PREVALENCE OF ANEMIA IN CONGESTIVE HEART FAILURE PATIENTS AT MUHIMBILI NATIONAL HOSPITAL DAR ES SALAAM – TANZANIA

A HOSPITAL-BASED CROSS SECTIONAL DESCRIPTIVE STUDY

By

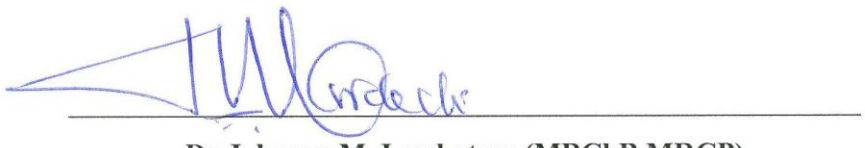
Dr Delilah Charles Kimambo

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Medicine (Internal Medicine) of the Muhimbili University of Health and Allied Sciences (MUHAS)

November, 2010

CERTIFICATION

The undersigned certify that he have read and hereby recommend for acceptance of dissertation entitled ***"Prevalence of Anemia in congestive heart failure patients at Muhimbili National Hospital Dar es salaam – Tanzania"*** in fulfillment of the requirements for the degree of Master of Medicine (Internal Medicine) of Muhimbili University of Health and Allied Sciences.



Dr Johnson M. Lwakatare (MBChB.MRCP)

(Supervisor)

Date: 25.11.2010

DECLARATION AND COPYRIGHT

I, **Delilah Charles Kimambo,** declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

Signature: _____ Date: 25 · 11 · 2010

This dissertation is copyright material protected under the Berne Convention, the Copyright Act 1999 and other international and national enactments, in that behalf, on intellectual property. It may not be reproduced by any means, in full or part, except for short extracts in fair dealing, for research or private study, critical scholarly review or discourse with an acknowledgement, without the written permission of the Directorate of Postgraduate Studies, on behalf of both the author and the Muhimbili University of Health and Allied Sciences.

ACKNOWLEDGEMENT

I thank God, the Almighty, for the gift of healthy life.

I wish to express my sincere thanks to my Supervisor, Dr. Johnson M. Lwakatare, for his invaluable time to guide and assist me with this dissertation work right from proposal development to the end.

Special thanks to the entire staff of the Department of Internal Medicine, MUHAS for accepting my dissertation title and offering me the necessary support throughout my term as a resident in the Department.

I would like to extend my gratitude to the department of Hematology and blood transfusion of the MNH for assisting me with the peripheral smear readings, the MNH staff in echocardiography room that assisted me in doing echo , the JICA laboratory staff for assisting me with the handling of serum Ferritin samples.

Many thanks to Dr Makwaya, Dr Rose Mpembeni, Dr Joel Malissa for helping me out with the data handling and eventual analysis, your guidance are highly appreciated.

Thanks to all the patients who accepted to participate in this study, they are the forefront of every part of this work. If not for their acceptance everything would be impossible.

Last but not least, I wish to express my extreme gratitude to my Husband, Werner for his love, patience, constant support and encouragement during the gloomy hours of this work. Special thanks to my son Christian- Deusdedit and my daughter Cathleen- Faith

DEDICATION

To my father; the late Charles Thomas Kimambo

ABSTRACT

Background: Anemia increases morbidity and mortality in patients with congestive Heart failure. Few studies have examined the prevalence of anemia and its impact among congestive heart failure patients in Africa. This study determined the prevalence of anemia in patients with congestive heart failure attending Muhimbili National Hospital, the national referral hospital in Dar es Salaam Tanzania.

Methods: This was a descriptive cross sectional study of patients admitted in medical wards and patients referred to medical out patient's clinics with a diagnosis of Congestive heart Failure at Muhimbili National Hospital. From October 2009 to January 2010 a total of 140 patients met the inclusion criteria and were recruited into the study. Anemia was defined as per WHO as hemoglobin level <13g/dl for men and <12g/dl for female. Patients were classified according to the NYHA. All patients had a full haemogram, serum Ferritin, biochemical profile, CXR, ECG and echocardiography.

Results: Anemia was found in 108/140 (77.1%) of patients. The mean age was 42±20. Males were older than females with median age of 47 (range 14-94) years as compared to median age of 35(range 10-85) years in females. The prevalence of anemia was significantly higher in males (84.9%) than in females (70.3%), p=0.0040.The risk of having anemia increased with severity of NYHA (p=0.0018). Most of the patients with anemia were found to be in NYHA functional class III and IV. Normocytic normochromic was the common type of anemia (78% of anemic patients), while microcytic hypochromic anemia was found in only 17% of the patients. Anemic patients were also found to have significantly low haematocrit (p=0.0001) and higher creatinine level (p= 0.0076) .Renal function impairment as a co-morbidity (estimated Glomerular filtration Rate <60mls/min) was found in 62% and was associated with the presence of anemia

Conclusion: The prevalence of anemia in patients with congestive heart failure attending Muhimbili national hospital was high (77%). The prevalence was higher in patients with NHYA class III and IV , and was significantly associated with low haematocrit level, increased serum creatinine level, impaired renal functions (estimated Glomerular filtration Rate <60mils/min)

Recommendation: Improve awareness that anemia is common in CHF and should be addressed as important co morbidity.

TABLE OF CONTENTS

Page

CERTIFICATION i
DECLARATION AND COPYRIGHT ii
ACKNOWLEDGEMENT iii
DEDICATION iv
ABSTRACT v
LIST OF TABLES x
LIST OF FIGURES xi
LIST OF ABBREVIATIONS xii
CHAPTER ONE 1
1. INTRODUCTION AND LITERATURE REVIEW 1
1.1. Definition and Epidemiology of anemia in heart failure 1
1.2.1. Haemogram 3
1.2.3. Challenges in diagnosis of anemia in heart failure 6
1.3. Mechanism of anemia in patients with heart failure 6
1.3.1. Hemodilution 6
1.3.2. Cardio renal syndrome 7
1.3.3. Erythropoietin production in Heart Failure 8
1.3.4. Drugs (ACE-I, ARB) 9
1.3.5. EPO Resistance 10
1.3.6. Chronic Disease Anemia 10
1.3.7. Ferropenic anemia 12
1.4. Pathophysiology of anemia in Heart Failure 13
1.5. Clinical presentation of patients with Anemia in congestive heart failure 14
1.6. Co-morbidity, Morbidity, and Mortality in CHF with Anemia 14
CHAPTER 2 17
2.1 PROBLEM STATEMENT 17
2.2: RATIONALE 18
2.3: OBJECTIVES 19
2.3.1. Broad Objective 19
2.3.2. Specific objectives 19
CHAPTER THREE 20

