 1: Population Characteristics.

Basic Study Characteristics	**N**	**%**	**Mean ± SD**
Total Patients	66	100	
Eutrophic Patients (Pre-transplant)	37	56.06	
Malnourished Patients (Pre-transplant)	29	43.94	
Sex			
Male	36	54.55	
Female	30	45.45	
Age at Transplant			2.59 ± 3.70 (years)

Anthropometric Characteristics in the Pre-transplant and Post-transplant Periods

About the characteristics of the anthropometric variables of interest in the pre- and post-transplant periods, the weight showed an increase from the pre-transplant period to the post-

transplant period, with a mean difference of 4.16 kg ($t = -10.06$, $p < 0.0001$). Height also exhibited a positive change, with an average increase of 11.42 cm ($t = -17.72$, $p < 0.0001$). BMI increased by 1.69 kg/m² after the transplant ($t = -5.56$, $p < 0.0001$). The Weight-for-Age Z-score improved by 1.39 ($t = -10.08$, $p < 0.0001$), while the Height-for-Age Z-score showed a more modest increase of 0.27 ($t = -2.31$, $p = 0.024$). Lastly, the BMI-for-Age Z-score saw a substantial improvement of 1.90 ($t = -6.58$, $p < 0.0001$). Table 2 summarizes the pre- and post-transplant anthropometric data.

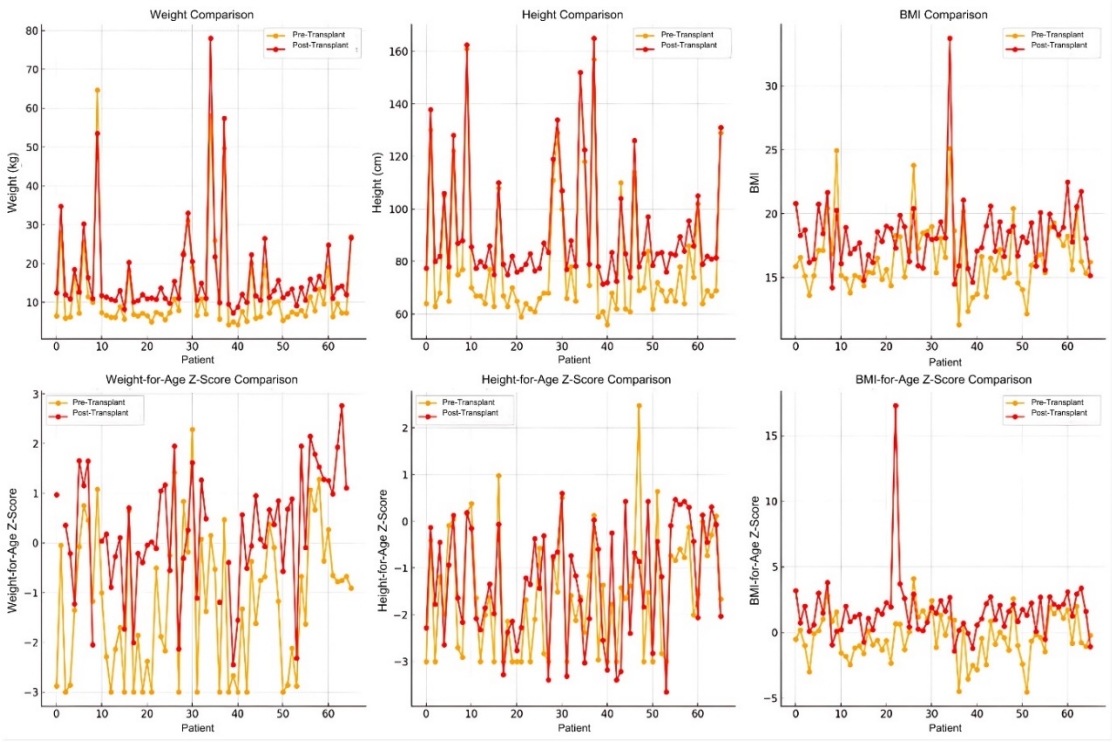
Table 2: Comparison of Pre- and Post-Transplant Anthropometric Measurements and Z-Scores.

