

Original Research Article

Evaluation of iron status in patients with end stage renal disease

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ABSTRACT

Background: Anaemia is almost universal in haemodialysis patients. Here, we evaluated the utility and clinical implications of the commonly employed tests in assessing iron status in haemodialysis patients.

Methods: In this prospective observational study, we enrolled 100 prevalent haemodialysis patients, and measured transferrin saturation (TSAT) and serum ferritin at enrolment. Patients were categorized to have normal, deficient, overload, or indeterminate status of iron based on KDOQI guidelines. To study anaemia trend, haemoglobin (Hb) level at time of enrolment, as well as levels 3-months before and 3-months after enrolment, were collected. Patient survival outcomes were also obtained till October 2016.

Results: Using serum ferritin and TSAT, iron status was determinable in 48% of the patients ie 20%-normal iron status, 25% - iron deficiency, 3% - iron overload. Fifty-two percent of the patients' iron status was indeterminate by current parameters. In spite of being on standard-of-care treatment in our centre, we observed that mean-Hb level of patients in the indeterminate group showed insignificant increases compared to normal- and deficient-groups. Mean delta-Hb levels over 6-months were 0.80 ± 1.54 g/dl in the indeterminate group, compared to 1.87 ± 1.95 g/dl in the deficient group ($P=0.03$). In our cohort, 57% had died and 5 lost follow-ups during the study ($P=0.30$ between groups).

Conclusions: Serum ferritin and TSAT accurately categorized the iron status of 48% haemodialysis patients in our study. Divergent serum ferritin and TSAT values, or an iron indeterminate state was prevalent in 52% of our urban dialysis cohort. The indeterminate group had inferior increases in Hb over time with current treatment, showing clinical relevance of this finding. Our data suggests the need for more sensitive indices to accurately assess iron status, and improve anaemia management.

Keywords: ESRD patients, Iron status, Serum ferritin, TSAT

INTRODUCTION

Anaemia is frequently found in chronic kidney disease (CKD) patients and is an almost universal finding in

patients with end stage renal disease (ESRD).¹ Additionally, anaemia is associated with increased cardiovascular morbidity and mortality in this patient population.²

The pathophysiology of anaemia in CKD is multifactorial.³ The proximate cause of the anaemia is relative deficiency of erythropoietin, a glycoprotein produced by renal tubular cells. Other factors which may cause or contribute to anaemia includes iron deficiency, vitamin B12 and/or folic acid deficiency, decreased erythrocyte survival, severe hyperparathyroidism, aluminium toxicity and hypothyroidism. The use of erythrocyte stimulating agents (ESA) such as recombinant human erythropoietin (EPO) began two decades ago and has revolutionized the treatment of anaemia in ESRD. This has decreased the need for blood transfusions and consequently the incidence of associated complications.⁴

Despite the widespread use of EPO, over 50% of the patients do not reach target haemoglobin levels.^{1,5} Resistance to erythropoietin most commonly is due to iron deficiency but chronic inflammation, infection, and/or hyperparathyroidism also contribute.^{6,7} Iron deficiency in ESRD is primarily due to impaired dietary intake and impaired gastrointestinal absorption but blood loss during haemodialysis and increased iron demands from ESA use also contribute.⁸ Management of iron deficit is crucial in haemodialysis patients. Adequate treatment of iron deficiency is vital to attain target haemoglobin concentration and avoid excessively high EPO doses, which has been associated with increased risk of malignancy.⁹ Furthermore, IV iron and blood transfusions both increase the risk of developing hospital acquired infections.^{10,11} Therefore effective treatment of anaemia in haemodialysis patients requires continuous assessment of iron status.

Serum ferritin and transferrin saturation (TSAT) are the commonly used tests for the assessment of iron status in ESRD. However, measurement of these parameters in ESRD patients may be altered by inflammation, infection, or nutritional status.¹² Therefore, we conducted this study to evaluate the utility of the common tests, serum ferritin and TSAT, in assessing iron status in haemodialysis patients. In order to examine the clinical utility of iron status as defined by the current guidelines, we evaluated anaemia in this cohort, as well as patient outcomes.

METHODS

This study was conducted from August 2011 to March 2012 in a large tertiary care teaching hospital in South India. The study was conducted among the ESRD patients undergoing haemodialysis. All ESRD patients on haemodialysis for at least 3 months were enrolled in the study after the application of the exclusion criteria and after obtaining informed consent. The study was done after obtaining institutional ethical committee clearance. The exclusion criteria were: age less than 18 years old, evidence of acute or chronic infection, trauma within the previous 4 weeks, recent bleeding episodes, blood transfusion within the last one month, malignancy, post-

transplant status, liver disease, haemoglobinopathies and other haematological diseases. The diagnostic biochemical tests used to assess the iron status were TSAT and serum ferritin.