3. Methodology....20
3.1 Study design....20
3.2. Study site....20
3.3. Study population....20
3.4. Sampling technique....20
3.5. Inclusion criteria....21
3.6. Exclusion criteria....21
3.7. Sample size....21
3.2. Definition of terms for this study....22
3.2.1. Anaemia....22
3.2.2. Diagnosis of congestive heart failure....22
3.2.3. NYHA Functional Classification for Congestive HF....23
3.2.4. Renal function....23
3.2.5. Co-morbidities....24
3.2.6. Data collection methods....24
3.2.7. Study Procedures....24
3.2.8. Laboratory Investigation....25
3.2.9. Echocardiogram....25
3.2.10. Data entry, cleaning and analysis....25
3.2.11. Ethical consideration....26
3.2.12. Disposal of Study patients....26
CHAPTER FOUR....27
4.1. RESULTS....27
4.1.1. Patients characteristics....27
4.1.2 Physical findings....28
4.1.3 Prevalence of anaemia....31
4.1.4. Red cell morphology of congestive heart failure patients....31
4.1.5. Iron studies....33
4.1.6. NYHA functional classification....34
4.1.7. Echocardiography findings of the patients....35
4.1.8. Left ventricular ejection fraction....35
4.1.9. Other Echocardiography findings....36
4.1.10. Co-morbidities of Congestive heart failure patients....37

4.1.11. Renal dysfunction 38
CHAPTER FIVE 40
5. DISCUSSION 40
5.1. Prevalence of anemia 40
5.2. NYHA functional classification 42
5.3. Co-morbidity 43
CONCLUSION 47
RECOMMENDATIONS 48
STUDY LIMITATIONS 49
REFERENCES 50
APPENDICES 57
Appendix: I: Questionnaire 57
Appendix II: Consent form to participate in the study – English version 61
Appendix III: Consent form to participate in the study – Swahili version 63
Annex 2c 66

LIST OF TABLES

Page

Table 1. Demographic characteristics of congestive heart failure patients according to their anemia status.....28

Table 2. Clinical characteristics of the patients with congestive heart failure according to their anemia status.....30

Table 3. Mean hematological indices and biochemical findings of patients with congestive heart Failure according to their anemia status.....32

Table 4. Serum Ferritin of the patient with congestive heart failure in relation to status of anemia.....34

Table 5. Co-morbidities of congestive heart failure patients in relation to anemia status.....37

Table 6. Clinical Characteristics of congestive HF patients with anemia according to their eGFR <60mls/min n=108.....39

LIST OF FIGURES

Page

Figure 1. Hemoglobin categories of patients with CHF according to sex.....31

Figure 2. Red cell morphology of congestive heart failure patients.....33

Figure 3. Echocardiography findings of patients with Congestive cardiac failure n=140 36

Figure 4. Prevalence of anemia in patients with CHF grouped according to eGFR calculated by the Cockcroft – Gault equation n=140 38

LIST OF ABBREVIATIONS

ACE-I ..... Angiotensin Converting Enzymes Inhibitors
ARB ..... Angiotensin Receptor Blocker
ANOVA ..... Analysis of Variant
BMI ..... Body Mass Index
CHF ..... Congestive Heart Failure
CRP ..... C-reactive Proteins
CRF ..... Chronic Renal Failure
CXR ..... Chest X-Ray
COPD ..... Chronic Obstructive Pulmonary Disease
DCM ..... Dilated Cardiomyopathy
ECG ..... Electrocardiogram
EPO ..... Erythropoietin
GFR ..... Glomerular Filtration Rate
HIV ..... Human Immunodeficiency Virus
Hb ..... Hemoglobin
HHD ..... Hypertensive Heart Disease
HF ..... Heart Failure
HJR ..... Hepatojugular Reflux
JVP ..... Jugular Venous pressure
JICA ..... Japan International Cooperation Agency
LVEF ..... Left Ventricular Ejection Fraction
MCV ..... Mean Cell Volume
MCHC ..... Mean Corpuscular Hemoglobin Concentration
MCH ..... Mean Corpuscular Hemoglobin
MNH ..... Muhimbili National Hospital
MUHAS ..... Muhimbili University of Healthy and Allied Sciences
MOPD ..... Medical Out Patients Department

NYHA	New York Heart Association
RAAS	Renin Angiotensin Aldosterone system
RBF	Renal Blood Flow
RDW	Red cell distribution width
RHD	Rheumatic Heart Disease
SD	Standard deviation
TB	Tuberculosis
TNF	Tumor Necrosis Factor
WHO	World Health organization

CHAPTER ONE

1. INTRODUCTION AND LITERATURE REVIEW

1.1. Definition and Epidemiology of anemia in heart failure

The world healthy organization (WHO) define anemia as hemoglobin <13.0g/dl in men and < 12g/dl in women. By using this definition, several studies have found the prevalence of anemia in CHF to have a wide range [1]. For patients with CHF, no specific Hb concentration has been acknowledged as being clinically meaningful. As a result, clinical surveys and trials use different anemia definitions when defining anemic and non anemic CHF patients. [1, 2]

The prevalence of anemia in heart failure varies depending on the study participants' selection and the level of hemoglobin decided to define anemia.[3, 4, 5, 6] In clinical trials and large Heart Failure (HF) registries, the prevalence of anemia in HF has been documented to range from 4% to 61%.[4, 5, 6, 7, 8] In a study by Nanas JN, Matsouka C et al among hospitalized patients, reported prevalence ranged from 14% to 70% .[1]

Several studies have been done in Africa. A study in Nigeria found that anemia was present in 40.5% of patients with Congestive Heart Failure (CHF).[7] Another study in Nigeria found that 36.7% of all patients with CHF had anemia [8]. A Hospital-based study in Kenya found the prevalence of anemia among patients with CHF was 13.2% [9]. In Uganda 64.3% of CHF patients admitted in Mulago National Referral Hospital medical wards had anemia. [5]

The Euro Heart Failure Survey which included 115 hospitals in 24 different countries found that 18% of male patients were anemic, if anemia was defined as Hb <11.0 g/dL. On the other hand if the Hb threshold was raised to 12.0 g/dL, the prevalence of anemia in this patient population increased to 33%. Thus, a 1.0 g/dL increase in the Hb threshold for defining anemia nearly doubles the percentage of "anemic" patients in the same study cohort. [10]

Al-Ahmad and colleagues showed that 22% of patients enrolled in the Studies of Left Ventricular Dysfunction (SOLVD) trial were anemic when a Hematocrit threshold of <39%

was used, but only 4.3% of the similar patient population was defined as anemic when the entrance was lowered to 35%. A Hematocrit of 36% would equate to a Hb concentration of 12.0 g/dL.[11]Silverberg and colleague defined anemia as Hb concentration <12.0 g/dL and reported a prevalence of 55.6% they also found that almost one-half of the patient population 79.1% was diagnosed with NYHA functional class IV and the mean LVEF of the entire cohort was 27.7 (±9.7). NYHA class I patients accounted for only 9.1% of anemic patients. [12]

Horwich and others defined Hb <13.0 g/dL in men and Hb <12.0 g/dL in women) in a cohort of 1061 patients with advanced CHF NYHA functional class III or IV; mean LVEF of 22% and found that 30% of all patients were anemic. [13] These authors also found that patients in the lower LVEF were more likely to be diagnosed with NYHA functional class IV (75.3%). This suggests that the prevalence of anemia increases with increasing severity of CHF.

