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Reticulocyte hemoglobin content: a simple parameter for detection of iron deficiency anemia in children with chronic liver disease

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Abstract

Background: Iron deficiency anemia is common among patients with chronic liver disease. Reticulocyte hemoglobin is a marker for iron availability in the bone marrow that is not affected by inflammation.

Objective: The aim of this study is to detect the diagnostic value of reticulocyte hemoglobin (Ret-Hb) in diagnosis of iron deficiency anemia among children with chronic liver disease.

Methods: This is a cross-sectional study that included thirty-three children with chronic liver disease (CLD) and *Hb* < 11 g/dL, *MCV* < 77 fl, regularly attending the Pediatric Hepatology Clinic, Cairo University Children Hospitals. Patients underwent full history taking, and full iron profile and reticulocyte Hb were done.

Results: The median age of our patients was 5.9 years with a median age of onset of CLD was 1.6 years. The mean reticulocytic Hb was 25.52 ± 4.53 pg (*N*: 28–36 pg). Mean serum ferritin was 89 ± 16.55 ng/ml (*N*: 7–140 ng/ml). There was a statistically positive significant linear correlation between S-ferritin and Ret. Hb, $r = +0.433$, $p = 0.012$. ROC curve analysis of reticulocytic Hb, at cutoff ≤ 29.3 pg for diagnosis of iron deficiency anemia in children with CLD, had an AUC of 0.824 with a sensitivity of 92.59% and a specificity of 83.33%, with $p = 0.012$.

Conclusion: Reticulocyte Hb is a sensitive and specific marker for detection of iron deficiency anemia in CLD patients. Anemia in CLD was mostly iron deficiency anemia.

Keywords: Iron deficiency Anemia, Chronic liver disease, Reticulocyte hemoglobin, Serum ferritin, Serum iron

Introduction

Iron deficiency anemia (IDA) is common among children with chronic liver disease (CLD) and is mostly secondary to gastrointestinal bleeding [1]. The gold standard for diagnosis of iron deficiency is bone marrow biopsy, but it is infrequently ordered as it is invasive, painful, and carries a risk of bleeding or infection from the puncture site [2]. In clinical practice, the iron status is usually assessed based on serum ferritin levels [3]. However, the diagnosis of IDA among patients with chronic inflammatory conditions remains challenging because ferritin is an acute phase reactant, and its levels are elevated in chronic inflammatory conditions [4].

Reticulocyte hemoglobin concentration (Ret Hb) has been identified as a marker of iron availability for recent hemoglobin synthesis [4]. Unlike many iron markers, it is not affected by inflammation [5]. It has been investigated thoroughly among young healthy population and was found to be a strong predictor of iron deficiency [6, 7].

Several studies have also assessed the Ret Hb as an indicator of IDA among various inflammatory conditions, including patients with chronic kidney disease on peritoneal dialysis [8], children with cancer [9], and children with inflammatory bowel disease [10].

The aim of this study was to assess the diagnostic value of Ret Hb in detecting IDA among children with CLD.

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Materials and methods

This cross-sectional study was conducted on thirty-three children diagnosed with CLD who were regularly attending the pediatric hepatology outpatient clinic, Cairo University Pediatric Hospitals for routine follow-up.

The Cairo University Pediatric Hospitals are tertiary care hospitals, and this specialized clinic serves children referred from all outpatient general pediatrics clinics in the hospital as well as from other hospitals from different cities.

After receiving the results of the routine hematological and biochemical tests including complete blood count, ferritin, transferrin saturation, liver function tests, and coagulation profile performed at the clinic, further samples were withdrawn from patients who fulfilled the inclusion criteria. Purposive sampling is used.

Inclusion criteria were patients with liver disease more than 6 months aged 1–15 years and hemoglobin (Hb) < 11 g/dl and *MCV* < 77 fl. Patients who had received iron therapy or blood transfusion within the last 4 weeks and patients with recent febrile illness were excluded from the study.