Patients were categorized to have normal, deficient, overload, or indeterminate status of iron based on serum ferritin and TSAT values. Based on NKF-DOQI guidelines, iron deficiency is taken as ferritin level less than 200mg/dl and TSAT less than 20%, iron overload as ferritin level more than 500 mg/dl and TSAT more than 50%. The values in between the above ranges (ferritin between 200 and 500 mg/dl; TSAT between 20 and 50 %) are considered as normal iron status, whereas values not conforming to these categories are said to be indeterminate. The combined utility of the above tests in assessing iron status was determined by dividing the number of patients in whom iron status was detected (normal, deficient or overload) by total number of patients and expressed in percentage. The haemoglobin level of all the enrolled patients at time of enrolment was collected. To determine haemoglobin trend within each group, we collected haemoglobin levels 3-months before and 3-months after enrolment from chart review. Patient outcomes (death, alive and lost follow up) were obtained by chart review and telephone-follow up till October 2016.

Statistical analysis

The data were analysed using Statistical Package for Social Science (SPSS) Version 19.0, Graphpad Prism-6 and Microsoft Excel 2010. Non-parametric characteristics between any two groups were compared using Mann-Whitney test, and proportions using Chi-square test. For comparing more than two mean values we have used one-way analysis of variance. P value less than 0.05 was considered as statistically significant.

RESULTS

Demographics of study population

A total of 100 prevalent ESRD patients on haemodialysis were studied. The key demographics of the study cohort are summarized in Table 1. Patients ranged from 18 to 80 years. The mean age of the patients was 48.5 years. Among 100 patients, 63 were male and 37 were female.

Description by iron status

We classified these patients based on their iron status as per the NKF-KDOQI (see methods). Using serum ferritin and TSAT, iron status could be determined in 48% of the patients; 20% had normal iron status, 25% had iron deficiency, 3% had iron overload. The remaining 52% of the patient's iron status was indeterminate (Table 1 and 2). In univariate analysis, patients who were iron indeterminate were nearly indistinguishable from other groups by clinical and epidemiologic variables (as shown

in Table 1). However interestingly, iron indeterminate and overload groups had significantly greater dialysis

vintage than the normal/iron-deficient groups.

Table 1: Baseline demographic characteristics.

Groups	Total n=100	Diagnosed n=48	Indeterminate n=52			P Value
		Normal-1 n=20	Deficient-2 n=25	Overload-3 n=3	Indeterminate-4 n=52	
	Mean (SD)	Mean(SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	48.5 (13.91)	43.85 (11.75)	48.56 (13.18)	48.66 (23.18)	50.25 (14.48)	0.38
Sex						
Male (%)	63 (63)	12 (60)	17 (68)	1 (33.3)	33 (63.5)	0.68
Female (%)	37 (37)	8 (40)	8 (32)	2 (66.7)	19 (36.5)	
Vintage (duration in months)	21 (18.76)	13.65 (11.96)	15.88 (13.09)	48.00 (41.56)	24.73 (19.75)	0.003
Diabetes mellitus (%)	30 (30)	5 (25)	9 (36)	0 (0)	16 (30.8)	0.57
Systemic Hypertension (%)	84 (84)	16 (80)	24 (96)	2 (66.7)	42 (80.8)	0.26
Cardiac disease (%)	12 (12)	2 (10)	5 (20)	0 (0)	5 (9.6)	0.51
Iron supplements (route and duration)						0.24
Oral >6months	27 (27)	2 (10)	6 (24)	2 (66.7)	17 (32.7)	
Oral < 6months	13 (13)	3 (15)	4 (16)	0 (0)	6 (11.5)	
IV > 6months	28 (28)	6 (30)	4 (16)	0 (0)	18 (34.6)	
IV<6months	16 (16)	6 (30)	5 (20)	0 (0)	5 (9.6)	
No iron supplements	16 (16)	3 (15)	6 (24)	1 (33.3)	6 (11.5)	
Haemoglobin (g/dL)	7.95 (1.74)	8.14 (1.76)	7.23 (1.60)	8.26 (2.39)	8.21 (1.71)	0.12
Ferritin (ng/mL)	423.12 (388.61)	346.40 (86.87)	114.2 (48.45)	1446.00 (549.06)	542.13 (390.31)	<0.001
TSAT (expressed in %)	23.94 (11.58)	27.68 (5.57)	14.69 (4.15)	61.27 (8.94)	24.80 (10.37)	<0.001
Iron (micro g/dL)	59.62 (25.91)	66.45 (20.86)	43.32 (12.83)	106.00 (72.95)	62.15 (23.95)	<0.001
TIBC (micro g/dL)	260.97 (63.31)	240.55 (57.80)	300.20 (71.09)	164.33 (89.01)	255.53 (48.46)	<0.001
Died (%)	57 (57)	9 (45)	14 (56)	3 (100)	31 (59.6)	0.30