In a study on hemodilution, which described a population of 196 patients with CHF referred for heart transplantation 61% of all patients were reported to be anemic (Hematocrit <41% in men, <38% in women).[14] However, the prevalence of anemia more than doubled from 33% in patients with NYHA functional class II to 68% in patients with NYHA class IV. [14]. Tanner et al report a prevalence of only 15% (Hb <12.0 g/dL). They also reported that prevalence of anemia increased from 8% in NYHA classes I and II patients to 19% in NYHA classes III and IV patients.[6] importantly, more than one-half of all patients in this study were diagnosed with NYHA functional class III or IV. [6]

The same trend was reported by Winsiacki et al in a cohort of 201 elderly patients with CHF, they report that 49.8% of all patients were anemic (Hb <12.0 g/dL), but the prevalence increased from 0% in NYHA class I to 52% and 65.9% in NYHA classes III and IV, respectively. However, approximately 70% of patients in this study were diagnosed with NYHA functional class III or IV [15]

Mild degree of anemia is associated with increased morbidity and mortality, it significantly impaired survival in women with Hb < 11.6g/dl and men with Hb < 12.5g/dl, values that may not be considered significant or associated with increased risk in clinical practice.[13] Hemoglobin is an independently risk factor for adverse outcome in patient with CHF with every 1g/dl decrease in Hemoglobin the risk of mortality increased by 16%,risk of death increased by 14.2% & this is independently of NYHA function classification.[13]

The occurrence of anemia in HF has been shown to be associated with several factors: older women were found to be more affected than men and younger women, Caucasians were affected more than other races. Other factors which were shown to be associated with anemia in HF were left ventricle systolic function, diastolic function and high serum creatinine.[16] Similarly, a study in Nigeria also found that more women (48%) were affected when compared to 31% males.[7]

1.2.1. Haemogram

A more conventional definition of anemia is a decrease in RBCs, Hb and Hematocrit below the previously established normal values for healthy persons of the same age, gender and race and under similar conditions. Problems with this definition may occur for several reasons. The blood values of non anemic persons may fall just below the normal level. Those of mildly anemic persons may fall within the low normal range. This latter group usually is not recognized unless the blood smear is evaluated or the RBC indices include mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) and RBC distribution width (RDW). In general, the clinical diagnosis of anemia is made from the history, physical examination, signs, symptoms and hematological values. [17]

1.2.2. Aetiology of anemia in CHF

The etiologies of anemia in CHF have until now to be prospectively determined. Retrospective work from Cromie et al.[18] and Ezekowitz et al.[19] have provided inadequate insight into the causes of anemia in CHF. A precise cause for anemia was not found in more than 58% of patients studied by Ezekowitz et al., with such patients labeled as having the "anemia of chronic disease."[19] Such retrospective studies fail to point up the various mechanisms in CHF that were likely to depress hemoglobin concentrations.

Modern automated blood cell analyzers generate a RBC histogram (RBC size frequency distribution curve).Abnormalities include a shift in the curve to the left (microcytosis) or to the right (macrocytosis), a widening caused by a greater variation about the mean, and two populations of cells.[17] The histogram complements the blood smear in identifying variant RBC populations. In addition, the RDW is a quantitative measure of the size variation of circulating RBCs and the reticulocyte count classifies anemia as hypoproliferative or hyperproliferative, thus indicating whether the bone marrow is producing adequate RBCs for the degree of anemia. However, there is 4-15% of false negative hypoproliferative or hyperproliferative, and 10-25% of false positive results can be found when using automated blood cell analyzers thus indicating that the bone marrow is producing adequate RBCs for the degree of anemia.[17]

The most important evaluation in the work-up of anemia is to examine the peripheral blood smear, giving particular attention to the RBCs as to variation in size, shape, color content, and inclusions.[17] The peripheral blood smear serves as a quality control to verify the results from automated blood cell analyzers with regard to the type of anemia.[17]

In their study Julius K, et al found the commonest type of anemia in CHF was normocytic normochromic affecting 88.2% of their anemic patients. [5] Folic acid and serum vitamin B12 have been found to be low in a few anemic patients with HF.[1] Nanas et al by using invasive bone marrow examination reported iron deficiency anemia as the primary cause of anemia in

HF patients, with a prevalence of 73%.[1] Others studies which do not use invasive bone marrow procedure reported prevalence of iron deficiency in CHF varying from 5% to 21% [19, 20]

Tests in search of an etiology of anemia included measurements of serum iron, Ferritin, erythropoietin, folic acid, vitamin B_{12}, thyroid-stimulating hormone, lactate dehydrogenase, bilirubin, Coombs test, albumin, globulin, creatinine, C-reactive protein, fecal occult blood test repeated three times, and bone marrow aspiration. Iron deficiency on bone marrow biopsy was defined as absence of iron stores. When the etiology of anemia was not clarified by these investigations, the patients underwent red cell mass measurement by ^{51}Cr assay [21,22].

In CHF, it is difficult to distinguish between absolute iron deficiencies anemia from anemia of chronic illness. Several studies have reported that patient with CHF had depletion of iron store on bone marrow aspiration.[1] The cause of high prevalence of iron deficiency anemia in patient with CHF is multifactor and it is partially resulting from defective release of iron from the cells, poor nutrition in advanced CHF, insufficient dietary intake of iron from acquired gastrointestinal malabsorption, chronic blood loss from gastritis due to use of NSAID and aspirin [21,22].

A study by Felker GM and others found that iron deficiency was present in CHF and the distribution of iron deficiency in patients with CHF was reported to be similar in anemia and non-anemic patients.[23]They found that 46% of patients who were defined as iron deficiency had normal hemoglobin. They also reported that that iron homeostasis plays a key role in oxygen transport and oxidative metabolism in skeletal muscles. Iron deficiency can exist without iron deficiency anemia. The presence of iron deficiency in CHF can be caused by chronic inflammatory process which also impairs iron utilization. [24]

It has also been reported that marginal iron deficiency may lead to reduction in exercise capacity long before the development of anemia. [22, 25] . This might explain an increase exercise capacity in patient supplemented with iron prophylactic

The "gold standard" for the diagnosis of iron deficiency is confirmation of absence of iron stores in a bone marrow aspirate sample. Bone marrow aspiration, however, is invasive and time consuming for laboratory staff. It is not advisable to be done as a routine diagnosis of anemia in patients with heart failure. Measurement of serum or plasma Ferritin is the best single blood test for the diagnosis of iron deficiency. Body iron is stored within molecules of Ferritin directly related to body iron stores of denatured Ferritin (hemosiderin) and appears to be in equilibrium with them [26]

1.2.3. Challenges in diagnosis of anemia in heart failure

Clinical studies and registry surveys have reported highly variable prevalence ranging from 4% to 61% (median 18%) in patients with CHF.[4, 5, 6, 7] .The results of these studies vary significantly because of differences in the definition of anemia and the selection of the study populations. This emphasizes the need for the establishment of generally accepted guidelines for the diagnosis and treatment of anemia in CHF. In general, anemia is more prevalent when higher Hb level concentrations are applied and in study cohorts which include more patients with greater cardiac function impairment. Anemic CHF patients share several clinical characteristics including advanced age, female gender, and poor cardiac function, history of renal insufficiency and hypertension.[21]

1.3. Mechanism of anemia in patients with heart failure

The mechanisms underlying anemia in HF patients have been postulated to be multifactorial:

1.3.1. Hemodilution

When relative anemia is coupled with hypervolemia, a frequent finding in HF patients, dilution anemia may occur. This is by the activation of the renin-Angiotensin Aldosterone system (RAAS) and vasopressin, leading to sodium and water retention. Androne and colleagues reviewed 196 patients with HF to assess the prevalence of true anemia or hemodilution and concluded that hemodilution was present in 46% of the anemic HF patients [14]. A study by Nanas and colleagues found that 5.4% of the patients had findings consistent with hemodilution and not true anemia. However, the presence of hypervolemia does not

prohibit the coexistence of true anemia.[1] The difference in prevalence between these two studies could be due to differences in techniques of blood volume measurements (^{51}Cr assay) in Nanas study versus radio labeled albumin in the study by Androne, and the small number of patients included in both studies might have contributed to this discrepancy. The other cause of the discrepancy could be the fact that iron-deficient patients also might be hemodiluted [1, 4]