This study has been approved on the 12th of October 2019 by the Research Ethics Committee at the Faculty of Medicine, Cairo University (Code: ms-112-2019).

After receiving an informed consent, all the recruited children were subjected to full history and examination suggestive of CLD and anemia.

Participants collected 2 ml blood samples anticoagulated with EDTA to perform reticulocytic count and reticulocyte hemoglobin and were analyzed using the Sysmex XE-2100 (by Sysmex Corporation Japan).

Normal reference range of ret Hb is 31.6 ± 1.3 pg [11].

Table 1 Presenting symptoms of the recruited patients (*N*=33)

Symptoms	Total Percentage *N*=33	
Abdominal pain	21	63.6%
Appetite loss	16	48.5%
Vomiting	9	27.3%
Diarrhea	8	24.2%
Nausea	7	21.2%
Jaundice	7	21%
Abdominal enlargement	6	18%
Flatulence	4	12.1%
Pruritis	4	11%
Constipation	3	9.1%
Dysentery	3	9.1%
Epigastric pain	2	6.1%
Dysphagia	1	3%
Hematemesis	1	3%

Data expressed by n (%)

Patients were divided into two groups according to serum ferritin being less or more than 100 ng/ml into anemia of chronic disease with or without iron deficiency respectively [12].

Mentzer index is an index used to differentiate IDA from beta thalassemia. Mentzer index = MCV/RBC count in millions. If > 13 then, IDA is more likely. If < 13 then, beta thalassemia is more likely [13].

Statistical analysis

The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version 24. Data were tested for normal distribution using the Shapiro-Wilk test. Qualitative data were represented as frequencies and relative percentages. Chi-square test (χ^2) and Fisher exact were used to calculate

Table 2 Hematological and biochemical parameters of all patients (*N*=33)

Parameter	Total *N*=33
Mean RBCs in 10^12/L ± SD	4.23±0.57
Median Hb in g/dl (range)	10.4 (8.4-10.9)
Mean Hematocrit in % ± SD	33.05±3.96
Mean MCH in pg ± SD	25.42±3.26
Median MCHC in g/dl (range)	33.5 (25.0-36.4)
Median MCV in fl (range)	72.6 (56.8-76.4)
Median RDW in %(range)	17.3 (13.1-26.3)
Mean WBCs in 10^9/L± SD	8.19±3.97
Median platelets in 10^9/L(range)	286.0 (51.0-564.0)
Mentzer index in % (range)	16.8 (13.3-23.9)
Reticulocytic count% (range)	1.0 (0.7-1.4)
Mean corrected reticulocytes ± SD	0.75±0.16
Mean reticulocytic Hb in pg ± SD	25.52±4.53
Mean serum iron in ug/dl ± SD	40.06±8.70
Mean serum ferritin in ng/ml ± SD	89.09±16.55
Mean TIBC in ug/dl ± SD	291.00±44.87
Mean transferrin saturation (TSAT%) ± SD	14±3
Median total protein in g/dl (range)	6.1 (5.1-8.7)
Mean albumin in g/dl ± SD	3.82±0.54
Median total bilirubin in mg/dl (range)	0.4 (0.1-20.0)
Median direct bilirubin in mg/dl(range)	0.1 (0.0-10.8)
Mean prothrombin time in sec ± SD	13.95±1.29
Median INR % (range)	1.1 (1.0-1.4)
Median AST in u/l (range)	75.0 (13.0-763.0)
Median ALT in u/l (range)	67.0 (10.0-891.0)
Median ALP in IU/L (range)	257.0 (133.0-972.0)
Median GGT in u/l (range)	54.0 (19.0-1116.0)

