College of Medicine and Health Sciences School of medicine and Pharmacy

IRON STATUS IN PATIENTS WITH END STAGE RENAL DISEASE ON CHRONIC HEMODIALISIS AT RWANDA MILITATY HOSPITAL AND KING FAISAL HOSPITAL

A prospective descriptive cross-sectional study

A Thesis Submitted in partial fulfillment of the Requirement for the award degree of medicine in Internal Medicine, school of Medicine and pharmacy, college of Medicine and Health sciences
University of Rwanda

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DECLARATION

I Dr NSANZUMUHIRE Leandre, to the best of my knowledge, I hereby declare and certify that the work presented on this dissertation entitled **"Iron status in patients with end stage renal disease on chronic hemodialysis at Rwanda Military Hospital and King Faisal Hospital, Kigali: Prospective descriptive cross-sectional study"** is entirely my own original work and it has never been presented and submitted in whole or in part for any other degree at University of Rwanda or any other institution.

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ABSTRACT

Background

Chronic kidney disease is a condition associated with a high rate of anemia as renal function declines. The anemia worsens is due to the insufficient production of erythropoietin. However, other causes of anemia such as iron deficiency were found to be linked with CKD. Before the anemia correction, it is important to know the iron status to improve the anemia treatment modalities.

Objectives: to assess the iron status of patients with ESRD on chronic hemodialysis at RMH and KFH using serum iron and serum ferritin, in addition to FBC as laboratory parameters.

Methods:

This was a cross sectional study. Over a period of 5 months from 1st January 2021 to 31st May.

In this period, we recruited 74 patients aged 18 years and above with ESRD on chronic hemodialysis at Rwanda military hospital and King Faisal hospital, Kigali.

We recorded all patients' demographics, date of starting their first hemodialysis session, history of blood transfusion and other use of medications notably iron and erythropoiesis stimulating agents. The samples were collected and sent to laboratory for FBC and iron studies (serum iron and serum ferritin levels).

Results: Seventy-four patients with ESRD on chronic hemodialysis were recruited in this study with mean age 51(19-77) with iron deficiency anemia and 63(43-84) with non-iron deficiency anemia. The male to female ratio was2:1 P value <0.001. The mean hemoglobin level for all participants was 9.59 g/dl ± 1.93 (SD). The desired HB being at least,11g/dl recommended by KDIGO guideline for patients with ESRD on chronic hemodialysis which was achieved by only 17 patients (23%) and the prevalence of anemia in our population of patients on chronic hemodialysis at KFH, and RMH was 77%.

Low iron status was observed in 62% (46) of the study population by using serum iron marker as criteria, whereas by using serum ferritin marker as criteria low iron status was met by 35% (26) participants.

Iron and EPO supplement was adequately supplied in patients with Iron deficiency anemia with 98.4% (62) of IDA patients on both parenteral IV iron and EPO, P value <0.001. Notably, the long duration of iron and EPO therapy defined by 6 months in this study was

associated with less incidence of developing IDA ,20.27% in IDA compared to 33.8 % in non-IDA, P value:0.011.

Conclusion: Iron deficiency anemia is highly prevalent and a major contributor of anemia in patients with ESRD on chronic hemodialysis at RMH and KFH dialysis units. Long duration of iron supplement and EPO use is associated with low occurrence of IDA. Assessment of iron status before and after starting iron therapy for our patients on chronic hemodialysis as per K/DIGO guidelines, is important to limit the prevalence of IDA.

Key Words: End stage renal disease, hemodialysis, anemia, iron deficiency anemia.

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LIST OF ABBREVIATIONS

CKD : chronic kidney disease

CHr :reticulocyte hemoglobin content

DRIVE: dialysis patients' response to intravenous (IV) iron with elevated ferritin trial

EDTA : (ethylene diamine tetra acetic acid)

EPO : erythropoietin

ESRD: end stage renal disease

ESA : erythropoiesis-stimulating agent

eGFR : estimated glomerular filtration rate

g/dl :gram per deciliter

Hb : hemoglobin

IDA : iron deficiency anemia

IL : interleukin

IV : intravenous

KDIGO: Kidney Disease Improved Global Outcomes

ml: milliliter

m^2: meter squared

mcg/l: microgram per liter

min: minutes

ng/ml: nanogram per milliliter

NFK/KDOQI: National kidney foundation/kidney disease outcomes quality initiative

NHANES: national health and nutritional examination survey

PBF: peripheral blood film

rHeupo: recombinant human erythropoietin

SD : standard deviation

TIBC : Total Iron Binding Capacity

TNF : Tumor Necrosis Factor

TSAT: transferrin saturation

USA : United States of America

WHO : World Health Organization

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I would like thank the almighty God for his endless support, guidance and for blessing me with strength through all my life, all my accomplishments and all steps of life including this dissertation.

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I would like also to thank my statistician Dr Jean De Dieu Habyarimana for his contribution in this work.

DEDICATION

To my father: IYOMENYAKARE Amiel

To my mother: NYIRABAKENGA Liberathe

To my siblings: MUKAMANA Clemence,

N. HAFASHIMANA Emerance

NSANZINEZA Ernest

DUFATANYE Darius

TUYIZERE Anny Olive

HESHIMA Olexa

BAZIKI Jean De Dieu

This research is dedicated to you with great pleasure

1 CHAPTER I: INTRODUCTION

1.1 Background

Anemia develops in patients with chronic kidney disease (CKD).(1) The change in iron metabolism alters the iron body levels in affected individuals mainly in stage 3 to 5 of CKD. In patients with stage 5 CKD classified as end-stage renal disease (ESRD) normocytic normochromic anemia is a hallmark complication seen as a result of insufficient production erythropoietin (EPO).(2)

Anemia is an independent indicator of CKD progression and its correction is a pillar of slowing down the CKD progression.(3)

The use of recombinant human erythropoietin (rhuepo) in replacing endogenous EPO results in a robust boost of erythropoietic activity in which iron stores are utilized.

The body needs enough iron stores to prevent resistance to EPO.

in addition to the underproduction EPO in CKD Patients , Iron deficiency anemia (IDA) has been reported to be around 40% in patients with ESRD on chronic hemodialysis. (4)

IDA arise also from repetitive iatrogenic blood loss from frequent sampling for laboratory parameters analysis, central lines placement and removal, gastrointestinal blood losses among others.(5)(6)

Enough iron stores in association with erythropoiesis stimulating agents (ESA) are pivotal to achieve maximum anemia correction in CKD patients on hemodialysis, as the reduced iron stores are among the main reasons of developing poor response to ESAs treatment.

Previous study in USA, in 10 different dialysis centers including 1283 patients on maintenance hemodialysis that analyzed monthly serum iron levels and TSAT, showed that low iron status was directly associated an 8-fold increase in mortality and longer hospital stay.(7)

Iron replacement is important to maintain the normal iron status in patients with end-stage renal disease on hemodialysis. The DRIVE study, an open randomized controlled multi-center trial in 37 different centers across USA, showed efficacy of iron replacement among dialysis patients on erythropoietin with ferritin levels between 500-1200ng/l and TSAT below 25%. The response of hemoglobin and TSAT increment was faster in those who received iron replacement compared to the placebo group. (8)

K/DOQI guidelines 2006 recommends that Hb, serum ferritin, TSAT and serum reticulocyte index be evaluated to provide a baseline status on iron stores required for erythropoiesis. It recommends evaluation of IDA before starting treatment with ESA. (2)

Taking into consideration our setting in Rwanda, where we have now four public hemodialysis institutions that are (CHUB,CHUK,RMH and KFH),we report the report the first study on iron status among patients with ESRD on chronic hemodialysis in Rwanda.

1.2 Study justification

Anemia is an independent risk factor for both cardiovascular mortality and morbidity. Among patients with ESRD on hemodialysis, IDA is a major etiologic factor with a prevalence of 40%. (3) The empirical treatment with hematinics like intravenous iron or erythropoietin without objective assessment of serum iron levels and recovery from IDA is associated with poor response.