1.3.2. Cardio renal syndrome

Reduced renal function is an important contributing factor to the anemia observed in CHF patients. The cardio renal syndrome occurs when there is concomitant HF, renal failure, and anemia. It has been extensively studied and is known to increase morbidity and mortality .In these cases there is reduction of erythropoietin (EPO) production as a consequence of chronic renal failure, Deficit in EPO has a key role in the pathogenesis of anemia.[19]

In a large study almost 50% of the chronic HF patients had an impaired renal function (eGFR, 60 ml/min).[20] In this study patients with anemia had a significantly more impaired renal function than those without anemia. Renal function (or eGFR) has been shown to be a powerful predictor of mortality in a wide spectrum of patients with HF, both in those with impaired and in those with preserved ejection fraction [21] Smith et al performed a meta-analysis on renal impairment and outcome in heart failure patients (n=80 098).[61] Mortality worsened incrementally across the range of renal function, with a 7% increase in mortality risk for every 10 ml/min decrease in eGFR. Patients with moderate to severe renal impairment had a significantly increased mortality rate (hazard ratio 2.31) compared to patients with normal renal function. [22]

A large registry on more than one million Medicare patients revealed that chronic renal failure (CRF), HF, and anemia are additive in increasing mortality. The annual mortality rate was 4% in patients without anemia, HF and CRF. The presence of either anemia or CRF was each

associated with an annual mortality rate of (8%), whereas the annual mortality rate for HF was 13%. The combination of these three co morbidities resulted in the highest annual mortality rate of (23%).Thus; these three components form a pathologic triangle, with notably increased mortality [27]

1.3.3. Erythropoietin production in Heart Failure

Erythropoietin is produced primarily in the kidney by specialized peritubular fibroblasts situated within the cortex and outer medulla.[28] The primary stimulus for erythropoietin production is low PO_2 that activates hypoxia-inducible factor-1 in the peritubular fibroblasts, which induces transcription of the erythropoietin gene. The kidney is very susceptible to hypoxia despite the fact that it receives nearly 25% of the cardiac output and uses less than 10% of the oxygen delivered. [28-30]

To maintain the osmotic gradient generated by the loop of Henley, the arterial and venous blood vessels supplying it run countercurrent and in close contact, which leads to shunt diffusion of oxygen between the arterial and venous circulations, causing PO_2 to decrease across the renal parenchyma, reaching around 10 mm Hg at the tips of the cortical pyramids where the erythropoietin is produced. This area is very sensitive to small changes in the PO_2, resulting from an imbalance between oxygen supply and oxygen demand related to increased proximal tubular sodium reabsorption caused by low renal blood flow (RBF) and glomerular filtration rate. [28-30]

During HF, Renal Blood Flow is decreased and some renal dysfunction is common, but structural renal disease that could reduce erythropoietin production is infrequent. Therefore, reduced RBF should increase erythropoietin. Indeed, erythropoietin is increased, in proportion to the severity of HF, but is lower than expected for the degree of anemia, suggesting a blunted erythropoietin production.[29] Studies of the complex relationship between RBF and erythropoietin secretion during HF have been inconsistent. [30]

1.3.4. Drugs (ACE-I, ARB)

Angiotensin-converting enzyme (ACE) inhibitors may play a role in causing anemia in HF patients. The Studies of Left Ventricular Dysfunction (SOLVD) trial [19] has shown that patients receiving enalapril had significantly lower haematocrit levels when compared with those who were not. It has been postulated that both ACE inhibitors and angiotensin receptor blockers (ARBs) inhibit growth of erythroid precursors.[31]Studies in patients with polycythemia have demonstrated that these agents are efficient in reducing hemoglobin concentrations.[12] In patients with normal renal function, the decline in RBC production is seldom clinically significant. Additionally; ACE inhibitors and ARBs may decrease EPO production, further contributing to HF patients' anemia.

The mechanisms by which ACE inhibitors might suppress erythropoiesis are; First, ACE inhibitors reduce circulating insulin-like growth factor-I and thereby reduce erythropoiesis.[15] Second, ACE inhibitors increase plasma levels of the natural stem cell regulator N-acetyl-seryl-aspartyllysyl- proline, which prevents the recruitment of pluripotent hematopoietic stem cells [32]

The potential for angiotensin receptor antagonist therapy to retard RBC production is still poorly defined. Plasma erythropoietin levels are elevated in congestive heart failure (CHF). These levels are return to normal with ACE inhibitor therapy and this process parallels clinical and hemodynamic improvement. The drop in erythropoietin levels probably reflects relief from the renal hypoxia characteristic of untreated CHF.[33] ACE inhibitors typically improve pulmonary congestion and thereby gas exchange, in addition to increasing renal blood flow.[34]Each of these changes can be expected to favorably influence renal hypoxia. This hypothesis is supported by a recent report showing that in patients with CHF, renal plasma flow and serum erythropoietin are considerably interconnected. [35]

The increase in circulating erythropoietin is associated with increased packed RBC volume in patients with severe CHF. Plasma volume also increases in CHF. Accordingly, the increase in packed RBC volume does not present as an increase in hemoglobin concentration, since its presence is masked by a relative hemodilution.[31] On the contrary, when ACE inhibitor therapy is begun and plasma volume decreases, the anticipated hemoconcentration is not observed, since RBC production has decreased in parallel.[36]

The clinical relevance of ACE inhibitor-related anemia is difficult to establish in the CHF patient. At the least, it is one of several causative factors to the low-grade anemia observed in many CHF patients.

1.3.5. EPO Resistance

EPO resistance is another important factor associated with anemia in HF, higher serum levels of EPO have been directly associated with increased mortality [36] . Hormone resistance is frequently seen in CHF and it is likely, in theory, that resistance to endogenous EPO may enlarge this phenomenon. Elevated plasma levels of inflammatory cytokines, particularly TNF, are implicated in this process and have been shown to interfere with the peripheral actions of EPO. [36, 37, 38] More studies in human CHF are considered necessary to explain how often EPO deficiency or EPO resistance are applicable to anemia in CHF.

1.3.6. Chronic Disease Anemia

This is also referred to as "anemia of inflammation", it is seen in chronic illness, such as TB, HIV/AIDS, chronic immune activation, connective tissue disorders or malignancy. It has been suggested that the syndrome is likely primarily the result of the body's production of hepcidin, a regulator of human iron metabolism.