RBC Red blood cells, *HB* Hemoglobin, *MCH* Mean corpuscular hemoglobin, *MCHC* Mean corpuscular hemoglobin concentration, *MCV* Mean corpuscular volume, *RDW* Red cell distribution width, *WBCs* White blood cells, *TIBC* Total iron binding capacity, *INR* International normalized ratio, *AST* Aspartate transaminase, *ALT* Alanine transaminase, *ALP* Alkaline phosphatase, *GGT* Gamma glutamyl transferase

difference between qualitative variables as indicated. Quantitative data were expressed as mean ± SD (standard deviation) for parametric and median and range for nonparametric data. Independent *T*-test and Mann-Whitney test were used to calculate difference between quantitative variables in two groups for parametric and nonparametric variables respectively. Pearson's and Spearman's correlation tests were used for correlating normal and nonparametric variables respectively.

ROC curve was constructed to permit selection of threshold values for test results and comparison of different testing strategies. Areas under ROC curves and their standard errors were determined using the method of Centor, and compared using the normal distribution, with correction for correlation of observations derived from the same cases.

Results

This cross-sectional study was conducted on thirty-three patients with chronic liver diseases regularly attending the Pediatric Hepatology Clinic, Cairo University Children Hospital, and fulfilling the inclusion criteria.

The study group consisted of 54.5% males with male to female ratio 1.2:1. Median patient's age was 5.9 years

Table 3 Characteristics of patients as regard the presence of Iron Deficiency Anemia (*N*=33)

	IDA				***P*-value**
	No *N*=6		**Yes *N*=27**		
Sex					
F	4	66.7%	11	40.7%	0.249
M	2	33.3%	16	59.3%	
Age, years	6.0 (2.3-11.6)		5.8 (1.7-13.2)		0.815
Age of onset, Years	2.5 (0.8-7.4)		1.3 (0.0-11.8)		0.375
Duration of illness, Years	2.8 (1.0-4.0)		2.0 (1.0-10.0)		0.310
Mean RBCs in 10^12/L ± SD	4.21±0.59		4.24±0.58		0.963
Median Hb in g/dl (range)	10.4 (8.4-10.9)		10.4 (8.7-10.9)		0.814
Mean Hematocrit in % ± SD	32.30±4.78		33.21±3.84		0.779
Mean MCH in pg ± SD	25.18±5.19		25.47±2.82		0.963
Median MCHC in g/dl (range)	32.6 (25.0-35.2)		33.5 (29.6-36.4)		0.135
Median MCV in fl (range)	72.7 (56.8-75.5)		72.6 (58.8-76.4)		0.657
Median RDW in %(range)	20.1 (15.1-23.0)		17.3 (13.1-26.3)		0.691
Mean WBCs in 10^9/L± SD	7.67±4.60		8.31±3.91		0.691
Median platelets in 10^9/L(range)	235.5 (58.0-518.0)		286.0 (51.0-564.0)		0.558
Mentzer index in % (range)	16.1 (13.8-22.2)		16.8 (13.3-23.9)		0.607
Median reticulocytic count% (range)	1.1 (1.0-1.2)		1.0 (0.7-1.4)		0.271
Mean corrected reticulocytes ± SD	0.79±0.13		0.75±0.17		0.640
Mean reticulocytic Hb, pg ± SD	30.33±4.80		24.46±3.79		0.014
Mean serum iron in ug/dl ± SD	38.33±10.65		40.44±8.40		0.575
Mean serum ferritin in ng/ml ± SD	113.33±7.45		83.70±12.68		**<0.001**
Mean TIBC in ug/dl ± SD	307.00±44.16		287.44±45.07		0.454
Mean transferrin saturation (TSAT%) ± SD	0.12±0.03		0.14±0.02		0.102
Median total protein in g/dl (range)	6.2 (5.6-6.9)		6.1 (5.1-8.7)		0.815
Mean albumin in g/dl ± SD	3.82±0.40		3.82±0.57		0.944
Median total bilirubin in mg/dl (range)	0.4 (0.3-0.9)		0.4 (0.1-20.0)		0.981
Median direct bilirubin in mg/dl(range)	0.1 (0.0-0.2)		0.1 (0.0-10.8)		0.200
Mean prothrombin time in sec ± SD	14.55±1.56		13.82±1.22		0.252
Median INR % (range)	1.1 (1.0-1.4)		1.1 (1.0-1.3)		0.814
Median AST in u/l (range)	58.5 (13.0-245.0)		75.0 (22.0-763.0)		0.691
Median ALT in u/l (range)	47.5 (12.0-301.0)		68.0 (10.0-891.0)		0.779
Median ALP in IU/L (range)	201.0 (169.0-380.0)		291.0 (133.0-972.0)		0.161
Median GGT in u/l (range)	39.0 (22.0-90.0)		57.0 (19.0-1116.0)		0.252

