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The influence of cholestasis on the direction of children's growth at Dr. Saiful Anwar Hospital, Malang

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ABSTRACT

Background: Cholestasis is a disturbance in the flow of bile that can disrupt the body's digestive and metabolic processes, especially in infants and children. Good growth during childhood is important for optimal health and development. This study aims to determine the effect of cholestasis on changes in body weight and differences in growth direction in children with cholestasis and children who do not suffer from cholestasis at Dr. Saiful Anwar Hospital, Malang.
Methods: The method used was a retrospective analytical observational study with a cross-sectional design approach. The Stratified Random Sampling approach randomly selected 12 children as research samples, including children suffering from cholestasis and healthy children. The Mann-Whitney statistical test was used to assess the data and determine whether there was a difference in means between the two sample groups.
Results: These findings demonstrate significant differences in growth trajectory between children affected by cholestasis and children who are free of cholestasis. Children who suffer from cholestasis tend to have more severe growth disorders, especially in terms of weight.
Conclusion: These findings suggest that cholestasis conditions significantly impact children's growth.

Keywords: cholestasis, growth direction, body weight, children.
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INTRODUCTION

Cholestasis is a pathological condition characterized by bile synthesis or transport disruption due to intrahepatic or extrahepatic disease. This obstructs bile flow in the liver, inhibiting its normal excretion into the digestive tract. If the patient's direct bilirubin level is more than 1mg/dL and the total bilirubin level is below 5 mg/dL, or if the total bilirubin level is more than 5mg/dL, then the patient is diagnosed with cholestasis. The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NAPSHGAN) say that 25–35% of cases of cholestasis in infants are caused by biliary atresia, 25% genetic disorders, metabolic diseases including TORCH 20%, α1-antitrypsin deficiency in 10%, and cholestasis related to enteral nutrition in premature babies in 5%.[1]

The incidence of cholestasis in neonates affects approximately 1 in 2500 babies. Cholestasis affects 15% of newborns, 60% of term babies, and 80% of premature babies in the first week of life. The incidence of neonatal cholestasis increases in premature infants, more so in those born at the limit of viability than in those born near term. The most common findings in neonates suffering from cholestasis are prolonged icterus, acholic stools, dark yellow urine, and hepatomegaly. Some infants show coagulopathy due to malabsorption, vitamin K deficiency, and bleeding, such as umbilical cord hemorrhage, gastrointestinal blood loss, and intracranial hemorrhage. The long-term impact of cholestasis itself, if not treated quickly, will cause liver damage and cirrhosis. Meanwhile, the urine looks dark yellow for the short-term impact of cholestasis, and the stool is alcoholic.[2]

Growth is related to changes in the number, size, and function of cells, organs, and individuals. In this way, the growth process can be measured quantitatively. Growth is divided into two aspects, namely growth direction and nutritional status. In the direction of growth, what is measured is the child's body weight, while in nutritional status, what is measured is the child's weight, height, head circumference, arm circumference, and body mass index. The direction of growth using the Kartu Menuju Sehat (KMS) contained in the Maternal and Child Health Book is classified into two types of growth: good and bad. The growth that is said to be good is divided into N1 (catch-up growth), where the growth line exceeds the standard line direction, and N2 (normal growth), where the growth line is parallel or adjacent to the standard line direction. Growth that is said to be not good is divided into three, namely T1 (inadequate growth or intermittent growth), the direction of the growth line is less than the standard line direction or growth is less than expected, T2 (not growing or flat growth) the direction of the growth line is flat or body weight fixed, and T3 (negative growth or loss of growth) the direction of the growth line is down from the direction of the standard line. Article 1, paragraph 1

in the Child Protection Constitution No. 35 of 2014 states that a child is someone who is not yet 18 (eighteen) years old, including children who are still in the womb. Children who are chronically ill will have their growth development and education disrupted. Apart from that, children will also experience prolonged stress due to their illness.[3]

Growth is influenced by two main factors: internal factors (genetics) and external factors (environment). Internal factors include gender, religion, race, and ethnicity, while external factors include nutrition, economics, and psychological stimulus. Things that can interfere with a child's growth include inadequate nutritional intake, poor parenting, lack of necessary stimulation, untreated growth and development disorders, and recurrent infections. Children who suffer from chronic pain will have a negative impact on their development both biologically, psychologically, and emotionally. Children with chronic illnesses usually tend to have developmental disorders.[4]

This study aimed to determine the effect of cholestasis on changes in body weight and differences in growth direction in children with cholestasis and children who do not suffer from cholestasis at Dr. Saiful Anwar Hospital, Malang. This research can provide additional information for researchers to identify the direction of growth in normal children and cholestasis, which can influence the direction of a child's growth. In addition, as information for the public to recognize the influence of cholestasis on the direction of children's growth.