In response to inflammatory cytokines, predominantly IL-6, the liver produces increased amounts of hepcidin. Hepcidin in turn stops ferroportin from releasing iron stores. Inflammatory cytokines also appear to affect other important elements of iron metabolism, including decreasing ferroportin expression, and probably directly blunting erythropoietin by decreasing the ability of the bone marrow to respond to erythropoietin. [12]

Anemia in patients with advanced CHF may be due to bone marrow suppression by inflammatory cytokines.[31] Interleukin-1 and tumor necrosis factor-α directly inhibit the in vitro production of erythropoietin in patients with inflammatory disorders who commonly exhibit a blunted response of erythropoietin to anemia Elevated plasma concentrations of tumor necrosis factor-α interfere with the peripheral effects of erythropoietin. [31]

Tumor necrosis factor-α, IL-6, and several other proinflammatory cytokines and CRP are increased in HF and inversely related to Hemoglobin. IL-6 and tumor necrosis factor-α also inhibit erythropoietin production in the kidney by activating GATA-2 and nuclear factor-κB, which could explain the blunted erythropoietin response in HF.[31,39] These cytokines also inhibit proliferation of bone marrow erythroid progenitor cells; IL-6 stimulates the production of hepcidin in the liver that blocks duodenal absorption of iron. Furthermore, IL-6 down-regulates the expression of ferroportin, preventing the release of iron from body stores. Thus, an activated proinflammatory state, an essential component of anemia of chronic disease can contribute to the development of anemia in CHF.[39]

Anemia is frequently associated with decreased body mass index [3, 19, 38], a finding that suggests that patients with cachexia are at greater risk for anemia.[33, 38] Serum levels of proinflammatory cytokines are increased in cachectic patients with CHF and may contribute to development of anemia by several mechanisms. Proinflammatory cytokines as indicated above disrupt multiple aspects of erythropoiesis,[38,40] including reduction of renal erythropoietin secretion, suppression of erythropoietin activity in red blood cell precursors in the bone marrow level, and reduction of bioavailability of iron stores for hemoglobin synthesis.[40]

1.3.7. Ferropenic anemia

A study by Christopher and others found that iron deficiency was present in CHF and the distribution of iron deficiency in patients with CHF was reported to be similar in anemia and non-anemic patients[21] They found that 46% of patients who were defined as iron deficiency had normal hemoglobin. They also reported that that Iron homeostasis play a key role in oxygen transport and oxidative metabolism in skeletal muscles. Iron deficiency can exist without iron deficiency anemia. The presence of iron deficiency in CHF can be caused by chronic inflammatory process which also impairs iron utilization .[21]

Iron deficiency may be detected by several diagnostic tests including indices at full haemogram, peripheral blood smear, bone marrow examination and serum Ferritin levels. Frequently recommended criteria for a diagnosis of iron deficiency anemia in an individual are a detection of total Ferritin <15 μg/L, hemoglobin <12 g/dL and haematocrit <36.[11] As early negative iron balance and storage depletion occurs well before these levels, these are either late indicators or insensitive. Furthermore, anemia also occurs in severe iron overload [11,41] Unfortunately, no current predictable serum indicator of iron status is diagnostic for iron deficiency.

Serum Ferritin declines as iron stores decline except when elevated by inflammation because ferritin protein is an acute phase reactant. Elevations in serum ferritin protein levels may occur without elevation of iron stores in acute inflammatory conditions or in liver disease or cancer [44] where serum ferritin protein is usually >400 ng/ml. A serum ferritin level ≤ 50ng/L is cited as evidence for iron deficiency in anemic patients with coexisting chronic disease states such as inflammation, infection, and malignancy. [42, 43]

Serum Ferritin value ≤ 100ng/L have a high specificity for diagnosing the presence of iron deficiency in patients with a wide variety of chronic and acute medical problems. If the ferritin level determination and bone marrow examination are performed within 24 hours of each

other, the sensitivity of a serum ferritin level ≤ 100ng/L for iron deficiency is also high. Herbert V et al suggest that the recommended serum ferritin threshold of ≤ 50ng/L for diagnosing iron deficiency in anemic patients with coexisting inflammation, infection, or malignancy may be too low in anemic patients with a wider variety of acute and chronic illnesses. [11, 41]

1.4. Pathophysiology of anemia in Heart Failure

Chronic, severe anemia may cause HF in absence of primary heart disease.[1] Correction of anemia in such patients improves symptoms of heart failure. Tissue hypoxia, due to the severely decreased hemoglobin concentration, causes vasodilatation. Consequently, the systemic blood pressure falls, and the sympathetic nervous system is activated, causing tachycardia and renal vasoconstriction.

Renal vasoconstriction reduces renal blood flow and GFR, and activates the renin-angiotensin aldosterone system which causes fluid retention, manifested as central and peripheral edema and cardiac dilatation.[1] Prolonged dilatation of the cardiac chambers, combined with hyperactivity of the sympathetic nervous and renin–angiotensin–aldosterone systems, progressively cause cardiac remodeling and chronic heart failure. Nanas and colleagues found that, in patients with preexisting chronic HF, lesser degrees of anemia can cause further deterioration by activation of neurohormonal mechanisms. [1]

The effect of anemia on cardiac remodeling has been studied experimentally. In rats, anemia induces eccentric hypertrophy accompanied by increased capillary proliferation and a 50% increase in heart mass[45] The connection between anemia and cardiac remodeling has also been studied broadly in patients with renal disease.[46] In patients with early renal disease, Levin and colleagues observed a decrease in hemoglobin concentration associated with an increase in LV mass index [46] Foley and colleagues found that in patients with end-stage renal failure each 1 g /dL decrease in mean hemoglobin concentration was independently related with the presence of LV dilatation and with the development of de novo and recurrent HF.[32]

1.5. Clinical presentation of patients with Anemia in congestive heart failure

The clinical profile of anemic CHF patients shows that anemic patients with CHF tend to have more severe symptoms and signs of heart failure; are older; female; have greater cardiac functional impairment and higher hospitalization rates. They may also have a history of diabetes, renal insufficiency and hypertension; and are frequently taking diuretics.[12]Ezekowitz and colleagues analyzed the risks and the odds ratios of independent factors predicting anemia in elderly patients with new-onset CHF. Four different factors were recognized that were likely to be related with anemia: age, female gender (20% increase in risk); chronic renal insufficiency (3-fold increase in risk); and chronic hypertension (30% increase in risk) [19]

In a study done at Mulago hospital Uganda [5] hypertensive heart disease was significantly associated with anemia (odds ratio (OR) 0.31, 95% confidence interval (CI) 0.13 - 0.74, $p<0.01$), as were increasing age (>50 years) (OR 2.92, CI 1.41 - 6.05, $p<0.01$) and raised creatinine (>133 μmol/L) (OR 0.17, 95% CI 0.08 - 0.37, $p<0.01$) and urea (>17.85 mmol/l) (OR 0.12, 95% CI 0.05 - 0.31, $p<0.01$)[5]

1.6. Co-morbidity, Morbidity, and Mortality in CHF with Anemia

Studies have labeled anemia as an independent risk factor for increased mortality in patients with CHF.[41, 42] Kosiborod and colleagues reported that a low haematocrit level was associated with greater mortality, and is an independent predictor of 1-year mortality in a group of hospitalized, elderly patients with heart failure. Furthermore, the survival rate of those patients decreased significantly with decreasing haematocrit when mortality was analyzed according to haematocrit quartiles.[41]

Similar observations were made by Horwich and colleagues, who showed that low Hb levels were a significant predictor of mortality in patients with advanced CHF.[13] The authors reported that even mild degrees of anemia were related with increased morbidity and mortality

and that a linear relationship exists between hemoglobin levels and mortality.[13] The study established that a lower haematocrit was strongly linked with death from progressive heart failure rather than sudden deaths or other deaths [13]. On the other hand, these investigators observed that no association between total mortality and anemia could be found when haematocrit levels were within or near normal values.