Variables	Mean ± SD	Median	Minimum	Maximum
Pre-transplant				
Weight (kg)	12.47 ± 11.88	7.42	4.30	64.70
Height (cm)	80.09 ± 25.85	68.50	56.00	161.00
BMI	16.60 ± 2.67	16.24	11.31	25.10
Weight-for-Age Z-Score	-1.16 ± 1.45	-1.09	-3.00	2.29
Height-for-Age Z-Score	-1.55 ± 1.28	-1.63	-3.00	2.48
BMI-for-Age Z-Score	-0.29 ± 1.72	-0.39	-4.53	4.12
Post-transplant				
Weight (kg)	16.63 ± 11.97	12.18	7.34	78.00
Height (cm)	91.51 ± 22.20	83.00	71.50	165.00
BMI	18.29 ± 2.71	18.15	14.20	33.76
Weight-for-Age Z-Score	0.23 ± 1.21	0.22	-2.45	2.77
Height-for-Age Z-Score	-1.28 ± 1.23	-1.20	-3.65	0.60
BMI-for-Age Z-Score	1.61 ± 2.31	1.49	-1.41	17.30

Note: All pre- and post-transplant variations in Weight, Height, BMI and their respective Z-scores, showed statistically significant differences ($p < 0.05$)

Figure 1 presents a set of graphs comparing anthropometric variables (weight, height, and BMI) and Z-scores (weight-for-age, height-for-age, and BMI-for-age) for each patient before and after liver transplantation, with an average follow-up interval of 12 months.

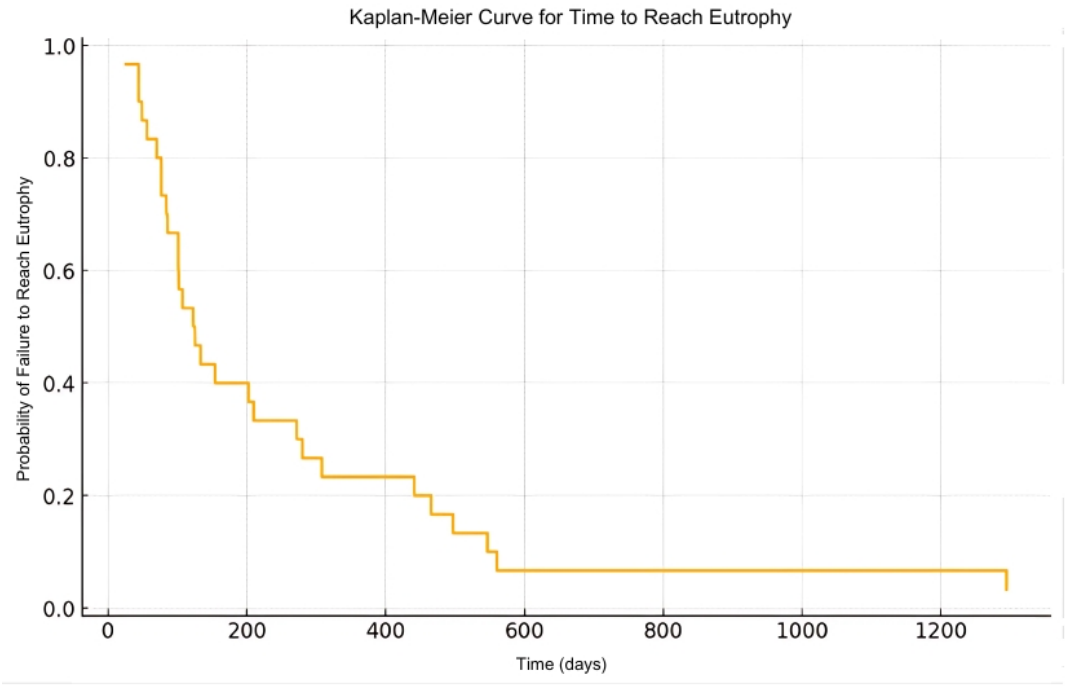
Figure 1: Variations in Anthropometric Measurements (Weight, Height, and BMI) and Their Z-Scores in Children Undergoing Liver Transplantation: A Comparison Before and After the Procedure.



Analysis of the Average Time to Reach Eutrophy

Figure 2 presents the Kaplan-Meier curve used to evaluate the time required to reach eutrophy in patients who were malnourished before liver transplantation. The analysis was based on data from 29 patients who were initially malnourished in the pre-transplant period, considering the time in days from the transplant to the moment they reached eutrophy. The Kaplan-Meier curve illustrates the probability of not reaching eutrophy at various points after transplantation. Each step in the curve represents a patient reaching eutrophy, thereby reducing the overall probability of not achieving this status.

Figure 2: Survival Analysis: Kaplan-Meier Curve for Time to Reach Eutrophy.



