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## Serum ferritin as an indicator of body iron stores in anemic patients

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### Abstract

Serum ferritin concentrations have been documented to give an accurate indication of the amount of storage iron not only in healthy individuals but also in cases of iron deficiency or iron over load. A low serum ferritin is highly indicative of deficient iron stores. Values less than 15ng/ml are indicative of negative iron balance or decreased stores. In cases of anemia of chronic diseases, serum ferritin levels are increased as serum ferritin is an acute phase reactant. Thus, in patients of anemia of chronic diseases with concomitant iron deficiency, serum ferritin may not be below 15ng/ml and serum ferritin may not give a true picture of deficiency in these patients. In the present study, we determined the role of serum ferritin as an indicator of body iron stores along with the cut-off value for serum ferritin to detect hypoferrremia in patients of anemia of chronic diseases.

**Keywords:** Serum ferritin, anemia, iron deficiency, anemia of chronic disorders

### Introduction

One third of the world population is affected by anemia, with nearly half of the patients with anemia suffering from iron deficiency <sup>[1]</sup> followed by other micronutrient deficiencies like folate and vitamin B12 <sup>[2]</sup>. Anemia of chronic diseases with or without concomitant iron deficiency is also very common in hospitalized patients. Various markers like serum ferritin, serum iron, transferrin saturation and total iron binding capacity, are used to assess the iron status of an individual, however for determining the total body iron stores, microscopic examination of the stainable iron in the bone marrow is considered the gold standard <sup>[3]</sup>. Serum ferritin concentrations have been documented to give an accurate indication of the amount of storage iron not only in healthy individuals but also in cases of iron deficiency or iron over load. A low serum ferritin is highly indicative of deficient iron stores. Values less than 15ng/ml are indicative of negative iron balance or decreased stores <sup>[4]</sup>. In megaloblastic anemia, serum ferritin levels are increased and an inverse correlation is seen between serum ferritin and hemoglobin values in these patients <sup>[5]</sup>. In cases of anemia of chronic diseases, serum ferritin levels are increased as serum ferritin is an acute phase reactant <sup>[6]</sup>. Thus, in patients of anemia of chronic diseases with concomitant iron deficiency, serum ferritin may not be below 15ng/ml. Hence, serum ferritin may not give a true picture of deficiency in these patients which mandates the need to perform bone marrow aspiration for iron stores. However, serum ferritin values less than 100ng/ml in these patients are generally associated with depleted iron stores <sup>[7]</sup>.

### Aim & Objective

To determine the role of serum ferritin as an indicator of body iron stores in anemic patients.  
To determine cut-off value for serum ferritin to detect hypoferrremia in patients of anemia of chronic diseases.

### Material and Methods

#### Source of data

The present study was conducted in the Postgraduate Department of Pathology in collaboration with Department of Medicine, Acharya Shri Chander College of Medical Sciences and Hospital, Sidhra, Jammu over a period of one year i.e. from 1<sup>st</sup> November 2017 to 31<sup>st</sup> October 2018.

Anemic patients admitted in the wards of the Department of Medicine, diagnosed during the study period, formed the study group. All the patients were explained the nature and purpose of the study. The patients were enrolled according to the following inclusion and exclusion criteria:

**Inclusion criteria**

1. Anemic patients referred to the pathology department by medicine department for bone marrow aspiration.
2. Patients with serum ferritin determinations performed the day before, or on the day of bone marrow aspiration.

**Exclusion criteria**

1. Patients on hematinics.
2. Patients who were given recent blood transfusions.

**Data collection**

A detailed clinical history regarding nature and duration of illness, loss of weight and any history of drug intake or blood transfusion in the past were taken. Besides this, history of any chronic disease like tuberculosis, inflammatory bowel disease, chronic pneumonitis, rheumatoid arthritis, dermatitis, allergy, as well as chronic kidney failure or any other kidney disease was taken. This was followed by general physical and systemic examination. The physical findings that were studied included general well being, pallor, plethora, breathlessness, koilonychias, gum hypertrophy, angular stomatitis, tongue smoothness, colour, lymph node examination and examination of abdomen.