RBC Red blood cells, *HB* Hemoglobin, *MCH* Mean corpuscular hemoglobin, *MCHC* Mean corpuscular hemoglobin concentration, *MCV* Mean corpuscular volume, *RDW* Red cell distribution width, *WBCs* White blood cells, *TIBC* Total iron binding capacity, *INR* International normalized ratio, *AST* Aspartate transaminase, *ALT* Alanine transaminase, *ALP* Alkaline phosphatase, *GGT* Gamma glutamyl transferase

with range between 1.7 and 13.2 years. A total of 57% of patients were the product of consanguineous marriages, and 24.2% had similar conditions of CLD in family.

The presenting symptoms were as follows: abdominal pain (63.6%) followed by loss of appetite in 48.5%, vomiting in 27.3%, diarrhea in 24.2%, nausea (21.2%), and others as presented in Table 1.

Patients presented mostly with manifestations of anemia in terms of easy fatigability in 60.6% of cases, loss of appetite in 42.4%, dyspnea in 21.2%, and Pica in 12.1%.

The most common diseases were glycogen storage disease (25%), followed by cholestasis (21%), extrahepatic portal vein obstruction (6%), hepatitis B virus (6%), autoimmune hepatitis (3%), chronic hepatic fibrosis (3%), failed Kasai (3%), fatty liver (3%), hepatitis C virus (3%), progressive familial intrahepatic cholestasis (3%), polycystic kidney and liver (3%), and Wilson disease (3%). In 18%, the etiology of the underlying chronic liver disease is still questionable.

The median age of onset of chronic liver disease was 1.6 years with range 0.5–11.8 years.

The various hematological and biochemical parameters of our study population are shown in Table 2. It is to be noted that the median Hb level was 10.4 gm/dl (8.4–10.9 gm/dl), and the mean reticulocytic Hb was 25.52 ± 4.53 pg.

We divided our patients into two groups according to serum ferritin level. The group of IDA had a serum ferritin below or equal to 100 ng/ml, and the group without IDA had a serum ferritin above 100 ng/ml [12]. We compared the hematological and biochemical parameters of the 2 groups (Table 3). Twenty-seven patients had IDA.

We found statistically significant difference between both groups regarding reticulocyte hemoglobin which were lower in the group with IDA ($p = 0.014$). There was no statistically significant difference otherwise as further shown in Table 3.

Correlations between Ret Hb and various parameters are shown in Table 4. A statistically positive significant linear correlation was found between serum ferritin and Ret-Hb, $r = +0.433$, $p = 0.012$.

Reticulocytic Hb, at cutoff $\leq$ 29.3 pg, had an AUC of 0.824 (95% *CI*, 0.652 to 0.934) with a sensitivity of 92.59% (95% *CI*, 75.7–99.1%) and a specificity of 83.33% (95% *CI*, 35.9–99.6%), $p = 0.012$, as presented in Table 5.

There was a statistically significant difference between IDA children and children with no IDA with regard to interpretation of retic. Hb with p-value < 0.001 as most IDA children had low retic. Hb, determined by ROC curve as shown in Fig. 1.