Assessing the magnitude of iron deficiency is important to provide a better treatment plan.

The differentiation from erythroblast into reticulocytes is an iron dependent process rather than EPO deficiency.

Iron stores have to be fully replenished before starting EPO with several potential benefits including minimizing frequency of blood transfusions and related risks and poor response to hematinics.

Currently, in Rwanda there are no studies that assessed iron status in patients with ESRD on chronic hemodialysis and regionally in sub-Saharan Africa studies are still few.

This study provides an overview of the iron status of patients with ESRD on chronic hemodialysis in two main hemodialysis units KFH and RMH. It provides the rationale of iron levels in patients with ESRD on hemodialysis. This will prompt clinicians to conduct timely the assessment of iron deficiency anemia in CKD patients with the goal to improve quality of life of patients.

1.3 Objectives

1.3.1 General objective

1. To determine the serum iron status in patients with ESRD on hemodialysis at KFH and RMH renal units.

1.3.2 Specific objectives

1. To determine the prevalence of anemia in patients with ESRD on hemodialysis at KFH and RMH renal units.

2. To determine the prevalence of iron deficiency anemia in ESRD patients on hemodialysis by use of serum ferritin, serum iron, Hb and MCV.
3. To determine the treatment modalities used in the treatment of anemia in patients with ESRD on hemodialysis: iron, erythropoietin or blood transfusion.

1.4 Research question

What is the iron status of patients with ESRD on chronic hemodialysis at two referral hospitals in Rwanda, RMH and KFH?

1.5 Research hypothesis

The iron deficiency anemia is prevalent in patients with ESRD on hemodialysis, and it is associated with increased cardiovascular mortality and morbidity if not adequately treated.

2 CHAPTER II: LITERATURE REVIEW

Anemia is defined by world health organization (WHO) as hemoglobin below 12g/dl in female and < 13 g/dl in male population, it is known as the most complication and finding in patients with CKD.(9)

The decline in kidney function is proportionally associated with a high prevalence of anemia from 7% prevalent in CKD stage I to as high as 50% in ESRD patients with eGFR less than 15ml/kg/m^2 (10), making the decline in eGFR a major risk factor to develop anemia.

A study assessing the prevalence of anemia in diabetic patients attending clinic in United Kingdom with 7331 studied population, anemia was newly diagnosed in 15% of all patients and based with further stratification based on eGFR the anemia was observed in only 9% with eGFR of > 60ml/kg per 1.73m^2 compared to as much as 36% patients with eGFR <60ml/kg per 1.73m^2. (11) Further highlighting the negative impact of renal function decline on development of anemia.

A combined cohort study analyzing 2 different data sets from National health and nutritional examination survey (NHANES)/USA 1988-2004 Involving 34782 patients with CKD not on dialysis they found that low levels of iron stores was directly proportional to a decline in creatinine clearance, also suggesting impact of inflammation noted in advanced stage altering the metabolism of proper iron utilization by body tissues.(12)

The inflammation in CKD is known to increases levels of ferritin and hepcidin disproportionally of iron stores resulting in reduction of iron availability.(13)

A systematic literature review assessing the impact of anemia in CKD patients on morbidity mortality and hospitalization found that the all-cause mortality was observed to be high in patients with level of Hb <10g/dl compared to those with Hb 10-12 and > 12g/dl with mean HRs (95CI) of 1.53, 1.17 and 0.91, respectively.

2.1 Pathophysiology

Iron is an important element of human cells and other mammals with a critical major function to carry oxygen to different tissues as part of hemoglobin molecule.(14) It can also be part of myoglobin in muscle and elementary in different important enzymes of the body including those heavily involved in cytochrome system of mitochondria. Hence iron deficiency results in anemia as consequence of impaired Hb synthesis.(14)

Iron metabolism in the body is regulated at multilevel stages of red blood cell cycles from erythroid lineage, which is controlled by EPO except from differentiation from erythroblast to reticulocyte, which is an iron dependent process.(14)

The iron absorbed from the gut or released from iron stores is transported bound to transferrin an iron binding protein (figure 1).

The plasma iron clearance time is reduced by erythropoiesis stimulation by EPO with a high demand of iron needed by erythroid cells and this process is deranged in iron deficiency. The half clearance time is reduced to 10 to 15 minutes compared to normal iron stores estimated at around 60-90 mins with a normal iron bound to transferrin turnover of 6-8 times per day.(14)

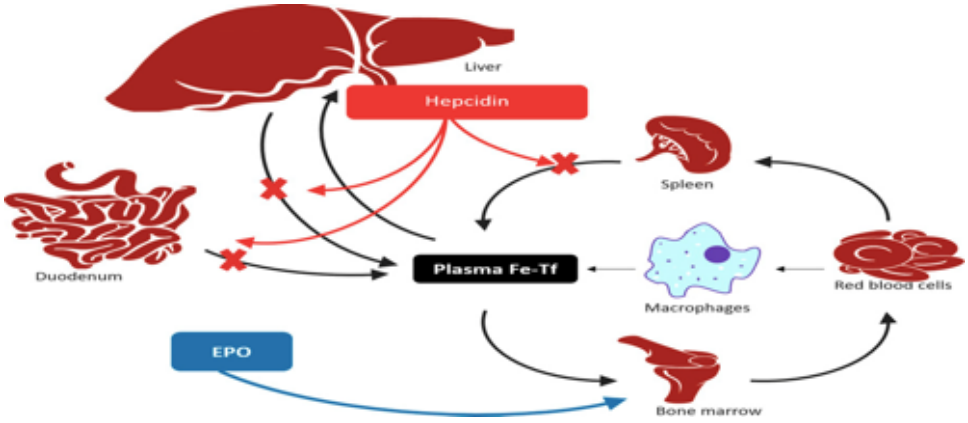

Figure 1 iron metabolism cycle

Iron absorbed at the intestine level I co-transported to the bone marrow for storage bound to transferrin. Another part of iron storages arises from destruction of RBC cells and reabsorbed by macrophages. Hepcidin a protein produced by the liver and it is mainly increased in inflammation and its effect decreases iron absorption at the gut level.

2.2 Types of iron deficiency anemia in ESRD patients in CKD

A. Absolute iron deficiency

This is defined by KDIGO 2012 as depleted circulating serum iron and iron stores evaluated as:

Non-hemodialysis CKD patients:

Criteria: TSAT < 20% and serum ferritin <200ng/ml

Hemodialysis CKD patients:

Criteria: TSAT < 20% and serum ferritin < 100ng/ml

B. **Functional iron deficiency** is a result from inadequate release of iron from stores to circulation to be utilized. This can be explained by two mechanisms: the first

being impaired iron release from iron stores due to chronic inflammation such as infection, increased radicals, cytokines like interleukin (IL) 1-6 and tumor necrosing factor (TNF) observed in CKD and other chronic conditions which impairs endogenous EPO release and function. Furthermore, in one study proinflammatory cytokines TNF was found to be around six times high compared to control groups 5.6 ± versus 0.9 ±0.1pg/ml.(16) With continuous use of exogenous EPO, and the second one is related to the stimulation of erythropoiesis which results in an increased iron demand to meet the required production of RBC. As with CKD there is an impaired timely supply by reticuloendothelial cells that results in demand supply mismatch, there is a vicious cycle progressively resulting, in the production of RBCs with low hemoglobin content.

With time the functional anemia develops and in extreme case this can cause what is defined as the reticulo-endothelial system blockade ,which is most of the time observed in case of severe infection.(16)

2.3 Causes of iron deficiency anemia in hemodialysis patients

IDA in patients with ESRD results from many different etiologies including:

a. **Blood loss** from frequent sampling for routine tests done to assess FBC, U&E, CMP, iron studies and other tests for clinical purposes. In this special population ,there are routine procedures like insertion and changes of hemodialysis catheters, arterio-venous fistulas formation, in addition to the amount of blood lost during dialysis, in the extra-corporeal circuits.