TSAT: Transferrin saturation, TIBC: Total iron binding capacity.

Table 2: Iron status of patients.

Iron status	Number of patients	Percentage (%)	TSAT (expressed in %)		Ferritin (ng/mL)	
			Mean	SD	Mean	SD
Diagnosed	48	48	23.02	12.81	294.18	346.62
Normal	20	20	27.68	5.57	346.4	86.87
Deficient	25	25	14.69	4.15	114.2	48.45
Overload	3	3	61.27	8.94	1446	549.06
Indeterminate status	52	52	24.80	10.37	542.13	390.31
High serum ferritin-normal TSAT	22	22	29.54	8.28	805.13	413.67
High serum ferritin-low TSAT	4	4	18.49	2.24	815	195.30
High TSAT- normal ferritin	1	1	67.95		496	
High TSAT-low ferritin	0	0				
Low ferritin-normal TSAT	11	11	25.49	4.35	154.54	40.18
Low TSAT-normal ferritin	14	14	15.53	2.98	358.71	87.84

TSAT: Transferrin saturation.

Outcomes by iron status

Anaemia outcomes: To examine the haemoglobin responses and anaemia, trends of patients according to

iron status, we tabulated haemoglobin levels of patients in each group by iron status at enrolment at different time points before- and after- study enrolment (Figure 1 and Figure 2).

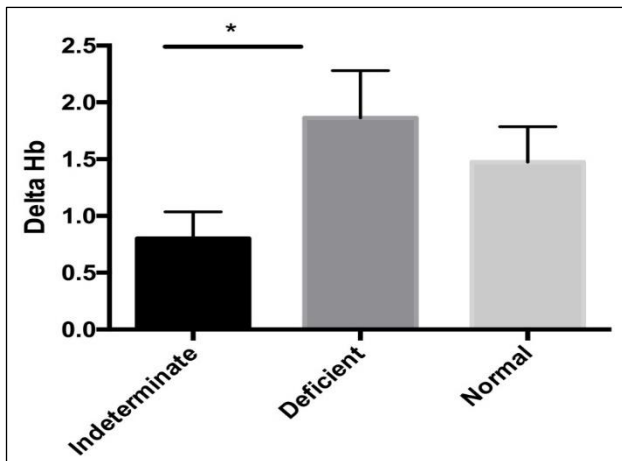


Figure 1: Compares Delta-haemoglobin in each study group, from 3-months before time of enrolment in study to 3-months after. [Columns represent means and error bars represent SEM. * = ANOVA (with post-test comparison) $P < 0.05$].

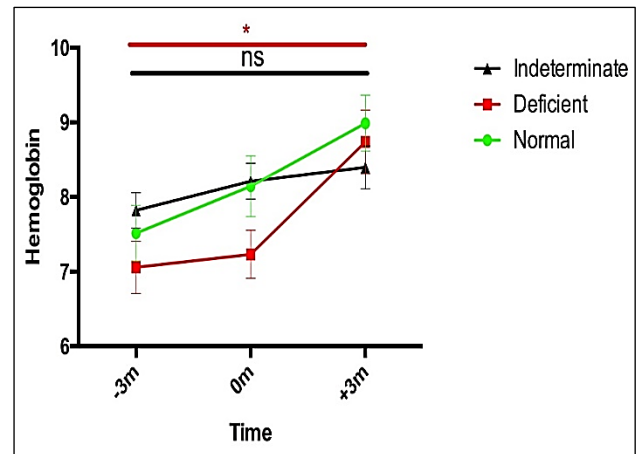


Figure 2: Trendlines of mean haemoglobin levels in each group by iron status. Indeterminate group had significantly inferior increases of haemoglobin over 6-months of follow-up. [Line represents mean, and error bars SD at each time point. * = Mann-whitney U $P < 0.05$].

Table 3: Haemoglobin trend.