This result suggests that a margin of risk may exist rather than a linear relationship between anemia and mortality [13] .In addition, the authors reported that heart failure patients in the lowest Hb quintile (haematocrit 25.4% to 37.5%) had a 52% higher risk of death than those in the highest Hb quintile (haematocrit 46.1% to 58.8%) [13]. This increased mortality risk was twice the risk associated with diabetes, smoking, 10 years of age, or a difference of 10% in the ejection fraction in this study population.[13]

Advanced age could be a likely reason for increased mortality in anemic patients with CHF. Ezekowitz and others performed a Cox proportional hazard analysis on a subset of patients representing the youngest and healthiest group of patients with CHF and found that anemia even more strongly correlated with mortality in these patients than in the entire cohort. [19]

Renal insufficiency is one of the characteristics commonly connected with anemia in patients with CHF [11, 44]. This remark raises the possibility that anemia in CHF may just be a marker for underlying renal disease. Al-Ahmad et al.[11] showed that in anemic patients with left ventricular dysfunction enrolled in the SOLVD study, both decreased kidney function and anemia were risk factors for all-cause mortality, especially when both conditions were present. The authors reported a weak, but statistically significant, correlation between haematocrit and predicted glomerular filtration rate.[11]

Even though the number of patients with renal impairment increased with increasing anemia, 40% of severely anemic patients had normal values for serum creatinine [41], [44]. Detailed analysis of the patient population revealed that a similar hazard ratio at 1 year was associated

with the presence of either anemia or renal insufficiency.[44] More notably, Kosiborod and colleagues calculated that mortality in anemic CHF patients without renal insufficiency was slightly higher with lower haematocrit than in patients with renal dysfunction (2.5% and 1.0% higher mortality per 1.0% lower haematocrit, respectively.[41]

Many studies have related anemia to undesirable clinical events in patients with HF. Sales et al observed 16.8% mortality in patients with anemia versus 8% in patients without anemia. Anand and others.[31] established that there was 28% and 16% mortality in anemic and non-anemic patients, respectively, with hospitalization rates of 56% and 33%, during a mean follow-up period of 12 months. The authors observed that each for each 1g/dL of higher serum hemoglobin is coupled with a reduction of 15.8% and 14.2% in risk of death and hospitalization, respectively. This effect does not depend on the type of HF according to the systolic function. However, the link between anemia, HF and events is not clear, because anemia may only be a marker of increasing severity of HF or merely yet another co morbidity, giving patients a poor prognosis.[31]

CHAPTER 2

2.1 PROBLEM STATEMENT

CHF is a common condition which affects the quality of life than most of the chronic conditions. Its 5-year mortality rate is worse than most of the chronic conditions including cancer [47, 49]. Recent reports have suggested that mild to moderate anaemia is a prevalent condition in HF patient population. But it is also known that severe and chronic anemia can itself lead to development of HF [47]

Anemia in CHF patients is associated with increased morbidity and mortality. [44] The exact cause of anemia in HF is not well established but it has been stipulated that, it may be due to fact that HF is a chronic disease which may lead to, bone marrow suppression from excessive cytokines production. Other causes could be malnutrition, concomitant renal disease and /or drug therapy like prolonged uses of aspirin with associated gastric erosion.[48] Others have given weight to hemodilution as a contributor. A reduced haematocrit can also result from an increase in plasma volume [1, 14]

There is a larger number of patients with HF in Africa due to various causes[47] and the prevalence of anemia in these countries due to various causes is high, therefore the occurrence of the two conditions probably leads to considerable morbidity and mortality in HF patients.[47] However, neither the prevalence nor the prognostic importance of anemia in CHF has been well defined in the developing countries such as Tanzania.

In Tanzania, anemia is common with a prevalence of 48% among non-pregnant females and 40% among males; and, it was found to be a common problem in those attending for hospital care.[50] The study showed that Iron deficiency state; iron deficiency anemia and HF are common in Tanzania. The prevalence of anemia in HF population and associated factors are not well described in Tanzania hence this study is aimed at determining the magnitude of anemia in heart failure patients and its associated factors.

2.2: RATIONALE

Several studies have shown that anemia in HF is a common problem and is an independent prognostic marker for clinical outcome.

Nevertheless, most of these studies have been carried out in the developed countries and only severe forms of heart failure have been widely explored. The prevalence and underlying cause of anemia in CHF is not well known and little is known about the magnitude and correlation of anemia and CHF in developing world including Tanzania.

Therefore this study will provide data on the magnitude of anemia in patients with CHF.It will also form the basic understanding of anemia in patients with CHF in our set up.

2.3: OBJECTIVES

2.3.1. Broad Objective

To determine the prevalence of anaemia in patients with CHF at Muhimbili National Hospital.

2.3.2. Specific objectives

1. To determine the prevalence of anaemia in patients with CHF aged 7 yrs and above
2. To determine the morphological type of anaemia in patients with CHF
3. To determine the association between NYHA functional class and anaemia in patients with CHF.
4. To determine the association between EF and anaemia in patients with CHF.
5. To assess the associated co-morbidities among anaemic patients with CHF.

CHAPTER THREE

3. Methodology

3.1 Study design

This was a hospital based cross-sectional descriptive study

3.2. Study site

The study was conducted on Medical wards and Medical Outpatient clinics at Muhimbili National Hospital (MNH)

MNH is a tertiary referral and teaching hospital, situated in Dar es Salaam. It also serves as a regional hospital for Ilala, Temeke and Kinondoni municipal hospitals. It serves about 1000 outpatients per day and has medical wards bed occupancy of about 300 beds. Administratively at MNH all patient above 7yrs of age are managed medical wards and in adult clinics.The Department of Internal medicine runs among other clinics, a specialized cardiac clinic every Friday afternoon and has facilities for echocardiography and ECG.

3.3. Study population

Patients admitted or referred at MOPD clinic with suspected heart failure. Inpatients includes both new and follow up patients, outpatients includes only first ever visit at MOPD

3.4. Sampling technique

Inpatients were consecutively selected from admitting medical wards on daily basis next day after admission. All files were screened and those with a diagnosis of heart failure were selected and further evaluated to see if they met the inclusion criteria. Patients were excluded based on history, case notes and/or presence on supportive investigations.

In medical out patient clinics, on each clinic day all patients referred with the diagnosis of heart failure were evaluated to see if they met the inclusion criteria.

3.5. Inclusion criteria

i) Those who met the Framingham criteria for clinical diagnosis of heart failure
ii) Age above 7yrs
iii) Consent to take part in the study
iv) Not known to have HIV
v) Not known to have pulmonary TB

3.6. Exclusion criteria

This was done by using history, case notes and investigations and it included those patients with heart failure by Framingham criteria but are

i) On treatment for anemia or have received transfusion in the past 4 weeks
ii) Patients with diseases known to cause anemia
iii) Having HF secondary to severe anemia

3.7. Sample size

The sample size was obtained using the following formula

$N= 4p\ (100-p)/\ \varepsilon^2$

Where

n =the required sample size

ε = maximum likely error, is 8 %

p = prevalence

The prevalence of anemia in Heart failure patient in patient readmitted due to HF at MNH was reported to be 33.3%.

Therefore, the minimum sample size was **138 patients**; a total number of 140 patients were included in the study.