The average time to reach eutrophy was 228 days (SD ± 261). The first quartile was 77 days, indicating that 25% of patients reached eutrophy within this time or less. The median time was 123 days, indicating that half of the patients reached eutrophy within this period. The third quartile was 280 days, indicating that 75% of patients reached eutrophy within this time frame. Finally, the minimum time recorded to reach eutrophy was 26 days, while the maximum was 1294 days.

DISCUSSION

Anthropometric measurements are regarded as the most practical and objective parameters for assessing the nutritional status of children undergoing liver transplantation.[6] A significant proportion of the children and adolescents undergoing liver transplantation exhibited nutritional deficiencies during the preoperative period. Conventional anthropometric measurements, including weight-for-age, BMI-for-age, and height-for-age, revealed malnutrition in approximately 43.94% of the cases. This finding is consistent with the study by Ferreira et al. (2011), which reported similar percentages of pediatric patients with chronic liver disease[2]. The pathophysiology of this malnutrition is intrinsically linked to liver dysfunction, which alters the

metabolism of carbohydrates, lipids, proteins, and vitamins, while impairing intestinal nutrient absorption.[8] Additionally, children with chronic liver disease exhibit a hypermetabolic state, characterized by increased energy expenditure.[9] Inflammatory activity, such as elevated interleukin-6 levels, also induces the loss of lean body mass, contributing to nutritional imbalance.[10] In this context, it is evident that patients with chronic liver disease require increased energy intake, which can reach up to 150% of the predicted value for their height and weight.[9] If this intake is not met, gradual deficiencies in weight, height, and BMI occur.

In this study, the average age at transplantation was 2.59 years, primarily due to the leading indication for transplantation: bile duct obstruction, particularly cholestatic biliary atresia. This finding aligns with current literature, as guidelines from the American Association for the Study of Liver Diseases (AASLD), the American Society of Transplantation (AST), and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) indicate that most patients with biliary atresia undergo liver transplantation before the age of 4.[11]

This study found significant improvements in the nutritional status of patients, with the intervention leading to positive changes in all anthropometric parameters (weight, height, and BMI), as well as their corresponding Z-scores. Both initially malnourished and eutrophic patients demonstrated notable progress, underscoring the positive and significant impact of liver transplantation on the health of these children. This is largely because liver transplantation corrects the underlying metabolic and nutritional deficiencies associated with end-stage liver disease. This improves the absorption and utilization of nutrients, facilitating weight gain and growth. This recovery is evidenced by improvements in weight, BMI, and their respective Z-scores during the post-transplant period. This is consistent with the normalization of the insulin-like growth factor (IGF) axis post-transplantation-a factor that is very important in aiding growth and weight gain.[12] Another relevant finding is that the statistical analysis corroborated

the studies by Hammad et al., demonstrating that the greatest relative weight gain occurs within the first six months post-operation and that full recovery of weight is generally achieved within the first year after transplantation, especially in patients with depleted total body mass.[13]

In this study, height exhibited the least variation among the anthropometric parameters between pre- and post-transplant Z-scores. This is because children under 24 months at the time of transplantation exhibited significant growth during the first year after transplantation, reaching height distributions comparable to those of age-matched populations. Although older children showed growth improvements, they often remained stunted compared to their peers.[14] This is because older children have less time to catch up in growth before puberty, when most linear growth occurs.[15] Another factor contributing to reduced height gain, as observed by Jara et al., is the use of daily steroid therapy.[16] In light of this, a systematic review and meta-analysis examined the relationship between corticosteroid use after solid organ transplantation, finding that drug withdrawal was associated with significant growth improvements compared to continued steroid use.[17] However, the practice of corticosteroid withdrawal remains controversial, primarily due to the risk of rejection and potential long-term graft loss associated with its absence.[18] Furthermore, a study by Leiskau et al. found that continuous low-dose steroid therapy was associated with impaired growth two years after transplantation, but not at five years, suggesting that the negative impact of steroids on growth may diminish over time.[19]