   During one session of each hemodialysis a patient loses an estimated 3g/day (20ml) of iron which is more than the daily dietary iron requirement of 1-2g /day.(17)

b. Other causes of IDA, on hemodialysis patients range from impaired intestinal absorption, chronic inflammation status of the CKD patients, the use of phosphorus binding medications impairing the iron absorption.(17)

2.4 Iron status evaluation in ESRD patients on HD by KDIGO guideline

KDIGO recommends to evaluate iron status (TSAT and ferritin) every 3 months with subsequent decisions to take or not Iron and ESA therapy.

Criteria to start iron therapy are:

- Adult CKD patients with anemia as defined by WHO, not yet on iron or ESA therapy after exclusion of active infection with a goal of desired rise of Hb before starting the ESA.
- Also, when TSAT is ≤ 30% and ferritin ≤ 500 mcg/l.

Criteria to take ESA therapy in adult CKD patients:

- To start ESA therapy when hemoglobin is between 9g/dl-10g/dl and avoid it to fall ≤ 9g/dl with ESA maintenance therapy adjusted regularly to maintain Hb between 11.5g/dl-13g/dl and avoid high ends to minimize risks associated with both iron and ESA therapy.(9)

3 CHAPTER III: Methodology

3.1 Study design

We designed a descriptive cross-sectional study whereby we recruited all patients with ESRD on chronic hemodialysis at RMH and KFH renal units aged 18 years and above meeting the study criteria,during a study period from 1st January 2021 to 31st May 2021. In this study, two nurses working in dialysis units at RMH and one at KFH were involved in sample collection and data collection of study population.

3.1.1 Study site

The study was conducted at KFH and RMH, two referral hospitals in Kigali, which possess two renal units with regular follow up of their respective patients with a team comprising a nephrologist, nurses among other medical staff.

From the 1st January to 31st May 2021, we recorded a number of 77 Patients on chronic hemodialysis averaging two to three dialysis sessions per week both renal units were operational seven days a week.

3.1.2 Study population

The study population consist of adult individuals from age 18 years and above with ESRD on hemodialysis.

3.1.3 Study duration

The duration of this was 5 months from January 2021 to May 2021

3.1.4 The sample size

Given the relatively small number of patients on chronic hemodialysis in Rwanda, we used non-probability convenience sampling method in order to maximize the number of patients. All patients who met the study inclusion criteria from both dialysis units KFH and RMH were included in the study.

3.1.5 Patient selection

3.1.5.1 inclusion criteria

1. Patients with ESRD on hemodialysis for 3 months at RMH and KFH
2. Patients with ESRD on hemodialysis aged 18 years and above
3. Patient with ESRD on hemodialysis who accepted to sign consent

3.1.5.2 Exclusion criteria

1. Patients on hemodialysis with different indication other than ESRD
2. Patients with acute renal failure

3. Patients with ESRD on hemodialysis, with neurological disabilities or critically ill making them unable to sign consent

3.2 Sampling method

All patients with end stage renal disease on hemodialysis at KFH and RMH renal unit who were eligible for inclusion criteria and consented for the study.

3.2.1 Clinical method

A questionnaire was given or read to recruited patients. Data including identification of patients age, gender, number of hemodialysis sessions per week and information on the use of rhuepo, iron and previous history of blood transfusions was recorded.

3.2.2 Case definition

Laboratory parameters used in this study to define iron status was defined by the desired HB of ESRD on maintenance HD of 11g/dl as a cut-off to anemia.

Low iron status was defined as serum ferritin below 200ng/ml and serum iron below 10.7mcmol/l, normal iron status as serum ferritin ranging between 200ng/ml to 500ng/ml and serum iron of 10.7mcmol/l to 29mcmol/l, iron overload was defined as serum ferritin above 500ng/ml.

3.2.3 Laboratory method

Before starting hemodialysis session ,8mls of blood was drawn from cubital vein. 4mls was then put in a sterile plain vacutainer (red) and sent immediately to respective hospital laboratory for serum iron, serum ferritin, analysis. The remaining 4mls was put in EDTA (ethylene diamine tetra acetic acid) vacutainer tube for FBC analysis.

Considering minimal risk of bleeding and infection during phlebotomy, the standard sampling procedure was adhered to.

A routine proper labelling and storage of specimens to minimize pre-analytical source of errors was also done.

3.3 Data collection

A questionnaire was used to collect data, on the questionnaire data consist of Identification: age, gender, year of commencement of hemodialysis, and number of weekly hemodialysis sessions, the use of erythropoietin, iron or records on previous blood transfusions.

We collected results of Hb, serum iron and serum ferritin level at routine three monthly sample analysis for patients with chronic ESRD undergoing hemodialysis.

3.3.1 Data entry and analysis

All collected data were entered using Microsoft Excel 2013 software and analyzed using SPPS 21 for windows, the confection and perfection of texts, tables, was done via Microsoft Word 2013 and Microsoft Excel 2013, Chi square test was used to compare categorical variables.

3.3.2 Participants recruitment

Study assistants, one renal unit nurse at KFH and two nurses at RMH were tasked to recruit all patients with ESRD on maintenance hemodialysis who met inclusion criteria and were informed of the study before being requested to fill the consent form.

After filling the consent form each participant was issued with a study registration number matching with the participant identity recorded in respective patient's file.

The above was intended to avoid double participation in next hemodialysis visit

3.4 ETHICAL CONSIDERATIONS

Ethical clearance was obtained from the Institutional Review Board (IRB) and the concerned hospitals' ethical committees. Study participants were given a written informed consent prior to study enrollment and after being informed of study procedures. Patients were informed the purpose of research and were involved voluntary after getting their consent.

4 CHAPTER IV: RESULTS

4.1 Patient selection

In this study 77 patients were on maintenance hemodialysis over the study period at KFH and RMH,74 patients met inclusion criteria and were recruited in the study.

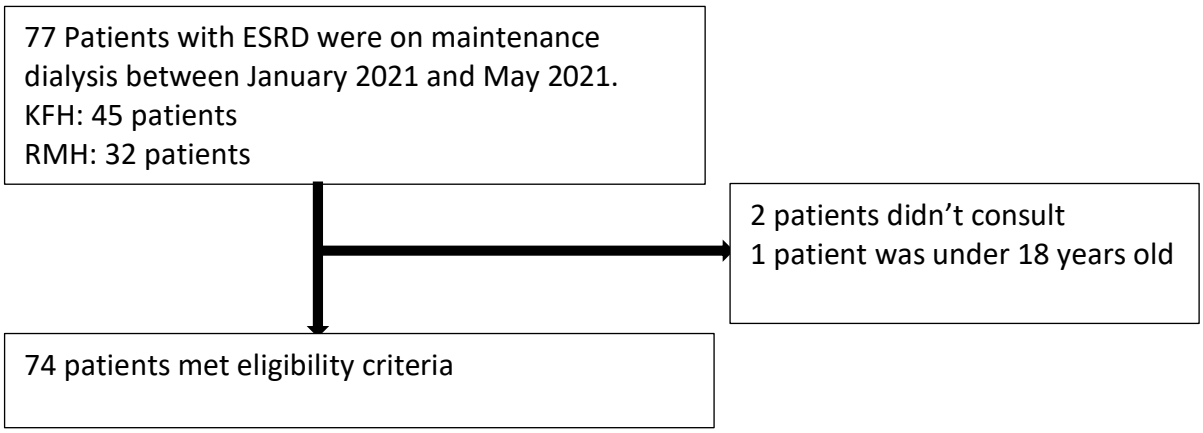

Figure 2. patients selection flow

The table below illustrates overall mean hematological and iron study results of all participants.

Table 1. **Hematological and iron profile of studied patients**

Variable	**Mean**±SD
Hemoglobin (g/dl)	9±13
Hematocrit (%)	30±9
MCV (ft)	88±11
Serum ferritin (ng/ml)	417±393
Serum iron (mcmol/l)	10±4
EPO dose (units/week)	10191±4218

In this study the mean HB was 9±13, hematocrit 30±9, MCV 88±11, for iron studies: serum ferritin 417±393ng/ml, serum iron 10±4ng/ml, about EPO use the mean EPO dose 10191±4218iu/week.

