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COMPARISON OF TRANSFERRIN SATURATION LEVELS IN ANEMIA OF CHRONIC DISEASE AND IRON DEFICIENCY ANEMIA: A CROSS-SECTIONAL STUDY

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Abstract

About 33 percent of the global population is anemic. Anemia of chronic disease (ACD) is caused by chronic inflammation. Iron deficiency anemia (IDA) is caused by a decrease in the body's iron reserves to form red blood cells. There are many clinical and laboratory similarities between ACD and IDA, but the treatment is very different. Transferrin saturation level can be used to differentiate between the two. This research is novel because it compares transferrin saturation levels in chronic and iron deficiency anemia. This study aims to determine the transferrin saturation level in patients with ACD and IDA. This research method uses a cross-sectional study. Data taken from medical records. The sample for this study were children with ACD and IDA aged 1 month to 18 years at Wahidin Sudirohusodo Hospital, Makassar. The results showed that the mean transferrin saturation value in DKA children (19.40%) was higher than that in ADB children (5.66%). The Mann-Whitney test showed that there was a significant difference between the two groups (p=0.001) with a transferrin saturation cut-off point between the DKA and IDA groups of 6.5% with a sensitivity of 73.6%, a specificity of 72.5%, positive predictive value (PPV) of 78%, negative predictive value (NPV) of 67%, and odds ratio (OR) of 19,476 (95% CI). In conclusion, transferrin saturation levels can differentiate IDA and ACD using a cut-off point of 6.5%.

Keywords: Iron Deficiency Anemia; Saturation Transfer; Chronic Disease Anemia; Pediatrics.

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INTRODUCTION

The World Health Organization (WHO) has determined that the highest prevalence of anemia is in pre-school-age children, accounting for around 43% of the world's population. And about 42% of them are caused by iron deficiency. ACD is the second most prevalent form of anemia after IDA. ACD is the most prevalent kind of anemia among hospitalized individuals (1)(2).

There are many clinical and laboratory similarities between ACD and IDA in daily clinical practice, but the treatment is very different. And conditions with ferritin levels ranging from 30-100 ug/dL are frequently classified as a mix of chronic disease anemia and iron deficiency anemia. In patients with a mixture of ACD and IDA, a trial of giving iron preparations is necessary for 5–10 days to determine the presence of ACD or IDA. When iron deficiency is associated with an inflammatory condition, the ferritin serum that is usually used is unclear. This is a problem because chronic inflammation can be associated with an increased incidence of iron deficiency. According to the French National Health Authority (2011), the diagnosis of iron deficiency should be routinely linked to transferrin saturation (TSAT) levels in inflammatory diseases (3).

Our study aims to describe transferrin saturation in anemia of chronic disease and iron deficiency anemia as a basis for determining the diagnosis in doubtful conditions to avoid over-threat or iron administration in patients with ACD. Because iron therapy is not very effective in ACD, so there is no absolute iron deficiency considering this disease.

MATERIALS AND METHODS

Study Design

The study design was a cross-sectional study. This research was conducted at the Department of Pediatrics, Faculty of Medicine, Hasanuddin University and Dr. Wahidin Sudirohusodo Hospital, Makassar, on April 2022 until May 2022.

Participants

Children aged 1 month to 18 years with chronic disease anemia or iron deficiency anemia participated in the study. Based on anamnesis, physical examination, and supporting tests, they underwent treatment at Wahidin Sudirohusodo Hospital Makassar. Inclusion criteria were patients with anemia of chronic disease and iron deficiency anemia who went to the pediatric polyclinic or who experienced hospitalization, aged 1 month to 18 years. Patients who had received iron and erythropoietin therapy, patients with prolonged anemia due to cancer, mixed iron deficiency anemia and anemia of chronic disease were excluded from this study.

Data collection

The collection of samples using consecutive sampling The data collection was obtained from the patient's medical record. Patient initials, register number, gender, age,

nutritional status, hemoglobin level, erythrocyte index, reticulocytes, peripheral blood smear, RDW, ferritin, ferritin serum total iron binding capacity (TIBC), and TSAT were all recorded for each sample. Patients were grouped into 2 groups, namely children with anemia of chronic disease and children with iron deficiency anemia.