Groups	Total	Normal-1	Deficient-2	Overload-3	Indeterminate-4
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Haemoglobin 3months before (g/dL)	n=94 7.56(1.64)	n=19 7.51(1.61)	n=23 7.05 (1.67)	n=3 7.46 (1.15)	n=49 7.82 (1.66)
Haemoglobin 0 month (g/dL)	n=100 7.95(1.74)	n=20 8.14(1.76)	n=25 7.23 (1.60)	n=3 8.26 (2.39)	n=52 8.21 (1.71)
Haemoglobin 3 months after (g/dL)	n=90 8.64 (1.91)	n=19 8.98(1.63)	n=23 8.73 (2.00)	n=3 9.56 (3.13)	n=45 8.39 (1.92)

Table 3 summarizes haemoglobin levels and patients (n) in each group at each of the different time points studied. As the overload group consisted of 3 patients only, we excluded these from subsequent analysis. We interestingly observed that the mean haemoglobin level of patients in the Normal and Deficient groups showed significant increases over a 6-month time period, while those in the indeterminate group had insignificant increases in haemoglobin levels in this period (Figure 1). Mean delta haemoglobin levels over 6 months (3-months before enrolment to 3-months after enrolment) were 0.80 ± 1.54 g/dl in the indeterminate group, compared to 1.87 ± 1.95 g/dl in the deficient group (Mann Whitney $P = 0.03$; Figure 2).

Patient outcomes

Overall during the follow up period, 29 patients continued on dialysis, 5 were at outside dialysis units, 8 patients received kidney transplants (4 of whom expired after transplantation). A total of 57 patients in our cohort had died during the follow up period (till October 2016). Five patients were lost to follow up in this time. There

were no significant differences detectable in number of deaths between any of the groups by iron status in the duration of our follow-up, although all 3 patients in the overload group had expired (Table 1 and Figure 3).

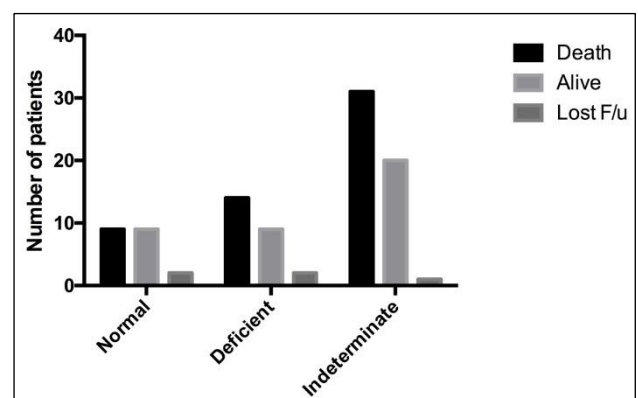


Figure 3: Patient outcomes in the study cohort till October 2016. No significant differences were observed in the proportion of patients that died in each group in this follow-up period (Chi square $P = ns$).

DISCUSSION

Anaemia contributes significantly to the morbidity and mortality in ESRD. ESA and iron supplementation are the most important factors in treatment of anaemia in ESRD patients.¹³ Iron deficiency has been identified as a major factor for anaemia in CKD patients, with a 43-90% prevalence in different series.^{6,14-16} Hence the periodical monitoring of iron status is crucial in ESRD.

There are two forms of iron deficiency, absolute iron deficiency and functional iron deficiency. Reduction of reticuloendothelial system iron in the bone marrow is referred to as absolute iron deficiency. Absolute iron deficiency may occur from impaired intestinal absorption, blood loss through the dialysis circuit, vascular access surgeries, repeated phlebotomies and increased iron utilization with erythropoietin therapy. In clinical practice, absolute iron deficiency is determined by serum ferritin less than 200ng/ml and TSAT less than 20%.¹⁷ In the non-ESRD population, "functional" iron deficiency is ascribed when iron reserves in the bone marrow are adequate, but iron mobilization is impaired as in states of chronic inflammation.¹⁸

The current study assesses the utility of combining serum ferritin and TSAT to assess iron status among an Indian haemodialysis population. The evaluation of iron status is straightforward when both serum ferritin and TSAT are either high or low. But when these parameters are divergent, for instance, if the TSAT is low and serum ferritin is high, the accurate interpretation of iron status is difficult. This entity was common in our study where the iron status of only 48% of the patients were clearly determined (20% had normal iron status, 25% had iron deficiency and 3% had iron overload), and was indeterminate in the remaining 52% of patients. Interestingly in our study, the only epidemiologic factor associated significantly with indeterminate status was dialysis vintage. Why patients with indeterminate or overload status appeared to have longer durations of dialysis, is unclear but requires further exploration. Our data suggest that in a significant proportion of haemodialysis patients in a typical urban dialysis unit in India, the conventionally applied parameters were insufficient to accurately categorize iron status. Similar data has emerged from other groups.¹⁹ Further, our data crucially demonstrates that patients with indeterminate status by conventional assessment have significantly inferior increases in haemoglobin levels with current therapy, suggesting the need for development of more specific diagnostic strategies to ascertain iron status in this group, to accurately manage iron status and anaemia.