A complete blood count (CBC) including haemoglobin estimation, total leucocyte count (TLC), differential leucocyte count (DLC), hematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), red cell distribution width (RDW) and platelet count, was performed for each patient.

Peripheral blood film was stained with Leishman’s stain for each patient and studied for RBC morphology and other blood cell components.

Anemia was graded according to WHO standards [8]. Serum ferritin estimation was carried out in each case. For serum ferritin, reference range of 15-300 µg/l was taken as normal. [9]. Serum ferritin values were estimated by Enzyme Linked Immunosorbent Assay (ELISA) method.

Bone marrow aspiration was done from posterior superior iliac spine under complete aseptic conditions using Salah’s aspiration needle. A written, informed consent was obtained from each patient undergoing the procedure. Air-dried films of bone marrow aspirates were fixed in methanol for 10 to 20 minutes, then stained by May-Grunwald Giemsa stain for morphologic study and by the Prussian blue reagent for evaluation of iron stores.

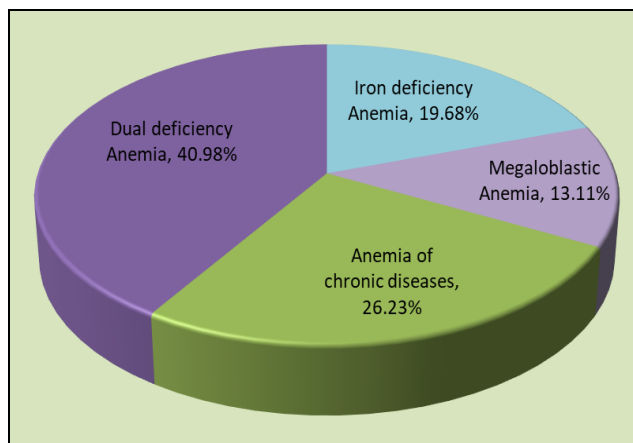
The amount of iron stores in the bone marrow aspirate were graded without previous knowledge of the serum ferritin value. Iron stores were graded from 0 to 6 according to the Gale’s criteria: [9].

All clinical and laboratory data was recorded in a pre-structured proforma.

**Observations**

A total of 61 patients were included in the present study. Mean age of the study group was 54.96 years with most of

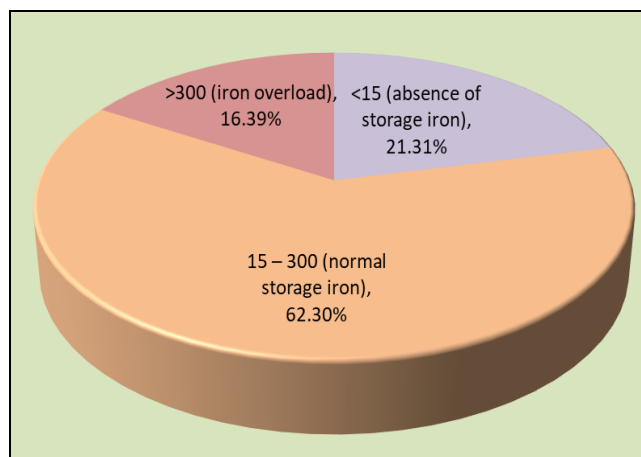
the patients being above 50 years of age. (59.02%). There were more female patients (55.74%) as compared to male patients (44.26%), with male to female ratio of 1:1.26. Moderate to severe anemia was present in the study group with a mean Hb of 5.53 (range, 2.8-10) g/dl. Dimorphic picture was the commonest pattern followed by microcytic hypochromic red cell morphology, constituting 3/4<sup>th</sup> of all cases of anemia. Diagnosis of iron deficiency anemia (IDA) and megaloblastic anemia (MA) and Dual deficiency anemia (DA) was based on complete blood count (CBC), peripheral blood film (PBF) and bone marrow examination. The patients who had known clinical history of kidney disease, liver parenchyma diseases, rheumatoid arthritis and malignancies, along with their CBC, PBF and bone marrow examination, were diagnosed as Anemia of Chronic Diseases (ACD).