3.2. Definition of terms for this study

3.2.1. Anaemia

Anemia for this study was defined as per WHO definition as hemoglobin <13.0g/dl in men and <12.0 gm/dl in female

3.2.2. Diagnosis of congestive heart failure

The diagnosis of congestive heart failure was done by using Framingham Criteria for Congestive HF.

Framingham Criteria requires the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria.

The Framingham Criteria

Major criteria

- Paroxysmal nocturnal dyspnoea
- Neck vein distention
- Rales
- Radiographic cardiomegaly (increasing heart size on chest radiography)
- Acute pulmonary edema
- S3 gallop
- Increased central venous pressure (>16 cm H2O at right atrium)
- Hepatojugular reflux
- Weight loss >4.5 kg in 5 days in response to treatment with diuretics

Minor criteria

- Bilateral ankle edema
- Nocturnal cough
- Dyspnoea on ordinary exertion
- Hepatomegally
- Pleural effusion. Tachycardia (heart rate>120 beats/min.)
- Decrease in vital capacity by one third from maximum recorded

3.2.3. NYHA Functional Classification for Congestive HF

NYHA is a semi quantitative symptom based (fatigue, palpitations, dyspnoea) assessment with regard to physical disability in patients with cardiac disease. The NYHA Functional Classification provides a simple way of classifying patients for clinical care and research. It places patients in one of four categories, based on how much they are limited during physical activity:

Class I: Patients with cardiac disease but without limitation of physical activity. They suffer no symptoms from ordinary activities.

Class II: Patients with cardiac disease resulting in slight limitation of activity; they are comfortable with rest. Ordinary activity results in symptoms

Class III: Patients with cardiac disease resulting in marked limitation of activity; they are comfortable only at rest. Less than ordinary physical activity causes symptoms

Class IV: Patients with cardiac disease resulting in inability to do any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest. Any physical activity brings on discomfort and worsens symptoms.

3.2.4. Renal function

Estimated glomerular filtration rate was calculated by Cockcroft-Gault equations

$$\frac{(140 - \text{Age}) \times \text{weight}}{72 \times \text{serum creatinine in umol/L}}$$

For females =answer x 0.85

The presence of probable renal dysfunction was identified according to a threshold of eGFR <60mils/min a definition used in many clinical trial in HF. (ref)

3.2.5. Co-morbidities

These are co-existing diagnosis that are indirectly (non cardiac) or directly (cardiac) related to the Congestive Heart failure but may alter the outcome. In this study the co –morbidities considered were: Hypertension, diabetes and chronic kidney disease.

Patients known to be hypertensive by history and case notes or patients with systolic blood pressure equal or above 140-159mmHg and diastolic blood pressure equal or above 90-99mmHg was classified as hypertensive.

Diabetes was defined as from history and case notes confirming a patients to be diabetic (for newly diagnosed patients, fasting plasma glucose (126 mg per dL [7 mmol per L] or higher) confirm the diagnosis of diabetes mellitus).[62]

3.2.6. Data collection methods

A structured questionnaire (Appendix I) was used for data collection.

3.2.7. Study Procedures

The investigator did thorough Clinical evaluation including history taking and physical examination. All patients had their weight, height, blood pressure and pulse taken. History taking included Socio-demographic characteristics, past medical history, drug history, and common symptoms of heart failure such as dyspnoea on exertion or at rest, fatigue, orthopnoea, paroxysmal nocturnal dyspnoea, palpitation and ankle swelling. A general examination and full cardiovascular assessment was done. The NYHA classifications were determined for each patient.

3.2.8. Laboratory Investigation

Venopuncture was done; 10mls of blood was collected for biochemical and haematological investigations. This included RBC count, haemoglobin, Haematocrit, MCV, MCHC, Serum creatinine, potassium, urea, phosphate, calcium, blood sugar, cholesterol level, serum Ferritin and Peripheral smear for red cell morphology.

Laboratory investigations were done in the Central Pathology Laboratory (CPL) of the Muhimbili National Hospital (MNH). Hematological and biochemical results from MNH laboratory of less than seven days before recruitment were accepted and considered valid results for the study. Peripheral smear were read by experienced hematologist at MNH laboratory.

3.2.9. Echocardiogram

Echocardiogram was done using a PHILIPS, HP 7550 Echocardiography machine with a 2.5.0MHz transducer for adults and 5.0MHz for children.

Standard M-mode, 2D and Doppler studies were done by the investigator under supervision of a cardiologist. Measurements included cardiac chamber size and anatomy; LV and right ventricular ejection fraction. Assessment was done to detect pericardial, valvular and septal defects. Echocardiography results done by a cardiologist at MNH in the last one month before recruitment were accepted and taken as valid results for the study.Additional work up investigations for each patient included ECG and CXR.

3.2.10. Data entry, cleaning and analysis

All questionnaires were daily checked for completeness and accuracy by the investigator. Pre-coded data were entered into computer Epi Info version 6 and data was cleaned before being transferred to Stata version 10 for analysis. Data was then summarized into frequency distribution tables and cross tabulations. Comparisons of proportions were done using χ^2 tests

especially when comparing different proportions. Comparisons of means were done using student's t test and ANOVA. Two tailed p value of 5% was termed significant.

3.2.11. Ethical consideration

The study received ethical clearance from the Research and Publication committee of MUHAS and the Ethics department of MNH. Patients were included after informed verbal and written consent. Confidentiality was adhered to when filling the data collection sheets. Physical examinations were conducted in privacy and whenever needed in presence of a nurse. For those who were under 18 years of age, their caretakers were requested to give written/verbal consent. Those who declined consent were not in any way deprived their right to receive medical attention and advice.

3.2.12. Disposal of Study patients

All clinical findings and results on study patients (hematological and ECHO) were immediately availed to the physicians looking after the patients to continue with standard care as per MNH management guidelines.

CHAPTER FOUR

4.1. RESULTS

Between the months of august 2009 to end of January 2010, a total a total of 204 patients were eligible for the diagnosis of heart failure at MNH. Of these 138 patients were admitted due to heart failure, while 66 patients were diagnosed from the out patient clinic. 26 patients did not meet the inclusion criteria.178 patients met the study inclusion criteria. Thirty eight (38) patients had incomplete data and were excluded from analysis; these were 11patients from inpatients and 27 from outpatients. Complete data was available for 140 patients and these form the basis for further analysis.

4.1.1. Patients characteristics

Table 1 reveals the characteristics of study population by their anemia status. Sixty six (47.1%) were males, seventy four (52.8%) were female. The median age for the study participants was 42.5± 20.3. Men with CHF and anemia were older than female. The age difference was statistically significant (p=0.001)

Proportionally more men (84%) than female (70.2%) had anemia and heart failure, the difference was statistically significant (p=0.04). Level of education had a significant influence on the prevalence of anemia, lack of formal education was associated with higher prevalence of anemia (p=0.012)

Table 1: Demographic characteristics of congestive heart failure patients according to their anemia status

Variable	Whole group N=140	Non anemic N= 32	Anemic N=108	P-value*
Gender				
Male	66(47.1%)	10(15.2%)	56(84.9%)	
Female	74(52.9%)	22(29.7%)	52(70.3%)	0.040
Respondents				
Education Level				
No formal education	21(15.0%)	2(9.5%)	19(90.5%)	
Primary	83(59.3%)	17(20.5%)	66(79.5%)	
Secondary	20(14.3%)	10(50.0%)	10(50.0%)	
Post Secondary	16(11.4%)	3(18.8%)	13(81.2%)	0.012

Data are mean (SD) for continuous variable (age) or percentage.