In this study, the average time for initially malnourished pediatric patients to reach eutrophy after transplantation was approximately 7.5 months, with a minimum of 26 days and a maximum of 3 years and 6 months. A 1997 study reported an average time of 12 months to reach eutrophy after liver transplantation.[20] This discrepancy can be attributed to differences in sampling methods between studies, as well as variations in the types of analysis and nutritional therapies available at the time. Additionally, recovery times can vary among patients depending on preoperative nutritional status, persistent medical conditions, glucocorticoid use, recurrence

of liver dysfunction, chronic rejection, and feeding-related behavioral challenges.[21] In this analysis, the main complications significantly impacting nutritional status in the short, medium, and long term were of biliary and infectious origin. Biliary complications, including bile leakage and anastomotic strictures, align with data reported in the literature, where these complications occur in approximately 10% of children in the immediate postoperative period and 20% in the long term, making them among the most frequent complications.[22] Infections also significantly contributed to nutritional deficits due to immunosuppression, as patients became more susceptible to infections, further compromising their nutritional status. A study from Brazil revealed that severe infections affect up to 52% of children who undergo transplants, becoming a major cause of illness, death, and nutritional deficits. These infections can lead to anorexia, nutrient malabsorption, and increased metabolic demands, further exacerbating malnutrition.[1]

Despite its relevant findings, this study has certain limitations. First, the sample was limited to a single medical center, which may not fully represent the pediatric population undergoing liver transplantation in other regions or institutions. However, Hospital da Criança Santo Antônio in Porto Alegre is a reference center for pediatric liver transplantation in Brazil, receiving patients from multiple regions across the country. Furthermore, the research adopted a convenience sampling method in which participants were sampled based on availability rather than randomly. However, all pediatric patients who underwent transplantation during the study timeframe and fulfilled the inclusion criteria were incorporated. Though anthropometric measure was basically the focus of analysis, excluding other relevant nutritional status indicators such as biochemical indicators and general diet, studies have however shown that anthropometric measures are simple, inexpensive, rapid and non-invasive techniques, hence can be used as an effective tool in the assessment of nutritional status.[23,24] Finally, postoperative complications and variability in the clinical and nutritional management of patients were not

fully explored, which may influence the observed nutritional recovery.

The study also highlights positive aspects, offering significant contributions to the literature on the nutritional status of children undergoing liver transplantation. Notably, despite the limitations, the study demostrated significant improvements in anthropometric parameters, reflecting nutritional recovery after transplantation. This is also a very innovative study regarding the average time spent to reach eutrophy by undernourished pediatric patients who underwent liver transplantation in Brazil. It gives the mean time to eutrophy, which provides nutritional planning for effective post-transplant interventions that help improve the care and health outcomes of the patients.

As the studies show, liver transplant massively improves the nutritional status in children and adolescents with serious liver diseases. Anthropometric data, reviewed pre- and post-transplantation, showed that weight, height, and BMI had significantly improved to further establish the efficacy of liver transplantation in correcting nutritional defects associated with end-stage liver disease. The improvements in the Z-scores for weight, height, and BMI can be interpreted as the fact that liver transplantation not only triggers the process of liver function restoration but also encourages the further growth and considerable nutrition recovery. One of the major and innovative results of the given study, however, is the fact that the average number of days that the pediatric patients took to make it to the eutrophic state was 228 days in the case of children and adolescents who were initially suffering from malnourishment. This finding establishes a temporal reference for post-transplant nutritional recovery and provides a solid foundation for planning more effective and personalized nutritional interventions, thereby optimizing strategies and promoting faster, healthier recovery. These findings can be used as the ground for further multicenter studies to confirm and extend the present observations, thus guiding more efficient clinical practice to optimally improve liver transplant outcomes in pediatric patients.

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CONCLUSÕES E CONSIDERAÇÕES FINAIS

Portanto, o presente estudo demonstra de forma clara e significativa a importância do transplante hepático na melhoria do estado nutricional de crianças e adolescentes com doenças hepáticas graves. A análise dos dados antropométricos pré e pós-transplante revelou melhorias significativas nos parâmetros de peso, altura e IMC, corroborando na eficácia do transplante na correção das deficiências nutricionais associadas à doença hepática terminal. As melhorias observadas no escore Z para peso, estatura e IMC evidenciam que o transplante hepático não só restaura a função hepática, mas também promove um crescimento adequado e uma recuperação nutricional significativa. Além disso, um dos achados mais notáveis e pioneiros deste estudo é o tempo médio para atingir a eutrofia em pacientes pediátricos inicialmente desnutridos, que foi de 228 dias, aproximadamente 7,5 meses. Esse dado estabelece uma nova referência temporal para a recuperação nutricional pós-transplante, além de oferecer uma base mais sólida para o planejamento de intervenções nutricionais mais eficazes e personalizadas no pós-transplante, possibilitando otimizar as estratégias dietéticas e de cuidado, promovendo, assim uma recuperação nutricional mais rápida e saudável. Outrossim, este estudo reforça a relevância da avaliação nutricional contínua como um componente central do cuidado de pacientes pediátricos submetidos a transplantes de fígado. A partir dos achados, é possível propor práticas clínicas baseadas em evidências que favoreçam uma abordagem preventiva e direcionada para minimizar os riscos de desnutrição e otimizar os resultados do transplante. Por fim, os resultados obtidos oferecem dados para futuras pesquisas multicêntricas, que possam confirmar e expandir esses achados. Estudos adicionais, incluindo o uso de outros marcadores nutricionais e bioquímicos, podem contribuir para um entendimento mais abrangente dos fatores que influenciam a recuperação nutricional e a qualidade de vida a longo prazo desses pacientes, bem como a interação com a antropometria. Esses avanços terão impacto direto nas diretrizes para cuidados pós-transplante, promovendo uma abordagem abrangente e integrada ao tratamento nutricional visando a plena recuperação da qualidade de vida desses pacientes.