**Fig 1:** Pie chart showing diagnostic categories

According to Gale’s grading, hypoferrimic state (Grade 0,1) was observed in 29 (47.54%) patients, normal iron stores (Grade 2,3) in 23 (37.71%) and increased iron stores in 9 (14.75%) patients. Serum ferritin concentration of 15-300 ng/mL indicating normal storage iron was observed in 38 (62.30%) patients, <15 ng/mL indicating absence of storage iron in 13 (21.31%) patients and >300 ng/mL indicating iron overload in 10 (16.39%) patients.

Mean serum ferritin concentration of the study group was 160.90 with a range of 0.96-1009 ng/mL.



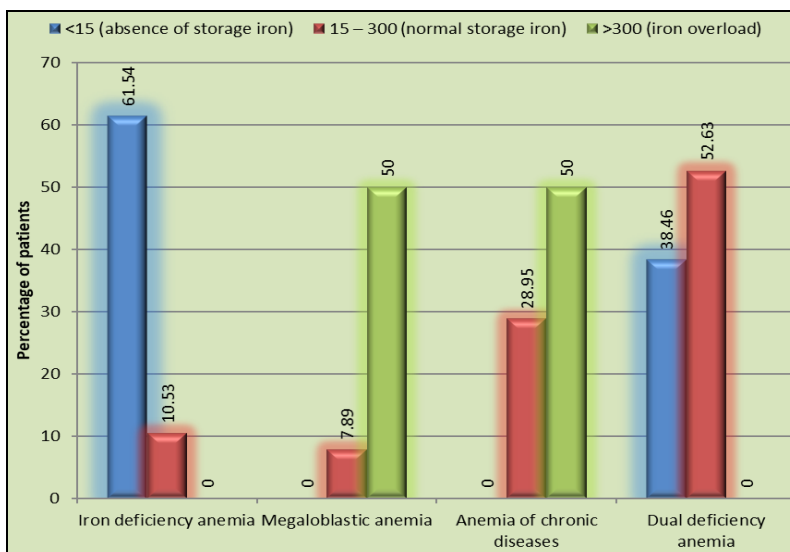
**Fig 2:** Pie chart showing distribution of patients according to serum ferritin concentration (ng/mL)

When serum ferritin concentration was <15 ng/mL, iron deficiency anemia was observed in 8 (61.54%) and dual deficiency anemia in 5 (38.46%) patients.

When serum ferritin concentration was in the range of 15-300 ng/mL, dual deficiency anemia was observed in 20 (52.63%), anemia of chronic diseases in 11 (28.95%), iron

deficiency anemia in 4 (10.53%) and megaloblastic anemia in 3 (7.89%) patients.

When serum ferritin concentration was >300 ng/mL, megaloblastic anemia and anemia of chronic disorder was observed in 5 (50%) patients each.