Table 4 Correlations between Reticulocytic Hb and certain studied parameters in the whole group

Parameter	Reticulocytic Hb, pg	
	Correlation Coefficient	*P*-value
RBCs	0.041	0.821
Serum ferritin	**0.433**	**0.012**
Hb	0.230	0.197
Hematocrit	0.140	0.437
MCH	-0.199	0.266
MCHC	-0.156	0.387
MCV	-0.049	0.787
RDW	0.007	0.971
Reticulocytic count%	0.099	0.584
Corrected reticulocytes	0.191	0.286
WBCs	0.175	0.331
Platelets	0.117	0.516
Mentzer index	-0.122	0.498
Serum iron	0.178	0.321
TIBC	0.258	0.148
Transferrin saturation (TSAT %)	-0.057	0.754

RBC Red blood cells, *HB* Hemoglobin, *MCH* Mean corpuscular hemoglobin, *MCHC* Mean corpuscular hemoglobin concentration, *MCV* Mean corpuscular volume, *RDW* Red cell distribution width, *WBCs* White blood cells, *TIBC* Total iron binding capacity

Discussion

Anemia is common among children with chronic liver diseases mainly iron deficiency anemia due to gastrointestinal bleeding. Mean Ret Hb in our study was 25.52 pg which is lower than that reported in other studies. Levels reported ranged between 29.8 and 32.4 pg, among patients with IBD, peritoneal dialysis, and hemodialysis [8, 10, 14]. This difference could be due to differences in the type, age, and duration of the primary illness.

There was no significant difference in hemoglobin values between both our patients' groups; however, Ret Hb was significantly lower among patients with IDA. This is in consistency with Singh et al. [15] in 2019 who evaluated the role of Ret Hb in classification of anemia among patients with rheumatological diseases in adults. Singh reported a significant difference in Ret Hb being lower among patients with IDA than patients with anemia of chronic disease.

In our study, Ret Hb correlated well with serum ferritin but not with transferrin saturation, hemoglobin, or reticulocytic count. This is in contrast with the study conducted by Davidkova [8] and colleagues in 2016 where Ret Hb modestly correlated with the same parameters. The poor association between Ret Hb and reticulocytic count may be expected due to the timing of observations. During erythropoiesis, Ret Hb increases earlier than reticulocytic count by a few days, with the reticulocyte count subsequently returning to normal once hemoglobin has been corrected. Therefore, a concurrent Ret Hb and reticulocyte count will not show a correlation unless improved iron status has only recently occured [8].

Table 5 The value of Reticulocytic Hemoglobin with area under the ROC curve as a diagnostic marker for Iron Ddeficiency Anemia in patients with Chronic Liver Disease

Cut-off	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	AUC (95% CI)	Z	*P*
≤29.3	92.59 75.7 - 99.1	83.33 35.9 - 99.6	96.2 80.6 - 99.3	71.4 38.6 - 90.9	0.824 0.652 -0.934	2.5	**0.012**

CI Confidence interval, *PPV* Positive predictive value, *NPV* Negative predictive value

In the current study, at cutoff ≤ 29.3 pg, we had an AUC of 0.824 with a sensitivity of 92.59% and specificity of 83.3%. Other studies reported a variable range of cutoff values from 27.5 to 34 pg with range of sensitivity from 74.3 to 90% and specificity from 60 to 75% among patients with different chronic inflammatory disorders [6, 8, 10, 14]. We think that our different cutoff values for Ret Hb could be due to lack of comparing our results to bone marrow iron as the "gold standard" [15] as well as the high prevalence of chronic inflammation in our study population.

Reticulocyte Hb has a better advantage in screening for iron deficiency because it is not affected by the variabilities that affect serum iron, TIBC, and serum ferritin levels [5]. However, there is no standardized cutoff point, and different researchers use varying cutoff values which affect its accuracy in diagnosing iron deficiency, and it should therefore be standardized.