ANEXO A - APROVAÇÃO DO COMITÊ DE ÉTICA EM PESQUISA

HOSPITAL DA CRIANÇA
SANTO ANTÔNIO

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação do antígeno leucocitário humano e a presença de anticorpo contra o doador no transplante de fígado pediátrico e sua associação com a evolução clínica.

Pesquisador: Melina Utz Melere
Área Temática:
Versão: 4
CAAE: 19926219.4.0000.5683
Instituição Proponente: Hospital da Criança Santo Antônio - Santa Casa/RS
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.900.764

Apresentação do Projeto:
A importância do antígeno leucocitário humano (HLA) nos transplantes de órgãos sólidos é um assunto bastante debatido. Nos transplantes renal, cardíaco, pulmonar e intestinal já é aceito que a presença dos anticorpos específicos do doador (DSA) são fatores de risco para diminuição da sobrevida do enxerto. A presença de qualquer DSA circulante no soro, sendo ele DAS pré formado ou DAS de novo ou ainda DAS não-HLA podem estar associados a lesão e a perda do aloenxerto hepático. Já se observam alguns fatores de risco para presença de DSA de novo como em pacientes jovens; baixa aderência a imunossupressão e um risco maior no primeiro ano pós transplante. Em alguns estudos foi encontrado mais DSA nos pacientes que haviam testes de função hepática normais, mostrando que apesar de confortante para familiares e profissionais não pode ser tranquilizador quando há DSA circulante.Nos últimos tempos este assunto vem sendo bastante debatido, até então, acreditava-se que no aloenxerto hepático haveria uma resistência aos anticorpos específicos de doadores, por esse motivo a maioria dos centros transplantadores dava pouca atenção para a presença ou a persistência dos DSA nesse tipo de transplante. Em uma revisão feita por Del Bello e col dados recentes confirmam o efeito prejudicial tanto de DSA pré-formados quanto de DSA de novo em transplantes hepáticos ABO compatíveis, mostrando haver uma piora clínica, laboratorial e histológica nos pacientes com esses anticorpos circulantes. A presença do anticorpo anti-HLA específico do doador, tanto os pré-formados quanto os novos,

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está relacionada a um aumento do risco de perda do enxerto, rejeição mediada por anticorpo, hepatite de células plasmáticas, estenose biliar e complicações também a longo prazo como rejeição crônica, ductopenia e fibrose hepática, principalmente nos pacientes em que o crossmatch é persistentemente positivo.É fundamental avaliar a presença de DSA tanto para o diagnóstico quanto para um início de tratamento precoce para RMA principalmente nos pacientes que apresentam testes de função hepática normal com resistência a esteroides ou com as características histológicas para rejeição. O desafio portanto, está em identificar qual DSA é patogênico e quando a presença de DSA é prejudicial para o enxerto. O papel do HLA no transplante de fígado tem sido um assunto de controvérsia nas últimas duas décadas. Atipificação do HLA do doador e do receptor e a avaliação do DSA facilitarão o diagnóstico e fornecerão dados, o que pode ajudar a orientar e realizar tratamento adequado. Investigações futuras podem ajudar a esclarecer o papel das intervenções terapêuticas.

Objetivo da Pesquisa:

Objetivo Primário:

Avaliar o perfil de HLA dos receptores e doadores respectivos e identificar a presença de DSA no momento do transplante e a partir de um ano póstransplante. Identificar se há associação entre a presença de incompatibilidade HLA e a presença do anticorpo DSA com a evolução clínica dos pacientes. Serão analisados eventos como rejeição aguda, rejeição crônica, complicações da via biliar, presença e grau de fibrose hepática, naqueles que realizarem biópsias, e a sobrevida do enxerto.