METHODS

The design of this study was a retrospective analytical observational approach using a cross sectional design approach using medical record data, namely child patients suffering from cholestasis and child patients who did not suffer from cholestasis at Dr. Saiful Anwar Hospital, Malang. The population of this study was pediatric patients who suffered from cholestasis and children who did not suffer from cholestasis or were healthy children. The method for selecting subjects for this research uses the Stratified Random Sampling method. Stratified Random Sampling is a method of taking samples that involve the population into smaller sub-groups. The subjects of this study were pediatric patients who suffered from cholestasis and children who did not suffer from cholestasis at Dr. Saiful Anwar Hospital, Malang. The sample size is determined using the formula depicted in Figure 1.

The explanation of each item in the equation is as follows: (1) $n_1 = n_2$ shows the minimum sample size of each group; (2) Zα shows Alpha standard deviation; (3) Zβ shows Beta standard deviation; (4) S shows the combined standard deviation; (5) X_1-X_2 shows the minimum difference between the means that is considered meaningful. From the calculations, the minimum total number of samples required is 24 children (12 children in each group).

Inclusion criteria of this study were pediatric patients who were diagnosed with cholestasis with two body weight measurements, pediatric patients who were not diagnosed with cholestasis and were healthy, patients who had medical record data and KMS books, and patients treated at Dr. Saiful Anwar Hospital, Malang. In contrast, the exclusion criteria were patients diagnosed with cholestasis with other comorbidities and patients not diagnosed with cholestasis with comorbidities.

This research was conducted at Dr. Saiful Anwar Hospital, Malang. This research was carried out in March - August 2023. The dependent variable in this research was the child's weight (N1, N2, T1, T2, and T3). The instruments for this research were medical records of pediatric patients diagnosed with cholestasis, pediatric patients not diagnosed with cholestasis, and the results of measuring the child's weight at Dr. Saiful Anwar Hospital, Malang.

The collected data goes through several stages before being analyzed. Firstly, an editing process is carried out to check the completeness of the data. Once the data is confirmed to be complete, the data is coded manually through a coding process followed by an entry process, namely, entering the data into a computer program. Next, the data is checked through a cleaning process to prevent errors in entering data and then saved through the saving stage. After that, the data was analyzed using the Statistical Product and Service Solution (SPSS).

$$n_1 = n_2 = 2\left[\frac{(Z_\alpha + Z_\beta)S}{X_1 - X_2}\right]^2$$

Figure 1. Sample size equations.

Statistical analysis begins with a univariate test to determine each research variable's characteristics. This test assesses the child's gender, age, and weight. Then, to find out the comparison between children with cholestasis and normal children regarding the direction of children's growth at Dr. Saiful Anwar Hospital, Malang, based on body weight and grouped according to the KMS book, namely N1, N2, T1, T2, and T3 tested again bivariate using the Mann Whitney test.

The data results in this study were analyzed using the SPSS Statistics 26 program using the Mann-Whitney analysis method. This method tests the average difference between two groups of unpaired samples with ordinal data scales. The purpose of testing this data was to test whether there was a significant average difference between the group of children who did not suffer from cholestasis and children who suffered from cholestasis based on the category of growth direction measured. The analytical hypothesis used is as follows: (1) H0: There was a non-significant mean difference between groups, and (2) H1: There were significant mean differences between groups. Testing criteria in this article are (1) if the significance value is < 0.05, then H0 is rejected, and (2) if the significance value is > 0.05, then H0 is accepted.

RESULT

This research was carried out from March 2023 to August 2023 by taking medical records of pediatric cholestasis patients at Dr. Saiful Anwar, Regional General Hospital, Malang. The medical record review results showed that there were 20 cholestasis pediatric patients, but based on the inclusion and exclusion criteria using the Stratified Random Sampling method, 12 cholestasis pediatric patients were obtained with two weight measurements.

This research also used data on 12 healthy children, which could be obtained from the KMS book. The distance from the first weighing to the second weighing is one month.