Table 2. Patients' demographic characteristics and clinical status

	IDA	No IDA	P value
	N=63 (%)	N=11 (%)	
Demographic data			
Age (mean, range):	51 (19-77)	63 (43-84)	
p<0.001			
Sex n (%):			p<0.001
Male	44 (59.5%)	8 (10.8%)	
Female	19 (25.7%)	3 (4.1%)	
Hospital n (%):			p<0.001
KFH	32 (43.2%)	11 (14.9%)	
RMH	31 (41.9%)	0	
Clinical status			
Duration on hemodialysis n (%):			p<0.001
< 3 months	4 (5.4%)	0	
3-6 months	21 (38.4%)	2 (2.7%)	
> 6 months	38 (51.4%)	9 (12.2%)	
Hemodialysis sessions per week n (%):			p<0.001
1	0	0	
2	16 (21.6%)	5 (6.8%)	
3	47 (63.5%)	6 (8.1%)	
Hemoglobin level n (%)			p<0.001
Low Hb, g/dl	54 (73%)	3 (4%)	
Normal Hb, g/dl	9 (12.2%)	7 (9.5%)	
History of blood transfusion n (%):			p<0.001
Yes	31 (41.9%)	4 (5.4%)	
No	32 (43.2%)	7 (9.5%)	

Table 2 shows the link between patients' demographic characteristics, clinical status and the presence or absence of Iron deficiency anemia (IDA). The study revealed a wide range of patients' age with a mean of 51(19-77) for IDA and 63 (43-84) for non-IDA; p<0.001.

There was an unequal distribution of gender, with predominance of male both in IDA and in No IDA groups. Male to Female ratio of almost 2:1.

King Faisal Hospital (KFH) recorded a big number of IDA (43.2%) while under hemodialysis compared to No IDA (14.9%) group; p<0.001. However, Rwanda Military Hospital (RMH) reported only patients with IDA (41.9%) which means all 31 patients at RMH qualified for IDA.

On the other hand, the duration on hemodialysis more than 6 months, is a general major contributing factor to develop IDA (51.4%) in comparison to No IDA (12.2%). Again, an increased numbers of hemodialysis sessions per week for example 3 sessions a week, contributed a lot to a high prevalence of IDA (63.5%) compared to No IDA (8.1%), p<0.001.

Table 3.Iron deficiency anemia (IDA) in relation to patients' Iron status

	IDA N=63	**No IDA** N=11	**P value**
Iron status:			
Serum Iron n (%)			0.019
Low	42 (56.8%)	4 (5.4%)	
Normal	21(28.4%)	5 (6.8%)	
Overload	0 (0%)	1 (1.4%)	
Ferritin n (%)			p<0.001
Low	21 (28.3%)	5 (6.8%)	
Normal	20 (27%)	1 (1.4%)	
Overload	22 (29.7%)	4 (5.4%)	

Table 3 shows a relationship between Iron deficiency anemia (IDA) and patients' Iron status. There was an increased number of patients with low serum Iron (56.8%) in IDA group compared to 5.4% in No IDA group, p= 0.019. This anemia type is also confirmed by low ferritin levels, 28.3% in IDA and 6.8 % in No IDA, p<0.001 among the same participants in the study. Although, there was almost an equal number of normal serum

Iron and ferritin in IDA group, the study revealed an overload of ferritin 29.7% without any incremental serum Iron level in the same group of IDA.

Table 4. Iron deficiency anemia in relation to the use of medications

	IDA	**No IDA**	**P value**
	N=63 (%)	N=11 (%)	
Duration on treatment n (%):			0.011
< 3 months	25 (33.8%)	10 (15.5%)	
3-6 months	23 (31.1%)	0	
> 6 months	15 (20.27%)	1 (1.4%)	
IV Iron n (%):			p<0.001
Yes	62 (83.8%)	0	
No	1 (1.4%)	11 (14.9%)	
Iron dosage per week n (%):			p<0.001
0 mg	3 (4.1%)	11 (14.9%)	
100 mg	59 (79.7%)	0	
200 mg	1 (1.4%)	0	
Erythropoietin n (%):			p<0.001
Yes	59 (79.7%)	3 (4%)	
No	4 (5.4%)	8 (10.8%)	
Erythropoietin dosage per week n (%):			p<0.001
0 iu	3 (4.05%)	7 (9.5%)	
4,000 iu	1 (1.4%)	0	
8,000 iu	1 (1.4%)	0	
12,000 iu	58 (78.4%)	4 (5.4%)	

Table 4 reveals an association of Iron deficiency anemia in relation to the use of medications. Three months duration on treatment was associated with an increased number of IDA (33.8%) cases, whereas 6 months or more duration on treatment was linked to a reduced number of IDA (20.27%) patients. Therefore, there is a negative correlation of duration on treatment (months) and IDA incidence. Following this, IV Iron supplement was most commonly used at 83.8% at a dosage of 100 mg (79.7%). Also, erythropoietin

supplement was used in 79.7% as well among patients with IDA.

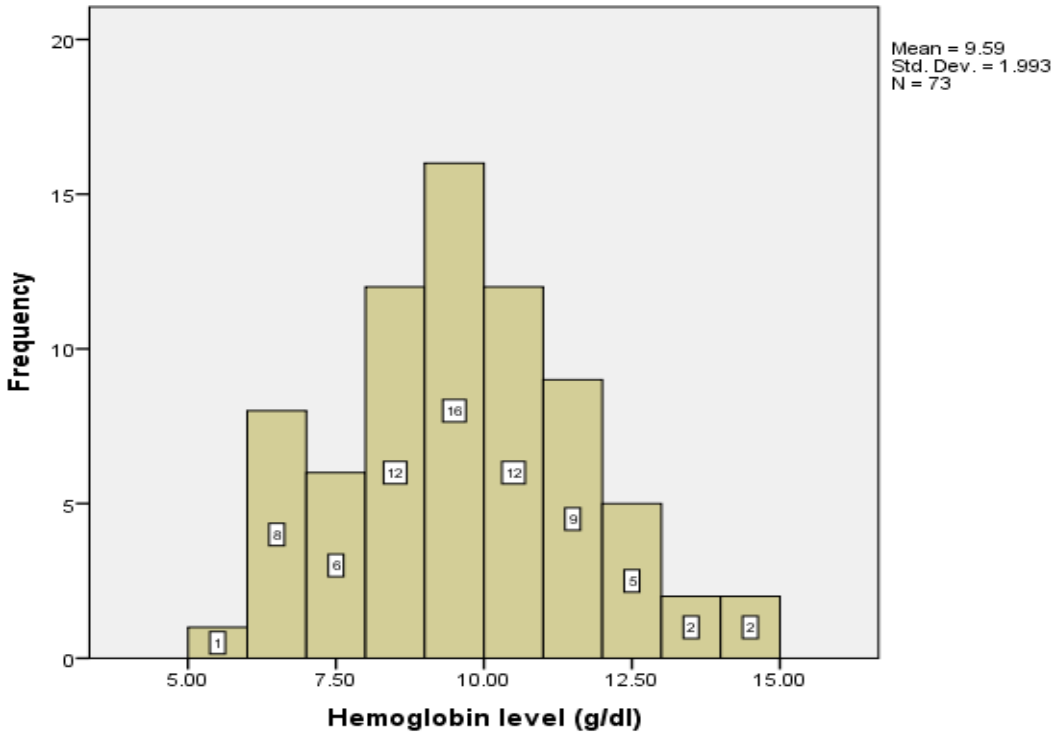

Figure 3.hemoglobin levels

This figure above is showing hemoglobin levels in Gaussian distribution. The hemoglobin distribution demonstrates one peak ranging from Hb 8 g/dl to 11g/dl. The mean HB levels was 9.59 g/dl ±1.93(SD) ,with the total prevalence of anemia in this study being 77% ,this is to mean 23% of study participants did not meet the desired HB 11g/dl and above per NFQ/KDOQI guideline .(19)