Objetivo Secundário:

1) Identificar a prevalência de pacientes com DAS pré formados no momento do transplante. 2) A partir de um ano pós transplante analisar quais pacientes persistiram com DSA e quais apresentaram DSA de novo.
3) Correlacionar pacientes que desenvolveram DSA de novo com sua evolução clínica.
4) Correlacionar a presença de C4d nas biópsias hepáticas com DSA pré formado ou DSA de novo.

Avaliação dos Riscos e Benefícios:

Riscos:

Apresenta risco mínimo dado o seu caráter de coorte observacional.

Benefícios:

A tipificação do HLA do doador e do receptor e a avaliação do DSA facilitarão o diagnóstico

precoce de uma possível rejeição podendo assim mudar esquema de imunossupressão. Podendo também no futuro optar-se por doador intervivo com HLA mais compatível possível.

Comentários e Considerações sobre a Pesquisa:

A identificação do HLA do doador e do receptor e a avaliação do DSA poderão facilitar o diagnóstico de rejeição e fornecer elementos de orientação terapêutica futura.

Considerações sobre os Termos de apresentação obrigatória:

Foram feitas as modificações sugeridas.

Conclusões ou Pendências e Lista de Inadequações:

Atendidas as alterações solicitadas, o presente CEP não encontra óbices quanto ao desenvolvimento do estudo nesta Instituição.

Considerações Finais a critério do CEP:

O pesquisador responsável deve encaminhar ao CEP, os relatórios de andamento dos projetos:

1) Relatórios parciais;

2) Relatórios finais:

3) Resultados obtidos (cópia da publicação).

Diante do exposto, o Comitê de ética em Pesquisa - CEP, de acordo com as atribuições definidas na Resolução 466/12 e na Norma Operacional nº 001/2013 do CNS, manifesta-se pela aprovação do projeto de pesquisa proposto.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1394752.pdf	07/02/2020 16:00:56		Aceito
Outros	Cartarespostajan20.docx	07/02/2020 16:00:11	Melina Utz Melere	Aceito
Projeto Detalhado / Brochura Investigador	projetojan20.pdf	07/02/2020 15:59:25	Melina Utz Melere	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	termosjan20.pdf	07/02/2020 15:58:35	Melina Utz Melere	Aceito
Outros	cartaresposta.pdf	03/11/2019 20:04:26	Melina Utz Melere	Aceito

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Continuação do Parecer: 3.900.764

Folha de Rosto	folharosto.pdf	09/08/2019 17:34:36	Melina Utz Melere	Aceito
Outros	isencaodeonus.pdf	31/07/2019 18:29:31	Melina Utz Melere	Aceito
Outros	confidencialidade.pdf	31/07/2019 18:28:43	Melina Utz Melere	Aceito
Outros	dadosdeprontuarios.pdf	31/07/2019 18:27:46	Melina Utz Melere	Aceito
Outros	chefia.pdf	31/07/2019 18:26:21	Melina Utz Melere	Aceito
Outros	formulario.pdf	31/07/2019 18:23:56	Melina Utz Melere	Aceito
Declaração de Manuseio Material Biológico / Biorepositório / Biobanco	materialbiologico.pdf	31/07/2019 18:22:34	Melina Utz Melere	Aceito
Outros	anuencia.pdf	31/07/2019 18:20:31	Melina Utz Melere	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

PORTO ALEGRE, 05 de Março de 2020

Assinado por:
Lisiane De Rosa Barbosa
(Coordenador(a))

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ANEXO B - REGRAS DA REVISTA JORNAL DE PEDIATRIA

As normas da revista Jornal de Pediatria podem ser acessada por meio do link a seguir: https://www.sciencedirect.com/journal/jornal-de-pediatria/publish/guide-for-authors

Before you begin

Types of article

Jornal de Pediatria accepts submissions of original articles, review articles, and letters to the editor.

Original articles include reports on controlled and randomized studies, screening and diagnostic studies, and other descriptive and intervention studies, as well as reports on basic research carried out with laboratory animals (see section **Results of Clinical Trials**). Manuscripts in this category should not exceed 3,000 words (excluding front page, references and tables), 30 references and four tables and figures. Please access http://www.equator-network.org/ for further information on how to publish this type of article.