Diagnosis

Chronic disease anemia is diagnosed based on disorders in low blood hemoglobin levels accompanied by chronic disease and found in ferritin levels > 100 ug/dL. Diagnosis of iron deficiency anemia is determined based on the presence of disorders in blood hemoglobin levels caused by iron deficiency and found ferritin levels <12 ug/dL (4).

Laboratory Test

Anemia if the hemoglobin level is <9.0-12.5 g/dL at ages of 2 months to 3 months; <11.0-14.5 g/dL at 6 months to 6 years; <11.5-15.5 g/dL at ages 6 years to 12 years; <13.0-17.0 g/dL at ages > 12 years (male) and <13.0-15.0 g/dL for female. Reticulocyte levels decrease if <0.5 % or < 100,000/uL; increase if >1.5% or > 100.000/uL. The results of the measurement of transferrin saturation levels were obtained from the comparison between serum iron and TIBC. The average value for transferrin saturation is 20 - 50%. Serum iron levels were measured by the Photometric test method using Ferene. It is said to decrease if <80 g/L and increase if >180 g/L. Total Iron Binding Capacity (TIBC) levels were measured using Immunoturbidimetry. It is said to reduce if < 300 g/mL and increase if > 360 g/mL (4).

Other Measurement

Nutritional status was assessed based on WHO for children under 5 years and CDC 2000 for children over 5 years (5)(6). For children > 5 years, good nutrition is achieved by multiplying the actual weight by 100 and dividing it by the recommended body weight for the person's height. According to age, between 90% and 110%; deficit, when the score is between 70% to 90%; and malnutrition, if <70% and there is a clinical condition in the form of a child looking very thin, the rib cage is visible, looks wasting. For children <5 years old, based on the z score curve from WHO (2006). Good nutrition if the weight/height is between -2 SD and 2 SD; deficit if it is between the -2 SD and -3 SD; and malnutrition if it is below the -3 SD or clinically in the form of a child who looks skinny ribs are visible, looks wasting, and upper arm circumference <11. 5 cm in infants 6–59 months.

Data Analysis

Data analysis using SPSS v.26.0. frequency, mean value, standard deviation and range were used for the characteristics of the subjects. T-test was used to assess differences in the characteristics of subjects who were normally distributed based on groups of chronic disease anemia and iron deficiency anemia. If it is not normally distributed, then

the Mann-Whitney test is used. Receiver Operator Curve (ROC) is used to determine the cut-off point. The chi-square test was used to compare the frequency of transferrin saturation results which were divided into 2 groups; ACD groups and IDA groups, which were tested at several cut-off points.

Ethical Clearance

This study with human subjects was carried out in accordance with the respective institution's ethical guidelines. Every action in this study was carried out only after information was provided and with the parents' informed agreement. Following the ethical guidelines, the Hasanuddin University Faculty of Medicine's Health Research Ethics Commission authorized this study protocol with permission letter number: 186/UN4.6.4.5.31/PP36/2022.

RESULTS

Subject Characteristics

53 children (56.9%) are in the ACD group, while 40 children (43.1%) are in the IDA group. Table 1 provides information about the subjects' characteristics. MCV, MCH, RDW, ferritin, ferritin serum, and TIBC levels in the ACD group and the IDA group were significantly different, with p-values of 0.001, 0.001, 0.001, 0.001, 0.013, and 0.001 respectively (Table 1).

Transferrin Saturation Levels in Anemia of Chronic Disease and Iron Deficiency Anemia

With a sensitivity of 73.6 percent, specificity of 72.5 percent, PPV of 78 percent, NPV of 67.4 percent, and OR of 19.476 with a 95 percent CI (2,914 - 18,510), we used the TSAT cutoff value that was considered to be the most optimal at 6.5 percent (figure 1 and table 2). TSAT levels significantly differed between the IDA and ACD groups (p=0.001). (Table 1)

Table 1. Subjects Characteristics

Characteristics	ACD	IDA	*P-value*
Sex			
Male	31	20	
Female	22	20	0.528
Nutritional Status			
Poor	14	7	
Deficit	8	5	0.678
Good	28	27	
Overweight	2	1	
Obesity	1	0	
Age (month)			
Mean	67.36	70.23	
Median	22.97	22.45	0.289
Standard Deviation	72.18	77.80	
Minimum-maximum	1.43 – 215.43	4.37 – 214.13	
MCV (fL)			
Mean	78.86	64.1	
Median	79.00	64.00	<0.001