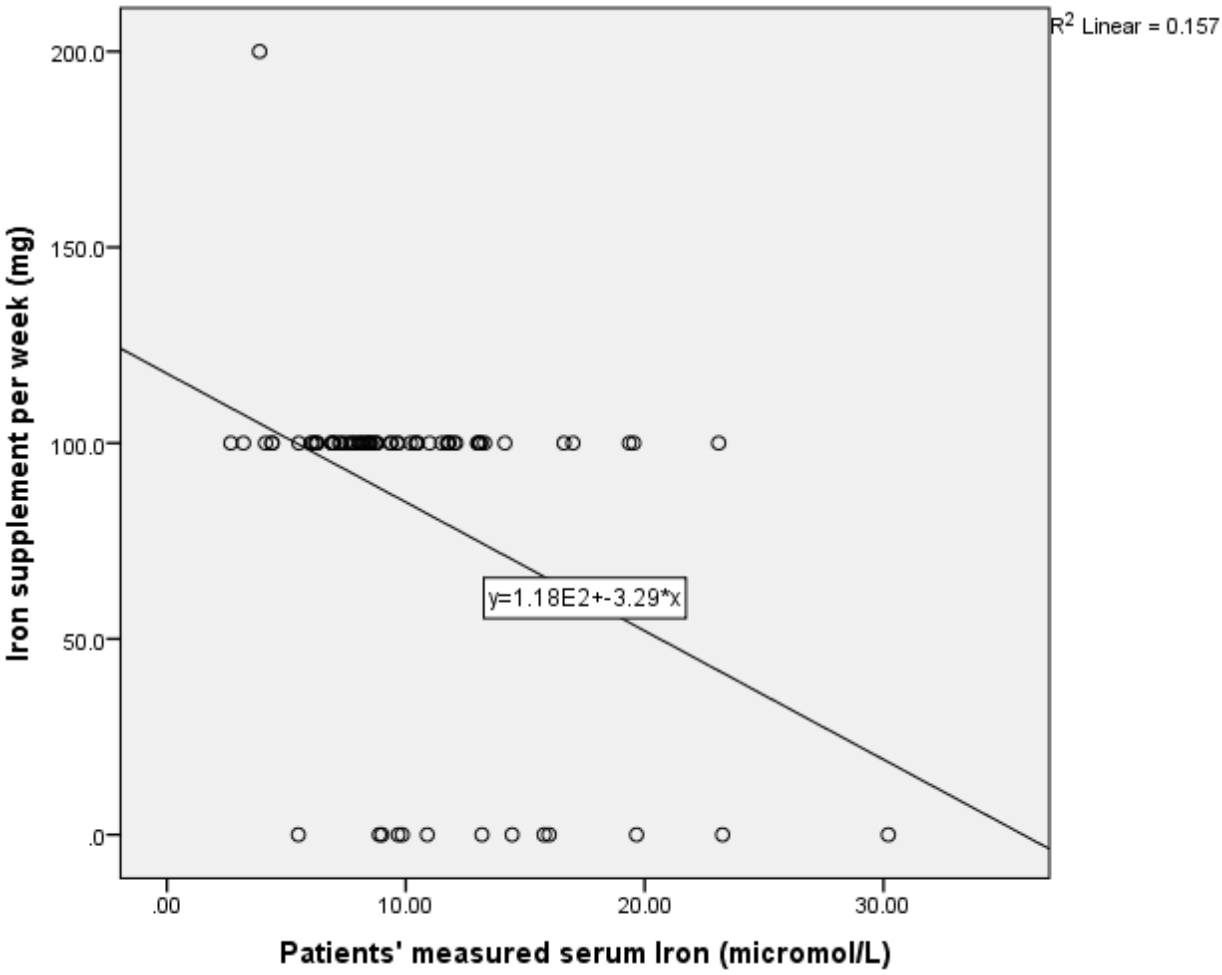

Figure 4.patients' measured serum iron

This figure illustrate the correlation between patients' measured Iron and Iron supplements per week.

This figure illustrates a correlation between patients' measured Iron and Iron supplement per week. There was no Iron supplement for a wide range of serum Iron due to No IDA group of patients. However, the study revealed a strong negative association. For instance, very low serum Iron was associated with the use of a high dose of Iron supplement and normal to high serum Iron was also linked with the use of low or zero Iron supplement.

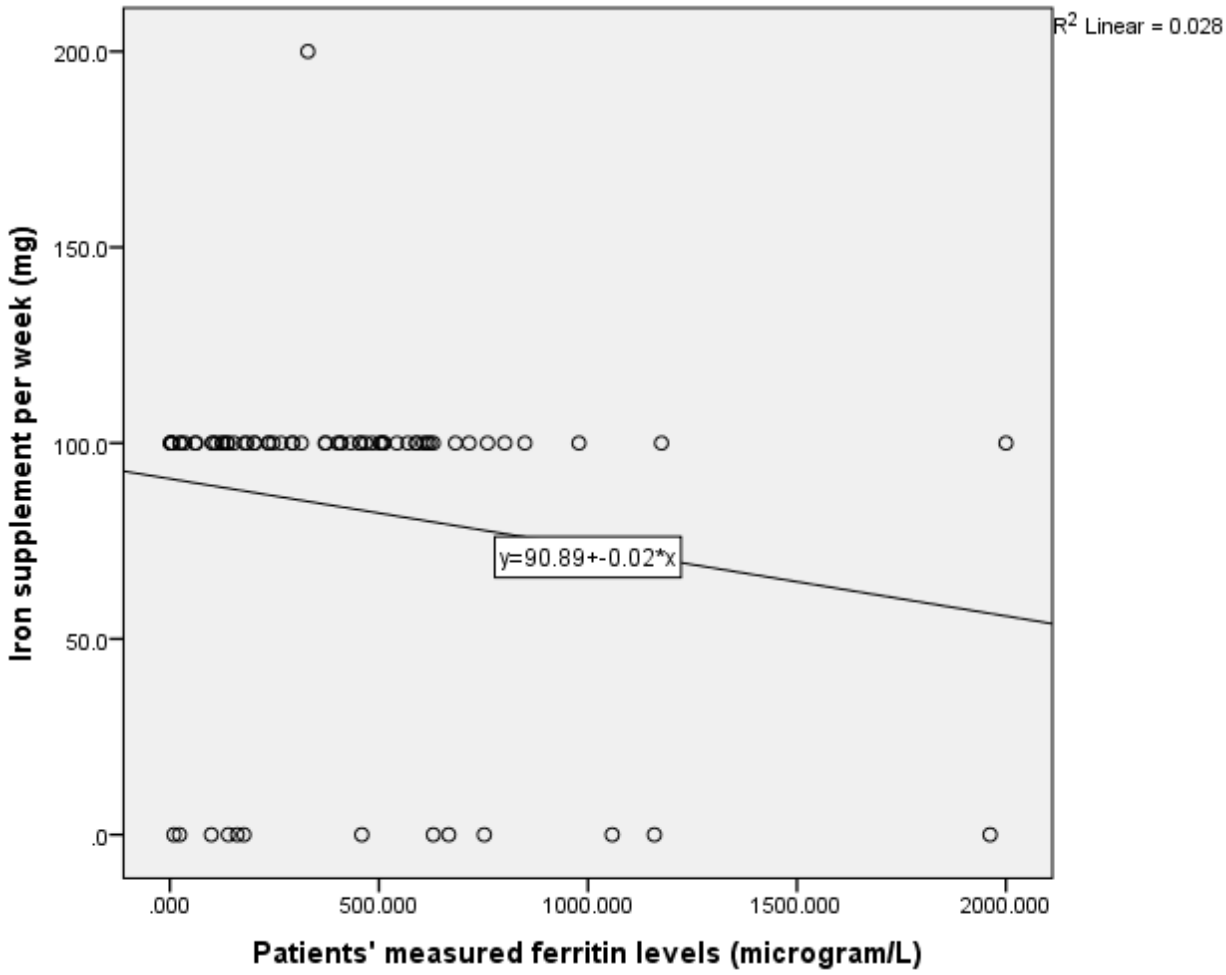

Figure 5. correlation between iron supplement and ferritin levels

this figure is demanstrating the correlation between patients' measured ferritin and Iron supplements per week.