Review articles are meta-analysis, systematic or critical assessments of the literature concerning topics of clinical relevance, with emphasis on aspects such as cause and prevention of diseases, diagnosis, treatment, and prognosis. Review articles should not exceed 6,000 words (excluding front page, references and tables) and a minimum of 30 up-to-date references should be cited. Usually, professionals of recognized expertise are invited to write review articles. Meta-analyses are included in this category. Jornal de Pediatria will also consider unsolicited review articles. Please contact assessoria@jped.com.br to submit a draft to the Editorial Board before sending the full review article. Please access http://www.equator-network.org/ for further information on how to publish this type of article.

Letters to the editor usually express an opinion, discuss or criticize articles previously published in Jornal de Pediatria. Letters should not exceed 1,000 words and six references. Whenever possible, a response from the authors of the article to which the letter refers will be published along with the letter.

Editorials and comments,, which usually make reference to selected articles, are solicited from experts in the field. The Editorial Board may consider the publication of unsolicited comments, as long as the authors send a draft to the Editorial Board before sending the full text.

Language

As of December 9th, 2019, papers must be submitted in English, as they will be published in English (html and pdf). American spelling is used.

Submission checklist

You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.

Ensure that the following items are present:

One author has been designated as the corresponding author with contact details:

- E-mail address;
- Full postal address;

All necessary files have been uploaded:

Manuscript:

- Include keywords
- All figures (include relevant captions)
- All tables (including titles, description, footnotes)
- Ensure all figure and table citations in the text match the files provided
- Supplemental files(where applicable)

Further considerations

- Manuscript has been 'spell checked' and 'grammar checked'
- All references mentioned in the Reference List are cited in the text, and vice versa
- Permission has been obtained for use of copyrighted material from other sources (including the Internet)

- Relevant declarations of interest have been made
- Journal policies detailed in this guide have been reviewed.

For further information, visit our Support Center.

Ethics in publishing

Please see our information on Ethics in publishing.

Declaration of interest

All authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. Examples of potential competing interests include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. If there are no interests to declare then please state this: 'Declarations of interest: none'. More information.

Declaration of generative AI in scientific writing

The below guidance only refers to the writing process, and not to the use of AI tools to analyse and draw insights from data as part of the research process.

Where authors use generative artificial intelligence (AI) and AI-assisted technologies in the writing process, authors should only use these technologies to improve readability and language. Applying the technology should be done with human oversight and control, and authors should carefully review and edit the result, as AI can generate authoritative-sounding output that can be incorrect, incomplete or biased. AI and AI-assisted technologies should not be listed as an author or co-author, or be cited as an author. Authorship implies responsibilities and tasks that can only be attributed to and performed by humans, as outlined in Elsevier's AI policy for authors.

Authors should disclose in their manuscript the use of AI and AI-assisted technologies in the writing process by following the instructions below. A statement will appear in the published work. Please note that authors are ultimately responsible and accountable for the contents of the work.

Disclosure instructions

Authors must disclose the use of generative AI and AI-assisted technologies in the writing process by adding a statement at the end of their manuscript in the core manuscript file, before the References list. The statement should be placed in a new section entitled 'Declaration of Generative AI and AI-assisted technologies in the writing process'

Statement: During the preparation of this work the author(s) used [NAME TOOL / SERVICE] in order to [REASON]. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication

This declaration does not apply to the use of basic tools for checking grammar, spelling, references etc. If there is nothing to disclose, there is no need to add a statement.

Submission declaration and verification

Submission of an article implies that the work described has not been published previously (except in the form of an abstract, a published lecture or academic thesis, see 'Multiple, redundant or concurrent publication' for more information), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. To verify compliance, your article may be checked by Crossref Similarity Check and other originality or duplicate checking software.

Use of inclusive language

Inclusive language acknowledges diversity, conveys respect to all people, is sensitive to differences, and promotes equal opportunities. Content should make no assumptions about the beliefs or commitments of any reader; contain nothing which might imply that one individual is superior to another on the grounds of age, gender, race, ethnicity, culture, sexual orientation, disability or health condition; and use inclusive language throughout. Authors should ensure that writing is free from bias, stereotypes, slang, reference to dominant culture and/or cultural assumptions. We advise to seek gender neutrality by using plural nouns ("clinicians, patients/clients") as default/wherever possible to avoid using "he, she," or "he/she." We recommend avoiding the use of descriptors that refer to personal attributes such as age, gender, race, ethnicity, culture, sexual orientation, disability or health condition unless they are relevant and valid. When coding terminology is used, we recommend to avoid offensive or exclusionary terms such as "master", "slave", "blacklist" and "whitelist". We suggest using alternatives that are more appropriate and (self-) explanatory such as "primary", "secondary", "blocklist" and "allowlist". These guidelines are meant as a point of reference to help identify appropriate language but are by no means exhaustive or definitive.