Characteristics	ACD	IDA	*P-value*
Standard Deviation	6.83	6.62	
Minimum-maximum	61.00 – 95.00	52.00 – 77.00	
MCH (pg)			
Mean	25.81	18.67	
Median	26.00	19.00	<0.001
Standard Deviation	2.90	3.20	
Minimum-maximum	18.00 – 33.00	13.00 – 26.00	
RDW (%)			
Mean	16.44	21.21	
Median	15.3	20.5	<0.001
Standard Deviation	4.7	5.62	
Minimum-maximum	12.00 – 44.10	13.60 – 42.20	
Ret (%)			
Mean	1.75	1.55	
Median	1.54	1.33	0.522
Standard Deviation	1.01	0.77	
Minimum-maximum	0.15 – 4.04	0.22 – 3.67	
Ferritin (ug/dL)			
Mean	487.86	5.4	
Median	357.64	4.1	<0.001
Standard Deviation	357.22	3.72	
Minimum-maximum	103.46 – 1205	1.4 – 11.9	
Ferritin serum (µg/L)			
Mean	37.71	22.27	
Median	36.00	17.00	0.013
Standard Deviation	28.55	17.22	
Minimum-maximum	3.00 – 141.00	3.00 – 96.00	
TIBC serum (µg/mL)			
Mean	235.99	409.52	
Median	239.00	399.50	<0.001
Standard Deviation	94.5	81.89	
Minimum-maximum	25.00 – 627.60	159.00 – 432.00	
Transferrin Saturation			
Mean	19.40	5.66	
Median	14.53	4.00	<0.001
Standard Deviation	19.01	4.59	
Minimum-maximum	1.46 – 100	0.65 – 21.43	

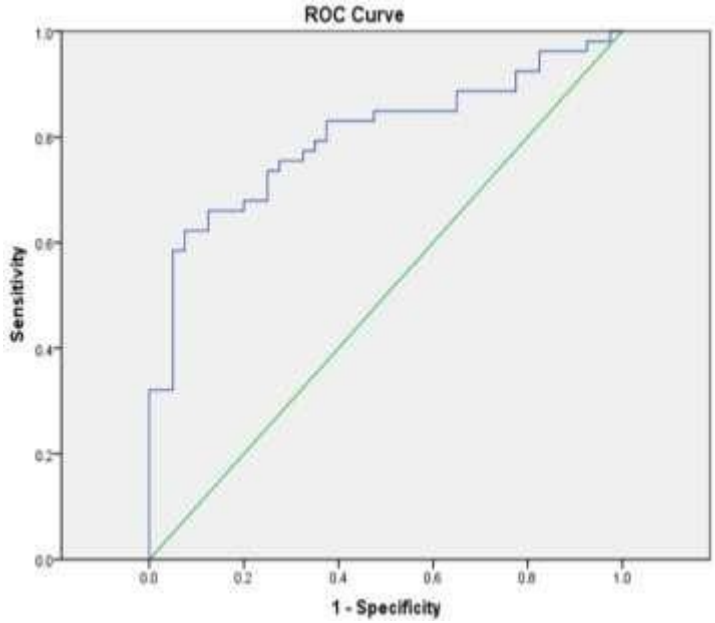

Figure 1. ROC Curve

Table 2. Comparison of Transferrin Saturation in ACD and IDA Groups

Group	Transferrin Saturation		Total	*P-value*	OR (95% CI)
	≥6.5%	<6.5%			
ACD	39 (78%)	14 (32.6%)	52 (57%)	<0.001	19.376
IDA	11 (22%)	29 (67.4%)	40 (43%)		(2.914-18.510)
Total	50 (100%)	43 (100%)	93 (100%)		

DISCUSSION

Anemia is a decrease in the number of erythrocytes and the concentration of hemoglobin (Hb) or hematocrit levels in the peripheral blood below the average values for age and sex so that the ability of the blood to provide oxygen to the tissues is reduced (7). Our study consisted of 93 people, with the ACD group of 53 people (56.9%) and IDA as many as 40 (43.1%). Based on the visit data from the Hospital Information System (SIRS), RSUP Wahidin Sudirohusodo showed that ACD was the most anemia, with the number of visits in 2019 as many as 267 and in 2020 as many as 221. While IDA in 2019 was 90 and in 2020 as many as 47. In this study, the frequency of ACD incidence is higher than IDA, which is 56.9% and 43.1% (1)(2).