**Fig 3:** Histogram showing relationship of serum ferritin concentration with different types of anemia

**Serum ferritin and Iron deficiency anemia**

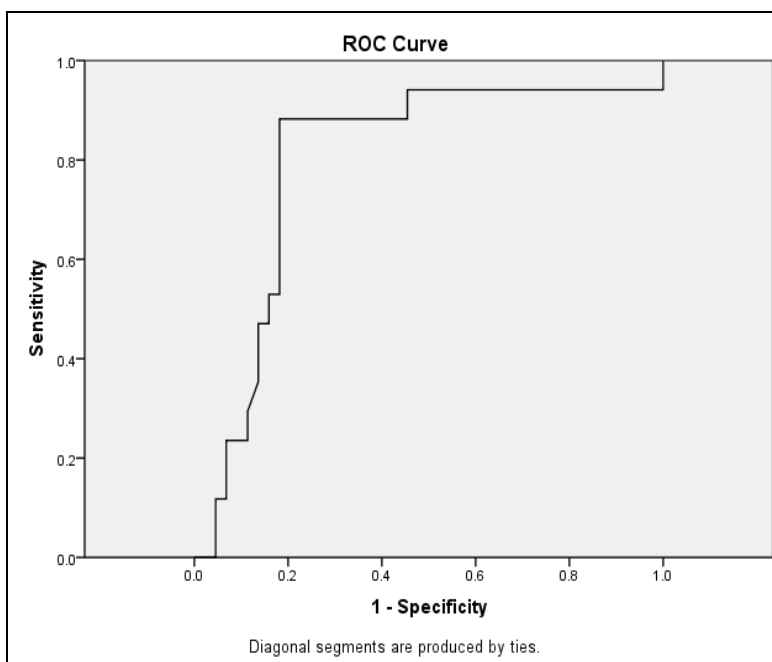
Out of 13 patients with iron deficiency anemia, 8 had serum ferritin values <15 ng/ml whereas 4 patients had serum ferritin values >15 ng/ml. Bone marrow iron stores for these 4 patients were reduced (Grade 0,1). On further history taking, it was revealed to us that out of the 4 patients who had serum ferritin >15ng/ml, 2 had active hepatitis and 1 had rheumatoid arthritis and 1 had acute gastro-enteritis.

**Serum ferritin and ACD**

Out of the 16 patients of Anemia of chronic diseases orders, 11 had serum ferritin values between 15-300 ng/ml and 5

patients had serum ferritin values >300 mg/dl. Out of the 11 patients with serum ferritin between 15-300 mg/dl, 6 patients had serum ferritin values ranging from 55.2-110 mg/dl. Perl’s stain for bone marrow iron showed that iron stores for these 6 patients were also reduced. This suggested that these patients also had concomitant iron deficiency.

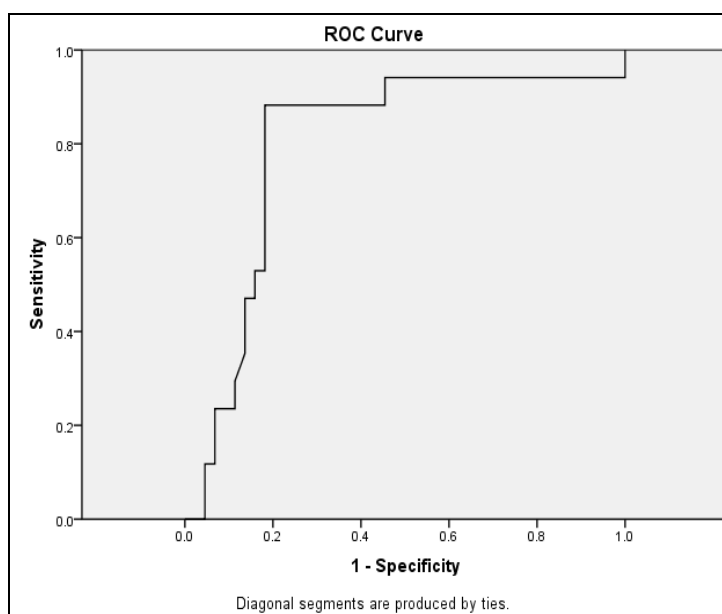
**Receiver operating characteristic curve (ROC):** Analysis when applied for the 11 patients with pure ACD, a cut-off value of 170.0 was 100% sensitive and 84.3% specific.



**Fig 4:** ROC curve for patients with pure ACD

**Receiver operating characteristic curve (ROC):** Analysis for the 6 patients of ACD with concomitant IDA gave a cut-

off value of 89.75 with a sensitivity of 88.2% and a specificity of 81.8%.