In addition to that, reticulocyte Hb is an easily available parameter as it is reportable on common automated hematology analyzers without extra blood requirements or technical intervention [16]. Thus, full blood count, reticulocyte count, and iron status of the patient can be obtained from a single blood sample which is beneficial especially in the case of young children.

Our study demonstrated that most of our chronic liver disease patients proved to be iron deficient. This illustrated that their anemia is more due to iron deficiency than just being a net result of their chronic inflammatory condition. Although the chronicity of liver disease is a quite enough reason for anemia to present as a result of chronic inflammation, bone marrow

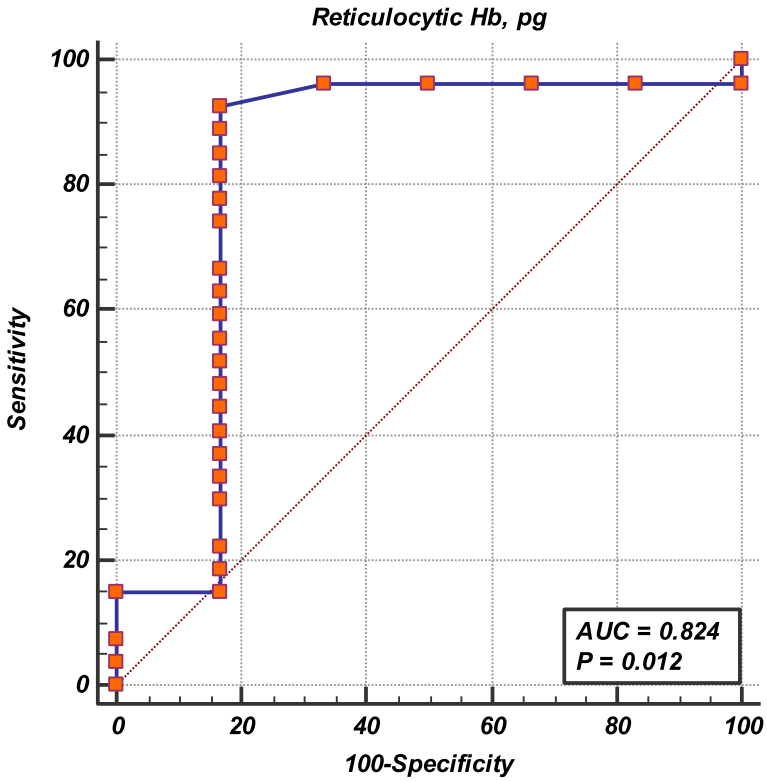

Fig. 1 The usefulness of Reticulocytic Hb with area under the ROC curve (AUC) as a diagnostic marker for iron deficiency anemia in patients with CLD

suppression, or ineffective erythropoiesis, patients with chronic liver disease who are anemic need to be regularly evaluated for iron deficiency and should be offered optimum management and follow-up.

Until the time of writing this manuscript, this is the first reported study to assess the Ret Hb among children with chronic liver disease. However, there are several limitations to our study. The small sample size does not allow for definitive diagnosis to be made. A CRP was not as well carried out to detect the inflammatory status of our patients.

In conclusion, reticulocyte hemoglobin correlated well with serum ferritin and is a useful and readily available parameter to check iron deficiency anemia among patients with CLD.

Abbreviations
IDA: Iron deficiency anemia; CLD: Chronic liver disease; Ret Hb: Reticulocyte hemoglobin; EDTA: Ethylenediaminetetraacetic acid; MCV: Mean corpuscular volume; RBC: Red blood cells; Hb: Hemoglobin; SSPS: Statistical Package for Social Science; ROC: Receiver operating characteristic curve; AUC: Area under the curve; CRP: C-reactive protein.

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Authors' contributions
KB collected and analyzed patients' data. MN was a major contributor in writing the script. The authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study has been approved on the 12th of October 2019 by the Research Ethics Committee at the Faculty of Medicine, Cairo University (Code: ms-112-2019).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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