We found significant differences in the parameters of MCV, MCH, and RDW levels ($p < 0.05$). In line with David YB, which showed significantly lower levels of MCV, MCH, and higher levels of RDW in the IDA group than in other groups. In IDA, the MCV, MCH, and MCHC erythrocyte index values decreased along with the decrease in Hb levels, and progressive microcytic hypochromic and increased RDW levels were

found due to the dysmorphic red blood cell population. Jain et al. showed that a microcytic sample (MCV <70 fl) was observed in 90% of IDA cases, but it was observed in only 9% of ACD cases. The anemia found in ACD is usually normochromic normocytic anemia but can become microcytic along with the severity of the underlying disease (4)(8)(9).

The median value of ferritin serum in the ACD and IDA groups revealed a statistically significant difference ($p<0.05$) between the two groups. According to Teke Hu, that evaluated laboratory signs of anemia in IDA and ACD in patients with heart failure and kidney failure, ferritin serum dropped in all three groups, indicating a significant difference between the IDA group and the ACD group with heart failure ($p=0,001$)

The decrease in ferritin serum is due to proinflammatory cytokines inducing ferritin expression and stimulating iron storage or retention in macrophage cells, resulting in a decrease in circulating iron concentration and then a limited supply of iron for erythroid cells, with the result being anemia. While the decrease in ferritin serum levels in IDA if the amount of iron from food is insufficient, there will be the use of iron from iron reserves to maintain Hb levels. Decreased iron reserves will be followed by decreased serum iron (1)(10)(11).

Our study also highlighted a statistically significant difference between the mean TIBC levels in the ACD and IDA groups ($p<0.05$). Our study showed TIBC levels in the ACD group decreased and increased in the IDA group. This is because the acute phase response decreases hepatic transferrin synthesis, thereby lowering TIBC levels. The study of Teke Hu et al. also showed the results of increased TIBC levels in the IDA group with a median value of 397 (370.5-427.5) ug/dl, and there was a significant difference between the IDA and ACD groups with heart failure with $p < 0.001$ (12)(13).

Given the variations in treatment for anemia of chronic disease and iron deficiency anemia, it is vital to search for markers that can facilitate differentiation between the two conditions. Transferrin saturation (TSAT) is the best determinant of iron exchange between plasma and iron reserves in the body (14)(15). It describes the supply of iron to bone marrow erythroid. We utilized a TSAT cutoff of 6.5 percent. This study revealed that the ACD group's TSAT score was more significant than the IDA group's TSAT score by 6.5 percentage points. A TSAT score of 6.5 percent indicates IDA, while a TSAT score of 6.5 percent indicates ACD. According to studies conducted by Mahajan et al., TSAT levels in the ACD group were more significant than in the IDA group. In this study, patients with anemia due to pure chronic disease, anemia due to chronic infection with iron deficiency, and iron deficiency anemia all had low TSAT levels. $p <0.001$ indicated a statistically significant difference across the three groups,

with the iron deficiency anemia group having the lowest TSAT level (2).

The decrease in TSAT levels in the ACD group could be caused by an underlying inflammatory condition in the ACD group. A study by Higgins V et al. stated that a negative association existed between TSAT and CRP levels. With the results of the Spearman statistical test of -0.280 ($p < 0.0001$). Although the correlation is not very strong, TSAT and CRP levels are significantly correlated (negatively), so the more severe inflammatory conditions underlying ACD can lead to low TSAT levels due to decreased TIBC and ferritin levels in inflammatory conditions. On the other hand, in the IDA group, TSAT levels 6.5% were found due to the stage of iron deficiency that occurred, so there was no significant compensatory increase in TIBC levels (11).

In conclusion, transferrin saturation levels can be used to differentiate chronic disease anemia from iron deficiency to provide appropriate therapy for patients. Transferrin saturation levels in the chronic disease anemia group were found to be higher than in the iron deficiency anemia group. The optimal cut-off value is 6.5%.

The strength of this study is that it uses a strict operational definition. The results of this study can make a major contribution to the detection and treatment of ACD and IDA in children so that they can be treated quickly and appropriately. The limitation of this study is that it uses secondary data from medical records, so several shortcomings are found, namely incomplete data or not what is needed.

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