The characteristics of research subjects are general characteristics adjusted to the conditions of confounding variables, including gender, age, difference in weight gain within one month, and type of cholestasis.

Based on Table 1, it was found that the research subjects with the variables were children with cholestasis and children without cholestasis. In cholestasis children, there were more than 10 male children (83%) and 2 female children (17%). There were also more male children without

Table 1. Characteristics of research subjects

Characteristics	Cholestasis children n = 12	Percentage (%)	Not cholestasis children n = 12	Percentage (%)
Gender				
Boy	10	83	8	67
Girl	2	17	4	33
Age (months)				
0-12	6	50	2	17
13-24	5	42	3	25
25-36	1	8	7	58
Difference between BB 1 to BB 2 (grams)				
<200	5	42	0	0
200-400	5	42	5	42
401-600	2	16	4	33
601-800	0	0	2	17
801-1000	0	0	0	0
>1000	0	0	1	8
Types of Cholestasis (underlying disease)				
Intrahepatic	6	50	0	0
Ekstrahepatic	6	50	0	0

Note: n = number of samples; BB 1 to BB 2 = difference in first weight to the second weight

Table 2. Characteristics of growth direction variables for children as research subjects

Direction of growth	Cholestasis children n = 12	Percentage (%)	Not cholestasis children n = 12	Percentage (%)
N1	3	25	10	83
N2	0	0	2	17
T1	3	25	0	0
T2	6	50	0	0
T3	0	0	0	0

Note: n = number of samples; N1= catch-up growth; N2 = normal growth; T1 = Growth faltering; T2 = flat-growth; T3 = loss of growth

Table 3. Characteristics of children's weight variables without cholestasis

Initial	1st age (month)	2nd age (month)	1st weight (Kg)	2nd weight (Kg)	Difference (gr)
AJ	31	32	9,6	9,9	300
AZ	7	8	6,1	6,4	300
GE	32	33	8,8	9,2	400
H	33	34	14,5	15,6	1100
BAH	30	31	10,1	10,7	600
CS	27	28	9,8	10,2	400
DG	20	21	12,3	12,8	500
IKA	15	16	9,1	9,9	800
JKU	31	32	11,5	12,2	700
JAI	33	34	10,5	11,1	600
KSR	6	7	10,9	11,4	500
KQS	23	24	9,7	10,2	500

Note: 1st age = age of 1st data collection; 2nd age = age of 2nd data collection; 1st weight = 1st data collection body weight; 2nd weight = 2nd data collection body weight

Table 4. Characteristics of weight variables in children with cholestasis

Initial	1st age (month)	2nd age (month)	1st weight (Kg)	2nd weight (Kg)	Difference (gr)
KSR	13	14	5,6	5,75	150
MADA	8	9	4,3	4,75	450
AGA	9	10	6,1	6,3	200
MO	19	20	6,0	6,2	200
LJMA	29	30	4,2	4,35	150
MARY	11	12	5,6	5,95	350
MAES	32	33	4,3	4,45	150
AZR	8	9	3,7	3,9	200
MH	14	15	7,6	7,75	150
SYAK	9	10	3,7	3,85	150
SQE	19	20	5,0	5,65	650
FHN	19	20	5,1	5,35	200

Note: 1st age = age of 1st data collection; 2nd age = age of 2nd data collection; 1st weight = 1st data collection body weight; 2nd weight = 2nd data collection body weight

Table 5. Results of analysis of the effect of cholestasis on children's growth direction

Group	Mean Rank	Z count	Significance
Children Who Do Not Suffer from Cholestasis	16,75	-3,243	0,001
Children Suffering from Cholestasis	8,25		

cholestasis, namely 8 children (67%) and 4 female children (33%). The age range for children with cholestasis is at most 0-12 months with 6 children (50%), followed by 13-24 months with 5 children (42%), and only 1 child with age 25-36 months (8%). In children with cholestasis, the dominant difference in weight gain was <200g for 5 children (48%), 200g-400g for 5 children (48%), and 401g-600g for 2 children (16%). The predominant difference in weight gain in non-cholestasis children was 200g-400g for 5 children (48%), followed by 401g-600g for 4 children (33%), 601g-800g for 2 children (17%), and 1 child (8%) whose difference in weight gain is >1000g. Based on the grouping, the cholestasis type only occurs in children with cholestasis. Cholestasis was divided into intrahepatic cholestasis in 6 children (50%) and extrahepatic cholestasis in 6 children (50%) with equal percentages.