**Fig 5:** ROC curve for patients ACD with concomitant IDA.

## Discussion

Dual deficiency anemia (DA) was the commonest pattern of anemia in the present study (39.35%). It has been seen among nutritional deficiency anemia, a good proportion of cases show combined deficiency of iron, vitamin B12 and folic acid, where multiple factors affect the diagnostic parameters, resulting in discordant results of tests like bone marrow morphology, iron stores and iron studies. Dual deficiency anemia was followed by ACD (26.23%), which is the most common cause of anemia in hospitalised patients [10], followed by iron deficiency anemia (21.31%) and megaloblastic anemia (13.11%). These diagnostic pattern of anemia was in contrast to the study by Pujara *et al*, 2014 [11] who reported that most of the patients in their study group had iron deficiency anemia, followed by megaloblastic anemia, dimorphic anemia and hemolytic anemia. Ferritin, the intracellular storage form of iron, is found chiefly in the cytoplasm of the cells of the reticuloendothelial system. It can be quantified in serum using immunoenzymatic assays. Serum ferritin concentrations have been documented to give an accurate indication of the amount of storage iron in healthy individuals as well as in patients with iron deficiency or iron overload. In ACD, there is disturbance in iron metabolism with normal or increased serum ferritin and increased/normal bone marrow iron stores but iron is not available for erythropoiesis [12]. Most of the patients of ACD, in the present study, had increased serum ferritin values with increased bone marrow iron stores. However, there were 6 patients of ACD out of 16 who had normal serum ferritin values, between 55.2-110 ng/ml, but their bone marrow iron stores were reduced (Grade1). Serum iron values done separately in these 6 patients also revealed reduced values. These patients thus had ACD with concomitant iron deficiency. It is in these patients of ACD, that serum ferritin is not a reliable marker to assess total body iron stores, which mandates these patients to undergo bone marrow aspiration. Based on our observations, serum ferritin value >170.0 ng/ml is always indicative of pure

ACD; whereas serum ferritin value <89.75 ng/ml indicates ACD with concomitant IDA. Sears *et al*, 1992 [13] gave a serum ferritin value  $\leq 50$  ng/ml, for iron deficiency in anemic patients with coexisting chronic disease states such as inflammation, infection, and malignancy.

Serum ferritin is the most specific biochemical test for iron deficiency anemia (IDA) as it correlates with total body iron stores and a low serum ferritin concentration reflects depleted iron stores [14]. According to the World Health Organization (WHO), IDA is diagnosed with serum ferritin cut-off levels of 15 ng/mL. However there are many problems associated with the interpretation of serum ferritin levels. In our study, 4 out of 12 patients with IDA had serum ferritin >15 ng/ml. Out of these 4 patients, 1 had rheumatoid arthritis, 2 had active hepatitis and 1 had acute gastroenteritis. Presence of these inflammatory conditions can be attributed to the raised serum ferritin values in these 4 patients. Our findings were in agreement with the previous studies by Prieto *et al*, 1973, [15] Giler *et al*, 1979 [16] and Bentley *et al*, 1974 [17] that hepatic-parenchymal disease, breast carcinoma and acute inflammatory states are conditions that can increase serum ferritin levels even in presence of iron deficiency. In such conditions, when iron deficiency is suspected, a bone marrow aspiration is necessary.

It is found that there is an inverse correlation between serum ferritin and hemoglobin concentration in patients with megaloblastic anemia. Serum ferritin reflects reticuloendothelial iron and the high levels in megaloblastic anemia are due to the shift in iron from hemoglobin to reticuloendothelial stores [18]. In our study, most of the patients (62.5%) with megaloblastic anemia had raised serum ferritin (>300 ng/ml) with raised bone marrow iron stores (grade 4). This corresponds to a study by Kalvakuri *et al*, 2016 [19] where mean serum ferritin for 38 children with megaloblastic anemia was significantly higher than mean of normal healthy controls.

Kalvakuri *et al*, 2016 [19] concluded that serum ferritin is

moderately raised in dimorphic anemia. Majority of patients (54.17%) with dual deficiency anemia in the present study, who had serum ferritin within normal limits (15-300 ng/ml), had normal bone marrow iron stores.

### Conclusion

Our study thus shows that serum ferritin is a good indicator of bone marrow iron stores in the body and is helpful in diagnosis of pure IDA as well as ACD. Bone marrow aspiration may not be required for estimation of body iron stores in these patients. However, in patients of ACD, who have concomitant iron deficiency, serum ferritin may be normal but bone marrow iron stores may be reduced. In these patients, bone marrow aspiration is advised, to determine total body iron stores.

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