Most studies have revealed that serum ferritin is very well related with iron stores in the bone marrow is the best surrogate of iron status in healthy individuals.²⁰⁻²² However, ferritin is an acute phase reactant increasing in states of chronic inflammation (such as dialysis), malignancy, or systemic disease, and ferritin levels alone

may not reflect iron stores available for haematopoiesis. Thirty-six patients had low ferritin (<200) in our study. Only 25 of them had iron deficiency (combined with low-TSAT), whereas ~31% of them were in indeterminate group. Further, 29 patients had high serum ferritin. Only 3 of these had iron overload (combining TSAT), while 4/29 had low TSAT (<20%). Hence, decision to treat these patients with iron supplements based on these parameters would likely be imprecise. Similarly, a transferrin saturation of less than 20% in patients on haemodialysis is considered to be suggestive of iron deficiency whereas other studies have suggested that a transferrin saturation < 20% versus >20% alone may be inaccurate for assessing iron deficiency.²³⁻²⁸ While most patients with TSAT less than 20% are iron deficient, few patients don't respond to an increase in iron supplements with either increase in haematocrit or maintenance of haematocrit with a decreased ESA requirement. On the other hand, numerous patients with a TSAT greater than 20% have functional iron deficiency respond to increased iron doses with elevations in the haematocrit, or maintenance of their haematocrit at decreased erythropoietin doses.²⁵⁻²⁸ In our study, 43 patients had low TSAT (<20%); only 25 of them had iron deficiency (combined with ferritin). We found that 57 patients had TSAT values more than 20%, out of which 11 had low ferritin (<200). TSAT values in these 11 patients may be falsely high because of low total iron binding capacity (TIBC) during inflammation and infection.

The difficulties in the interpretation of iron status using TSAT and serum ferritin in ESRD patients and the consequent hematologic implications we show, warrant the application of other erythrocyte and reticulocyte based indices, such as the percentage of hypochromic red blood cells (Hypo) and the reticulocyte haemoglobin content (CHr). CHr requires a special analyser and is recommended as an alternative iron status indicator as well as an initial measure of the response to iron treatment in haemodialysis population.²⁹⁻³¹ Fishbane et al evaluated the reticulocyte haemoglobin content among 32 haemodialysis population and showed it to have a sensitivity of 100% and specificity of 80%.²⁹ Mittman et al evaluated reticulocyte haemoglobin content among 364 haemodialysis population receiving EPO and proved it to be an indicator of functional deficiency of iron.³⁰ Based on these and other data, NKF DOQI recommends a target of CHr greater than 29pg/cell.³²⁻³⁵ The Hypo is an indicator of the percentage of red blood cells that contain low haemoglobin. Thus, it indicates only the functional iron availability and does not reflect storage iron. A Hypo level of greater than 10% indicates definitive functional iron deficiency. European Best Practice Guidelines stated that Hypo >10% is the most accurate marker for ID.³⁶ However, there are other studies which suggested lower threshold values for Hypo.^{32,37-40} Both these tests are not widely available in India.

Here, we report that the combination of serum ferritin and TSAT accurately categorized the iron status in only 48%

of ESRD patients in our study. When serum ferritin and TSAT values diverged, they become unreliable for accurate interpretation of iron status, signaling an iron indeterminate state that was prevalent in 52% of our urban dialysis cohort. As we show here, this group of iron-indeterminate patients has inferior increases in haemoglobin over time, showing clinical relevance of this finding. Our data suggests that more sensitive indices such as Hypo and/or CHr may need to be employed (along with conventional tests) to accurately assess iron status, and improve management tools. This could lead to more accurate dosing of iron and ESAs, decrease overtreatment of anaemia, and possibly translate to cost savings from medication usage. Future studies on iron markers including both traditional and newer indices are required to improve iron management in ESRD population, especially in Indian population, where iron deficiency is common and similar studies are lacking.

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