The research data consists of independent and dependent variable data for the independent variable, namely children who suffer from cholestasis and children who do not suffer from cholestasis, and for the dependent variable, namely the child's body weight (N1, N2, T1, T2, and T3). Apart from that, data regarding the difference in children's weight over two periods between children who suffer from cholestasis and children who do not suffer from cholestasis supports the main research data, namely the direction of children's growth.

Table 2 shows that the growth direction data obtained for children with cholestasis and children without cholestasis shows a different distribution. The majority of children with cholestasis were in T2, namely 6 people (50%), 3 people in T1 (25%), and 3 people in N1 (25%). For non-cholestatic children, the majority were in N1 with 10 people (83%) and N2 with 2 people (17%).

Based on Table 3, it can be seen the distribution of 12 samples of non-cholestatic children aged 0-36 months at the first weighing and second weighing. The distribution of body weight can also be seen when first weighed and a month later at the second weighting. There is a spread of differences between the first and second weights.

Based on Table 4, it can be seen the distribution of 12 samples of cholestasis children from 0-36 months of age at the first weighing and second weighing. Body weight distribution can also be seen when first weighed and a month later at the second weighting. There is a spread of differences between the first and second weights.

Table 5 shows that the average ranking of children who do not suffer from cholestasis is 16.75, which is higher than the average ranking of the group of children who suffer from cholestasis, which is 8.25. The Mann-Whitney test was carried out to determine whether there were real differences between groups.

After testing with the Mann-Whitney test, it showed that the calculated Z value was smaller than the Z table (-3.243 < -1.960), and the significance value was smaller than α (0.001 < 0.050), a decision was made to reject H0. This means that there is a significant mean difference between children who do not suffer from cholestasis and children who suffer from cholestasis based on the category of growth direction measured. It can be seen from the variable data descriptive table that many children do not suffer from cholestasis with a growth direction in the N1 category, and many children suffer from cholestasis with a growth direction in the T2 category. The difference between the two groups is significant.

DISCUSSION

This research aims to determine the effect of cholestasis on the direction of growth of children at Dr. Saiful Anwar Hospital, Malang. The parameter used in this study is the difference in body weight between children who suffer from cholestasis

and children who do not. The collected medical record data was then tested using Mann Whitney to test whether there was a significant mean difference between the group of children who did not suffer from cholestasis and children who suffered from cholestasis based on the category of growth direction measured.

In this study, the subjects were 12 children, each who suffered from cholestasis and children who did not. It is known that there are studies that state that the growth trajectory of children suffering from cholestasis is worse than that of normal children. The age interval of children who were the subjects of this research ranged from 0-36 months, and most subjects were male. This is in accordance with the Law of the Republic of Indonesia Number 35 of 2014, which states that the definition of a child is someone who is not yet 18 years old (eighteen years old), including children who are still in the womb. This research also uses body weight parameters taken from medical record data and KMS books.[5] Body weight parameters will later be changed into categories according to the direction of growth using the difference in body weight from the first and second weighing with a time difference of one month.[6]

The direction of growth is to see the increase in size and several cells and intracellular tissue, partial or total body size, so that it can be measured in weight units. Based on these data, the average value of the direction of growth in children who suffer from cholestasis and children who do not suffer from cholestasis has quite significant differences. Children who suffer from cholestasis have a disturbed growth direction compared to children who do not suffer from cholestasis, whose growth direction tends to be normal. The worst growth direction is T2 (not growing or flat-growth), dominated by children who suffer from cholestasis, and the best is N1 (catch-up growth), dominated by children who do not suffer from cholestasis. N1 (catch-up growth) was also found in children suffering from cholestasis but not in half of the total sample; there were 3 children whose growth remained good even though they suffered from cholestasis.[6]

Cholestasis is the failure of bile to flow into the small intestine in normal amounts. Clinically, cholestasis can be defined as the accumulation of substances excreted into the bile, such as bilirubin, bile acids, and cholesterol in the blood and body tissues. This condition can occur at any age, including newborn babies.[7] Organs that are closely related to cholestasis are the liver and gallbladder. Growth is related to changes in the number, size, and function of cells, organs, and individuals.[8] In this way, the growth process can be measured quantitatively. Growth is divided into two aspects: the direction of growth and nutritional status. The direction of growth that is assessed is the child's body weight.[9]