This figure demonstrates an association between participants' measured ferritin and Iron supplement dosage per week. The study shows that Iron was not supplemented for almost all ferritin levels in No IDA patients. On the other hand, there is a strong negative correlation between ferritin levels and Iron supplements. For example, very low ferritin levels were supplemented with high Iron dosage whereas high ferritin levels were supplemented with low dose Iron, even if Ferritin overload was documented by Iron status on table 2.

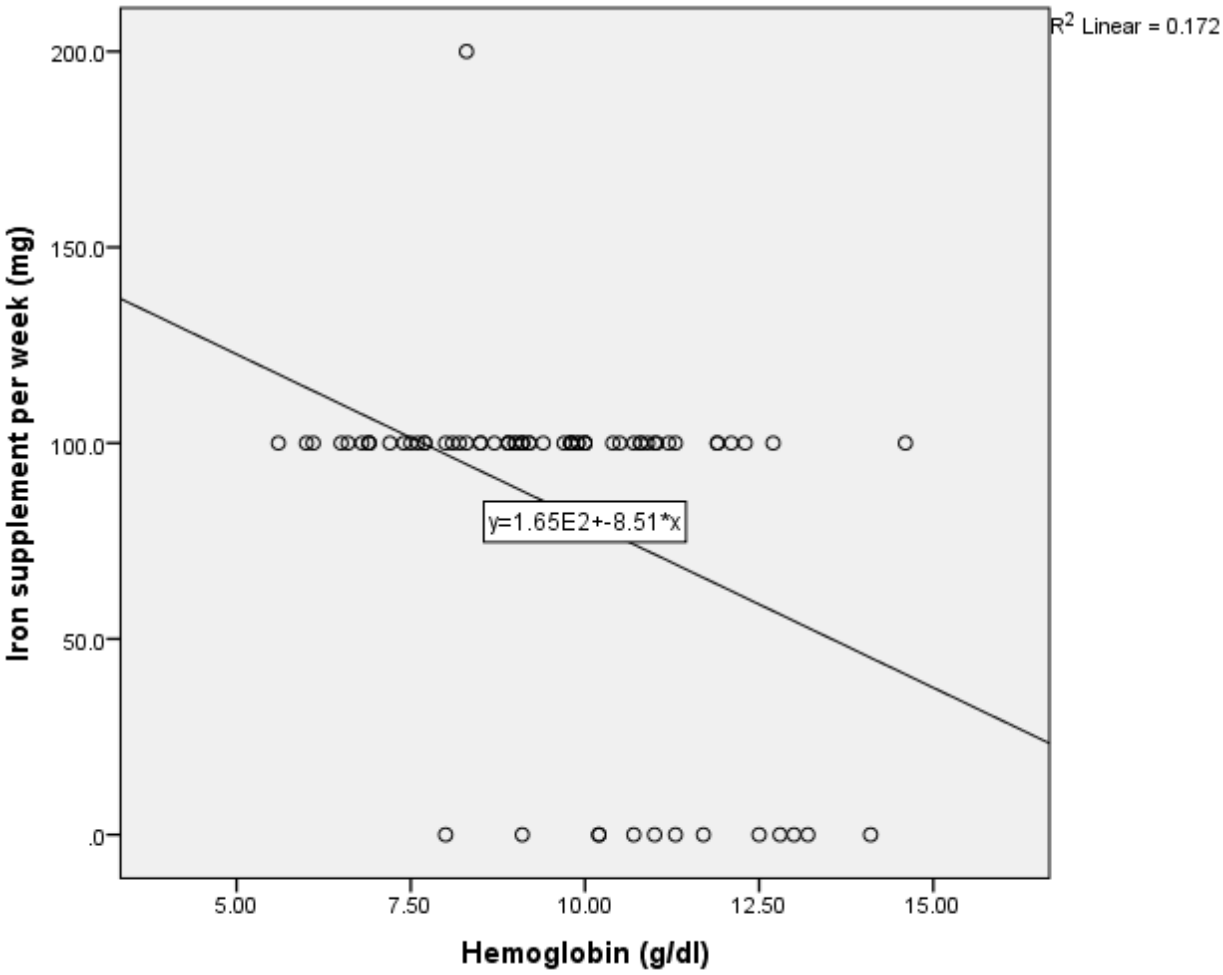

Figure 6.relationship between iron supplement and hemoglobin levels

The figure above shows the link between patients' measured hemoglobine level and Iron supplements per week.

This figure revealed a relationship between patients' measured hemoglobin levels and Iron supplement per week. There was no Iron supplement for a wide range of hemoglobin levels in No IDA group of patients. However, anemic patients with intense anemia were (hemoglobin: 5-7.5 g/dl) supplemented by a high dosage of Iron per week whereas a group of patients with normal hemoglobin were supplemented by a low Iron dosage.

5 CHAPTER V: DISCUSSIONS

Assessing iron status regularly in patients with end stage renal disease on hemodialysis is important to limit the progression to anemia which is a major contributor to poor outcome and quality of life in patients with ESRD.

Guideline-oriented and patient to patient selection for treatment with iron therapy and ESA have to be properly adjusted with iron indices and Hb levels (18).

In this study 74 patients were studied at 2 different hemodialysis units in Kigali, RMH 31 patients (41.9%) and 43 patients (58.1%) at KFH during the study period of 5 months from January 1st 2021 to May 31st 2021.

The total the prevalence of anemia in our population of patients on chronic hemodialysis at KFH and RMH was 77% of study using the desired HB of 11g/dl and above as the cutoff per KDIGO guideline recommendation with only 23% of patients meeting the targeted recommended HB.

The mean HB was 9.59± 1.93(SD),in comparison with other studies done in USA by Fishbone et al (12) ,found the mean Hb of 10.9±1.3(SD).

In contrast with a study from Sudan with comparable demographics to Rwanda, in a total of 534 patients with ESRD on maintenance dialysis, the mean HB level was significantly low at 7.89±1.24(SD) with an observed major association to anemia being lack of insurance coverage to EPO and iron supplements(19) .

The primary outcome of this study was to assess and analyze the serum iron status of participants. We observed that 46 patients (62%) had low serum iron levels below 11mcmol/l most remarkably 42 of them were qualified to have iron deficiency anemia. Low serum iron finding is a major predictor of developing iron deficiency anemia.

Using serum ferritin levels, 26 patients 35.1% of study population, met criteria of low iron status,22 patients (29.8 %) had normal serum ferritin levels and the remaining 26 patients (35.1%) having iron overload defined as serum ferritin >500ng/ml.

Iron administration in ESRD patients on maintenance HD with high ferritin levels (>500ng/ml) has to be well weighted with benefits as it has been reported to be associated with increased mortality over benefits.(7)

The findings suggest that the use of serum ferritin to assess iron status should be used along with other parameters such as TSAT as recommended by KDIGO guideline as with inflammation status observed generally in patients with ESRD.

Serum ferritin alone can poorly reflect iron stores as it can falsely be raised in patients ESRD taking into consideration a high rate of inflammation and infection and other chronic state like liver disease and malignancy these lead to poor sensitivity linked to serum ferritin.(20) (22)

As per this study results the longer the duration spent on hemodialysis defined as more than 6 months directly correlated with negative impact on developing iron deficiency anemia with 5-fold increase in patients on HD more than 6 months (51.4%) this might explain that a proper assessment of iron status has to be addressed before starting iron supplement and ESA.