Reporting sex- and gender-based analyses

Reporting guidance

For research involving or pertaining to humans, animals or eukaryotic cells, investigators should integrate sex and gender-based analyses (SGBA) into their research design according to funder/sponsor requirements and best practices within a field. Authors should address the sex and/or gender dimensions of their research in their article. In cases where they cannot, they should discuss this as a limitation to their research's generalizability. Importantly, authors should explicitly state what definitions of sex and/or gender they are applying to enhance the precision, rigor and reproducibility of their research and to avoid ambiguity or conflation of terms and the constructs to which they refer (see Definitions section below). Authors can refer to the Sex and Gender Equity in Research (SAGER) guidelines and the SAGER guidelines checklist. These offer systematic approaches to the use and editorial review of sex and gender information in study design, data analysis, outcome reporting and research interpretation - however, please note there is no single, universally agreed-upon set of guidelines for defining sex and gender.

Definitions

Sex generally refers to a set of biological attributes that are associated with physical and physiological features (e.g., chromosomal genotype, hormonal levels, internal and external anatomy). A binary sex categorization (male/female) is usually designated at birth ("sex assigned at birth"), most often based solely on the visible external anatomy of a newborn. Gender generally refers to socially constructed roles, behaviors, and identities of women, men and gender-diverse people that occur in a historical and cultural context and may vary across societies and over time. Gender influences how people view themselves and each other, how they behave and interact and how power is distributed in society. Sex and gender are often incorrectly portrayed as binary (female/male or woman/man) and unchanging whereas these constructs actually exist along a spectrum and include additional sex categorizations and gender identities such as people who are intersex/have differences of sex development (DSD) or identify as non-binary. Moreover, the terms "sex" and "gender" can be ambiguous--thus it is important for authors to define the manner in which they are used. In addition to this definition guidance and the SAGER guidelines, the resources on this page offer further insight around sex and gender in research studies.

Contributors

Each author is required to declare their individual contribution to the article: all authors must have materially participated in the research and/or article preparation, so roles for all authors should be described. The statement that all authors have approved the final article should be true and included in the disclosure.

Authorship

All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Changes to authorship

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Articles in journals

1. Up to six authors:

Araújo LA, Silva LR, Mendes FA. Digestive tract neural control and gastrointestinal disorders in cerebral palsy. J Pediatr (Rio J). 2012;88:455-64.

2. More than six authors:

Ribeiro MA, Silva MT, Ribeiro JD, Moreira MM, Almeida CC, Almeida-Junior AA, et al. Volumetric capnography as a tool to detect early peripheric lung obstruction in cystic fibrosis patients. J Pediatr (Rio J). 2012;88:509-17.

3. Organization as author:

Mercier CE, Dunn MS, Ferrelli KR, Howard DB, Soll RF; Vermont Oxford Network ELBW Infant Follow-Up Study Group. Neurodevelopmental outcome of extremely low birth weight infants from the Vermont Oxford network: 1998-2003. Neonatology. 2010;97:329-38.

4. No author given:

Informed consent, parental permission, and assent in pediatric practice. Committee on Bioethics, American Academy of Pediatrics. Pediatrics. 1995;95:314-7.

5. Article published electronically ahead of the print version:

Carvalho CG, Ribeiro MR, Bonilha MM, Fernandes Jr M, Procianoy RS, Silveira RC. Use of off-label and unlicensed drugs in the neonatal intensive care unit and its association with severity scores. J Pediatr (Rio J). 2012 Oct 30. [Epub ahead of print]

Books

Blumer JL, Reed MD. Principles of neonatal pharmacology. In: Yaffe SJ, Aranda JV, eds. Neonatal and Pediatric Pharmacology. 3rd ed. Baltimore: Lippincott, Williams and Wilkins; 2005. p. 146-58.

Academic studies

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant, MI: Central Michigan University; 2002.

CD-ROM Anderson SC, Poulsen KB. Anderson's electronic atlas of hematology [CD-ROM]. Philadelphia: Lippincott Williams and Wilkins; 2002.

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