Monitoring children's growth and development requires significant attention from parents. This is very important because it will impact physical and mental health in the future. One condition that needs to be watched out for is inadequate growth, often known as growth faltering. Growth faltering is a condition where the direction of the growth line is less than expected due to stagnant body weight or low weight gain in children based on age. The cause is a lack of energy. Many studies have found that children with growth faltering have significantly lighter and shorter bodies compared to children their age. Growth faltering is classified into organic eating disorders (due to medical conditions/diseases), non-organic (due to faulty eating behavior or psychosocial factors), and both. Cholestasis is an organic eating disorder caused by chronic pain. Based on previous research conducted by Aryani, growth problems in pediatric patients with cholestasis can arise for several reasons, such as poor diet, impaired nutrient absorption, increased energy requirements, and endocrine system disorders.[10] In this research, we deepen the influence of cholestasis on the direction of children's growth with weight variables. It is hoped that the results of this research will provide benefits and improve the quality of life for cholestasis sufferers in Indonesia.[6]

Apart from that, there was a significant correlation between body weight and children suffering from cholestasis, which shows that body weight is positively or significantly correlated with children suffering from cholestasis with a strong correlation. These results indicate that children who suffer from cholestasis weigh less than normal limits, or their growth direction is disturbed compared to children who do not suffer from cholestasis. This is also supported by previous research conducted by Paulo, who stated that liver and pancreatic diseases have a significant impact on growth direction and nutritional status.[11] Often, the impact of growth direction is not diagnosed until it affects the immune response, reduces muscle mass, worsens functional status, quality of life and is associated with increased mortality.[12]

The appropriate treatment for children suffering from cholestasis is to prevent further liver damage, and growth and development can be optimized by improving the flow of materials produced by the liver into the intestines and protecting the liver from toxic substances. Regarding anatomical pathology, cholestasis is an accumulation of thrombus found in the bile in liver cells and the biliary system. Based on the most common causes, cholestasis is divided into extrahepatic and intrahepatic cholestasis. Extraheptic cholestasis occurs due to blockage or damage to the bile ducts, while intrahepatic cholestasis occurs due to a buildup of bile components such as bilirubin, bile acids, and cholesterol in the liver. The main aim of evaluating children with cholestasis is to differentiate between extrahepatic and intrahepatic cholestasis as early as possible.[13]

This research, apart from looking at the direction of growth in children who suffer from cholestasis, also looks at the direction of growth in children who do not suffer from cholestasis; the aim is to compare the direction of growth. In children who do not suffer from cholestasis or can also be called healthy children, their growth direction is normal; there are very few whose growth direction is disturbed. The term growth tends to refer to quantitative changes visible in an organism's physical, organ and body structure. This growth can be seen from increases in size and weight, such as increases in height and weight. In children who do not suffer from cholestasis, weight gain within the measurement period is above the normal limit according to WHO regulations

regarding child growth and development. The direction of growth in children who do not suffer from cholestasis, seen from their absolute body weight, always shows an increase in body weight every month in accordance with the weight gain in healthy children.[12]

The limitation of this research is that there are still confounding variables in the research data in the form of uneven age intervals, gender, and minimum sample size, which may influence the research results, so a larger number of research subjects with more diverse variations is needed. Apart from that, cholestasis is not the only factor that can cause disturbances in the direction of growth in children, and body weight cannot be an absolute measure of the cause of disturbances in the direction of growth in children.

CONCLUSION

Based on this research, it can be concluded that the influence of cholestasis on disruption of children's growth direction in the form of weight loss was found at Dr. Saiful Anwar Hospital, Malang found a significant influence of cholestasis between body weight and the direction of children's growth at Dr. Saiful Anwar Hospital, Malang, it was found that cholestasis had a significant effect on differences in growth direction in children with cholestasis and children who did not suffer from cholestasis at Dr. Saiful Anwar Hospital, Malang. Based on this research, the researcher provides suggestions for improving future research, as follows: further research by increasing the number of subjects in order to evaluate the influence of confounding variables and further research regarding confounding variables in the form of age, gender, difference in weight gain within one month, and type of cholestasis to increase validation of research results.

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CONFLICT OF INTEREST

None.

ETHICAL STATEMENT

The local ethics commission has approved this study. Patients' parents also agreed and signed the written informed consent of this study.

AUTHOR CONTRIBUTION

All authors contributed to manuscript preparation and agreed that this final version of the manuscript to be submitted.

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