Expectedly in this study iron supplement was adequately supplemented in patients meeting criteria of IDA 62 out of 63 patients (98.4)% , p value: <0.001) were on parenteral IV iron with a large proportion of them on a dosage of IV iron 100mg once a week with only one patient with IDA missing out on iron supplement, same positive observation was noted with use of EPO with 59 out 63 patients (93.6 % ,P value <0.001) of IDA patients receiving EPO however cautious clinical assessment of iron stores has to be put into consideration to prevent more depletion of iron stores with further anemia worsening as consequence.

These findings on anemia treatment coverage in this study are in contrast with findings from Sudan(19), with only 61% of HD patients on ESA and iron therapy.

It is important to note that in this study, the long duration of iron supplement defined as 6 months per this study prevented IDA with only 20.27% developing IDA compared 33.8% found to have IDA in 3 months group this to support that long lasting treatment is required while on hemodialysis.

As previously studied by Ornt D et al(23),the ESA and IV iron maintenance therapy achieved a desirable HB levels of (11.2 to 12g/dl) at 12months period of dialysis patients with ESRD supporting the above finding in this current study.

Study strength

This is the first study in Rwanda assessing iron status in patients with ESRD on chronic HD, it was conducted in two among main dialysis units in Rwanda that can roughly represents the majority of patients with ESRD on chronic HD in Rwanda, the sample size though it is small but it is comparable to other previous studies conducted in HD patients in different parts of the world.

In this study we were able to associate different correlations associated with iron deficiency anemia such as duration of dialysis, treatment modalities among others

Study limitations

TSAT is among of the parameters used to assess iron studies and recommended by KDIGO guideline that was not used in this study due to temporally not being done our laboratories during the study period, serum iron was used instead.

This study could not eliminate patients with other chronic comorbidities that can affect iron studies and anemia in general like chronic liver diseases, malignancies although we maximized to exclude patients with clinical status in favor of active infection.

PBF and bone marrow iron studies are among cornerstone used in assessing iron levels with the latter being gold standard but also invasive.

6 CHAPTER VI: CONCLUSION AND RECOMMENDATION

6.1 CONCLUSION

The study demonstrates the high prevalence of anemia in patients with ESRD on chronic hemodialysis and highlights low iron status among others major contributing factors to developing anemia .

The assessment of the iron status has shown that a large portion of the study population have low iron status despite being already on iron supplement ,which can be addressed with early start of iron therapy in early stages of CKD stage 3 and stage 4. The atudy has shown that the duration of iron and ESA are of clinical significance to prevent the anemia progression and the multiple transfusions.

Parenteral IV iron and EPO are the main treatment options for anemia, in patients with ESRD on hemodialysis at RMH and KFH dialysis units.

6.2 RECOMMENDATIONS

1. Strict evaluation of iron status in anemic patients with ESRD on chronic hemodialysis is strongly indicated before starting EPO and the use of KDIGO 2012 guideline on anemia evaluation and treatment should be strongly considered for a routine follow up.
2. Follow up monthly of FBC and iron parameters once in 3 months has to be maintained to limit unnecessary iron and EPO treatment which , to avoid unnecessary drugs related side effects, iron overload the burden due to high costs of iron infusion and EPO.
3. TSAT which is measured based of TIBC (unavailable during the time of the study) is necessary to evaluate iron status in patients with CKD. It implies, that our laboratories should make TSAT a routine and readily available to better have accuracy on iron stores.
4. Another study with more participants, involving different dialysis centers, evaluating the different etiologies of anemia in CKD patients is needed for more discussions and recommendations regarding the management of anemia of patients on chronic hemodialysis.

REFERENCES

1. del Vecchio L, Minutolo R. ESA, Iron Therapy and New Drugs: Are There New Perspectives in the Treatment of anemia, Journal of Clinical Medicine. 2021 Feb 18;10(4):839.
2. Executive Summary. Vol. 47, American Journal of Kidney Diseases. W.B. Saunders; 2006.
3. Rossert J, Froissart M, Jacquot C. Anemia management and chronic renal failure progression. In: Kidney International. 2005.
4. Tessitore N, Solero G pietro, Lippi G, Bassi A, Faccini GB, Bedogna V, et al. The role of iron status markers in predicting response to intravenous iron in haemodialysis patients on maintenance erythropoietin.
5. Fishbane S, Maesaka JK. Iron Management in End-Stage Renal Disease. Vol. 29, Am&an Journal of Kidney Diseases. 1997.
6. Nissenson AR, Strobos J. Iron deficiency in patients with renal failure. Vol. 55, Kidney International, Supplement. Blackwell Publishing Inc.; 1999.
7. Kim T, Streja E, Soohoo M, Rhee CM, Eriguchi R, Kim TW, et al. Serum Ferritin Variations and Mortality in Incident Hemodialysis Patients. American Journal of Nephrology. 2017 Aug 1;46(2):120–30.
8. Coyne DW, Kapoian T, Suki W, Singh AK, Moran JE, Dahl N v., et al. Ferric gluconate is highly efficacious in anemic hemodialysis patients with high serum ferritin and low transferrin saturation: Results of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) study. Journal of the American Society of Nephrology. 2007 Mar;18(3):975–84.
9. OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease [Internet]. Available from: http://www.kidney-international.org
10. Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. PLoS ONE. 2014 Jan 2;9(1).
11. Jones SC, Smith D, Nag S, Bilous MT, Winship S, Wood A, et al. Prevalence and nature of anaemia in a prospective, population-based sample of people with diabetes: Teesside anaemia in diabetes (TAD) study. Diabetic Medicine. 2010 Jun;27(6):655–9.
12. Fishbane S, Pollack S, Feldman HI, Joffe MM. Iron indices in chronic kidney disease in the National Health and Nutritional Examination Survey 1988-2004. Clinical Journal of the American Society of Nephrology. 2009 Jan 1;4(1):57–61.
13. Ueda N, Takasawa K. Impact of inflammation on ferritin, hepcidin and the management of iron deficiency anemia in chronic kidney disease. Vol. 10, Nutrients. MDPI AG; 2018.
14. Harrison's Principles of Internal Medicine (19th Ed) (Vols 1+2)(gnv64).
15. Brinkkoetter PT, Marinaki S, Gottmann U, Fleckenstein S, Stump C, van der Woude FJ, et al. Altered CD46-mediated T cell co-stimulation in haemodialysis patients. Clinical and Experimental Immunology. 2005 Mar;139(3):534–41.
16. Wish JB. Assessing iron status: beyond serum ferritin and transferrin saturation. Vol. 1 Suppl 1, Clinical journal of the American Society of Nephrology : CJASN. 2006.
17. Eschbach JW, Cook JD, Scribner BH, Finch CA. Iron Balance in Hemodialysis Patients [Internet]. Available from: https://annals.org/

18. IV. NKF-K/DOQI CLINICAL PRACTICE GUIDELINES FOR ANEMIA OF CHRONIC KIDNEY DISEASE: UPDATE 2000. 2001;
19. Abdelkarim OA, Abdelraheem MB, Abubakar U, Ekheir HK. Prevalence and factors predicting anemia in sudanese hemodialysis patients. 2020;
20. Rafi A, Karkar A, Abdelrahman M. Saudi Journal of Kidney Diseases and Transplantation Brief Communication Monitoring Iron status in End-Stage Renal Disease Patients on Hemodialysis [Internet]. Vol. 18, Saudi J Kidney Dis Transplant. 2007. Available from: http://www.sjkdt.org
21. Kalantar-Zadeh K, Kalantar-Zadeh K, Lee GH. The fascinating but deceptive ferritin: to measure it or not to measure it in chronic kidney disease? Vol. 1 Suppl 1, Clinical journal of the American Society of Nephrology : CJASN. 2006.
22. Ornt DB, Larive B, Rastogi A, Rashid M, Daugirdas JT, Hernandez A, et al. Impact of frequent hemodialysis on anemia management: Results from the Frequent Hemodialysis Network (FHN) Trials. Nephrology Dialysis Transplantation. 2013 Jul;28(7):1888–98.
23. Batchelor EK, Kapitsinou P, Pergola PE, Kovesdy CP, Jalal DI. Iron deficiency in chronic kidney disease: Updates on pathophysiology, diagnosis, and treatment. Vol. 31, Journal of the American Society of Nephrology. American Society of Nephrology; 2020. p. 456–68.

APPENDIX 1. IRB APPROVAL

UNIVERSITY of RWANDA

COLLEGE OF MEDICINE AND HEALTH SCIENCES

DIRECTORATE OF RESEARCH & INNOVATION

CMHS INSTITUTIONAL REVIEW BOARD (IRB)

Kigali, 20th May 2020

Dr NSANZUMUHIRE Leandre
School of Medicine and Pharmacy, CMHS, UR

Approval Notice: No 080/CMHS IRB/2020

Your Project Title ***"Iron Status In Patients With End Stage Renal Disease On Chronic Hemodialysis At Rwanda Military Hospital And King Faisal Hospital"*** has been evaluated by CMHS Institutional Review Board.

		Involved in the decision		
			No (Reason)	
Name of Members	**Institute**	Yes	**Absent**	**Withdrawn from the proceeding**
Prof Kato J. Njunwa	UR-CMHS		X	
Prof Jean Bosco Gahutu	UR-CMHS	X		
Dr Brenda Asiimwe-Kateera	UR-CMHS	X		
Prof Ntaganira Joseph	UR-CMHS	X		
Dr Tumusiime K. David	UR-CMHS	X		
Dr Kayonga N. Egide	UR-CMHS	X		
Mr Kanyoni Maurice	UR-CMHS		X	
Prof Munyanshongore Cyprien	UR-CMHS	X		
Mrs Ruzindana Landrine	Kicukiro district		X	
Dr Gishoma Darius	UR-CMHS			X
Dr Donatilla Mukamana	UR-CMHS	X		
Prof Kyamanywa Patrick	UR-CMHS		X	
Prof Condo Umutesi Jeannine	UR-CMHS		X	
Dr Nyirazinyoye Laetitia	UR-CMHS			X
Dr Nkeramihigo Emmanuel	UR-CMHS		X	
Sr Maliboli Marie Josee	CHUK	X		
Dr Mudenge Charles	Centre Psycho-Social	X		

After reviewing your protocol during the IRB meeting of where quorum was met and revisions made on the advice of the CMHS IRB submitted on 20th May 2020, **Approval has been granted to your study.**

Please note that approval of the protocol and consent form is valid for **12 months**.

Email: researchcenter@ur.ac.rw P.O Box 3286 Kigali, Rwanda www.ur.ac.rw

You are responsible for fulfilling the following requirements:

1. Changes, amendments, and addenda to the protocol or consent form must be submitted to the committee for review and approval, prior to activation of the changes.
2. Only approved consent forms are to be used in the enrolment of participants.
3. All consent forms signed by subjects should be retained on file. The IRB may conduct audits of all study records, and consent documentation may be part of such audits.
4. A continuing review application must be submitted to the IRB in a timely fashion and before expiry of this approval
5. Failure to submit a continuing review application will result in termination of the study
6. Notify the IRB committee once the study is finished

Sincerely,

Date of Approval: The 20th May 2020

Expiration date: The 20th May 2021

Professor GAHUTU Jean Bosco
Chairperson Institutional Review Board
University of Rwanda College of Medicine and Health Sciences

Cc:
- Principal College of Medicine and Health Sciences, UR
- University Director of Research and Postgraduate Studies, UR

APPENDIX 2 .STUDY QUESTIONNAIRE

Iron status in patients with ESRD on hemodialysis at KFH and RMH renal units.

Patient record form.

Identification

Name initials ……..

Age …… study No. …….

Sex. …….. study date …….

1=male ….. 2=female ……..

First Date of start of hemodialysis
……/……/……

Number of hemodialysis sessions per week.

……

History of blood transfusion.

1=Yes ….. 2=. No ……

History of blood loss not related to hemodialysis
1=Yes …… 2=No…….
If Yes indicate site of bleeding
Skin, GIT melena, hematochezia, blood vomitus, epistaxis, AUB/metrorrhagia

Modality of anemia treatment

Drug	Trade name	Date of start of medication	Dose
Iron IV			
Iron po			
erythropoietin			
Others			

Laboratory parameters

Lab test	Results	date
Hb		
PCV		
RBC		
WBC		
MCV		
MCH		
MCHC		
Platelets		
Serum iron		
Serum ferritin		

APPENDIX 3. INFORMED CONSENT

INFORMED CONSENT FORM FOR IRON STATUS IN PATIENTS WITH END STAGE RENAL DISEASE ON CHRONIC HEMODIALYSIS AT KING FAISAL HOSPITAL AND RWANDA MILITARY HOSPITAL.

This consent form is for those who are invited to participate in our study on "Iron status on patients with end stage renal disease on chronic hemodialysis at King faisal hospital and Rwanda military hospital."

Meaning what is Iron status of patients with ESRD who are on hemodialysis

This form comprise of two sections:

1.Introduction to the study.

2.Consent form .

SECTION I : **Introduction to the study:**

We are going to explain and invite you to participate in this study. You will think about it and ask questions if necessary so that you understand the whole process, benefits and possible risks (although there are no expected risks) before you decide to accept to participate in this study.

I'm by the names **NSANZUMUHIRE LEANDRE** , a medical doctor by profession I'm also a third year student in Internal medicine specialization program (masters degree) at University of Rwanda college of medicine and health sciences. We are carrying out a research on Iron status of patients with end stage renal disease on chronic hemodialysis at King Faisal Hospital an Rwanda Military Hospital.

Objective of the study:

assessing iron levels of patients with ESRD on chronic hemodialysis is important to tackle and prevent anemia which is one of complication related chronic kidney disease , this will help in optimization of their general well being by preventing anemia

Methods of the study intervention:

In our study we will do sampling of blood and assess parameters of iron panel and full blood count and analyze it accordingly.

Participant selection:

We invite all patients admitted in internal medicine renal unit on hemodialysis with ESRD.

Right to participation:

Your participation in this study is fully voluntary. You will continue to get same treatments as you have been receiving even if you choose not to participate. You are allowed to stop your participation even during the process of the study. This will not affect in anyway your deserved treatments.

Duration of study:

This study will last for 4 months period one sample only will be collected once at time . It will not delay your treatment schedules.

Risks :

This study is entirely safe there is no expected risks.

Benefits and reimbursement:

There are no reimbursement for any one's participation in this study.

Confidentiality:

The information that will be recorded from your charts or collected from you, will be highly confidential. This information will be stored on a secured file in our password protected computer. Our questionnaire files have not included a NAME to protect the participant and only the researchers will have access to them.

Sharing the results :

We plan to publish the results for academic and research purposes and we shall feed back to the treatment team for self evaluation ,your confidentiality will always be protected through out.

CONTACTS:

Door for questions is always open and in case you can contact the following:

NSANZUMUHIRE Leandre : +250788802611, leyanho@gmail.com

Kabahizi Jules : +250788824874, jukabahizi@yahoo.fr

CMHS IRB Chair Person: +250788490522.

CMHS IRB Deputy Chair Person: +250783340040.a

SECTION II**: consent form.**

I have read and understood information provided or read to me above, all my questions have been answered to my satisfaction. I consent voluntarily to participate in this study.

Printed name of participant :…….

Signature of participant:…….

Dates: ……..

If illiterate

I have witnessed the accurate reading of study information and consent form to the potential participant, and the individual has had chance to ask questions and obtain satisfying responses. I confirm that the individual has given consent freely.

Printed names of witness: …….

Signature of witness:…….

thumb print of participant:……..

Dates :…….

Statement by the researcher/individual obtaining consent:

I have accurately read out the information sheet to the potential participant, and made sure that the participant understands the above information to my best of ability.

I confirm that the participant was given opportunity to ask questions about the study, and all the questions have been answered correctly to best of my knowledge.

I confirm that the individual has not been forced into giving consent, and the consent has been given freely.

A copy of this consent form has been provided to the participant.

Print name of Researcher/ person obtaining consent:…….

Signature of Researcher/ person obtaining consent:……

Dates :…….