* χ^2 Anemic versus non-anemic groups.

4.1.2 Physical findings

Table 2 reveals the various clinical findings with regard to anemic status. The most common findings were lower limb edema in 96.40%, basal crepitation in 86.3%, tender Hepatomegally in 82.8%, elevated Jugular venous pressure in 77.6%.Pallor was found in 10.0% of the patients. The difference in distribution of the above symptoms among anemic and non anemic patients was not statistically significance. Other finding found includes severe hypertension, goiter, atria fibrillation, massive Ascitis and peripheral neuropathy.

Resting Tachycardia was found in 40.71% of the patients. The mean pulse rate per minute for the study patients was 99.45 ± 16.97. Anemic patients had a higher mean pulse rate of 105.06 ± 22.3 compared to non-anemic patients. 97.78 ±14.74 .The difference was found to be statistically significant by using t test p=0.0329

Normal weight was seen in 50.7% of patient (BMI 18.5-24.9 kg/m^2),12.8% of patients were underweight (BMI <18.5 kg/m^2) and 36.4% were overweight (BMI >25 kg/m^2). Which means

patients with BMI <18.5 kg/m^2 present more with anemia compared to other BMI categories. (Table 2)

The difference between BMI categories in anemic patients were found to be statistically significant p=0.004(by using fishers exact test).All patients with BMI below 18.5 were found to have anemia compared to other BMI categories

Table 2: Clinical characteristics of the patients with congestive heart failure according to their anemia status

Variable	Whole group N=140	Non anemic N= 32	Anemic N=108	P-value*
Duration of HF				
<6months	29(20.7%)	10(34.5%)	19(65.5%)	
≥6months	111(79.3%)	22(29.8%)	89(80.2%)	0.094
BMI kg/m²				
<18.5	18(12.9%)	0(0.0%)	18(100%)	
18.5 – 24.9	71(50.7%)	14(19.8%)	57(80.2%)	
>25	51(36.4%)	18(35.4%)	33(64.6%)	0.004
Physical findings				
Pulse rate**	99.45±16.9	97.78±14.7	105.06±22.3	0.032
JVP/HJR	108(77.1%)	22(20.4%)	86.0(79.6%)	0.198
Basal crepitation	117(83.6%)	29 (90.6%)	88 (81.5%)	0.220
Acute pulmonary Edema	7(5.0%)	0(0.0%)	7(100%)	Ns
Pleura effusion	17(12.1%)	3(17.7%)	14(82.3%)	0.585
Hepatomegally	116(82.8%)	27(23.3%)	89(76.7%)	0.795
Ascitis	61(43.6%)	14(22.9%)	47(77.1%)	0.981
Lower limb Edema	135(96.4%)	30(22.2%)	105(77.8%)	0.353
Pallor	13(10.0%)	2(15.4%)	11(84.6%)	0.501
NYHA				
Class I	3(2.1%)	2(66.7%)	1(33.3%)	
Class II	15(10.7%)	7(46.7%)	8(53.3%)	
Class III	59(42.1%)	14(23.7%)	45(76.3%)	
Class IV	63(45.0%)	9(14.3%)	54(85.7%)	0.013

**Data are mean (SD) for continuous variable (pulse rate in beats/minutes)

* χ^2 Anemic versus non-anemic groups.

4.1.3 Prevalence of anaemia

Overall prevalence of anemia was 77.1% at the time of assessment, with greater frequency in males (82.9 %) compared to females (70.3 %). The overall mean hemoglobin was 10.84±2.7; Mean Hemoglobin was 10.9 ± 2.4 for males and mean Hemoglobin was 10.7± 2.1 for females Mild anemia, moderate anemia and severe anemia was seen in 63(45.0 %), 39(27.8%), and 6(4.3%) of the patients, respectively; and there was no statistically significant difference in gender distribution, p=0.180 .

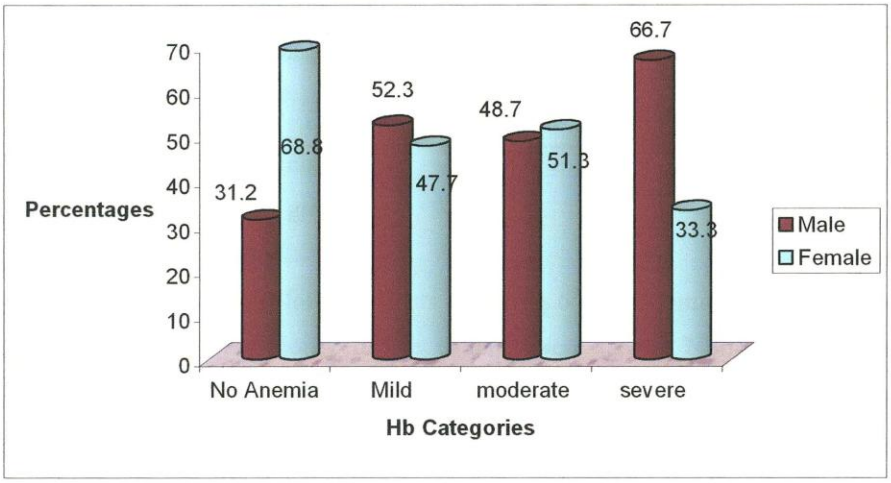


Figure 1. Hemoglobin categories of patients with CHF according to sex
KEY: No anemia Hb ≥12F or Hb≥13M, Mild anemia Hb 10-<13, Moderate anemia Hb 7-<10, Severe Hb ≤ 7

4.1.4. Red cell morphology of congestive heart failure patients

Table 3 shows mean hematological indices and biochemical findings of the patients. Mean haematocrit was statistically different between anemic and non anemic patients, being 41.05±4.86 for non anemic patients vs. 32.01 ± 8.6 in anemic patients. P-value =0.0001. The mean haematocrit was found to be 33.68 ± 9.7 in all patients

Table 3. Mean hematological indices and biochemical findings of patients with congestive heart Failure according to their anemia status

Variable	Whole group N=140	Non anemic	Anemic	P-value*
Hemoglobin	10.84±2.7	13.3±1.4	10.5±2.5	0.00001
MCV(median)	79.16±13.1	80.85±11.2	79.3±12.8	0.165
MCH	27.31±4.7	28.9±3.7	27.2±4.2	0.195
MCHC	32.07±2.1	32.5±1.4	32.0±2.4	0.760
Hematocrit	33.68±9.7	41.05±4.8	32.01±8.6	0.0001
Platelets	250.27±24	243.88±16.2	252.16±12.1	0.730
Serum creatinine(median)	202.5	93.5	234.8	0.007

Data are mean (SD) for continuous

*Anemic versus non-anemic groups.

A full haemogram was done for all patients regardless of their anemic status and the results are as shown in figure 3. Majority of the patients were having Normocytic normochromic (77.9%), of those (27.5%) were having normal hemoglobin value according to their sex, and (79.5%) were having anemia. Microcytic hypochromic was found in (17.1%) 0f the patients and among them (91.7%) were having anemia; three patients had leukoerythroblastic reaction reported from their peripheral blood film. The differences between the groups were not found to be statistically significance p=0.178

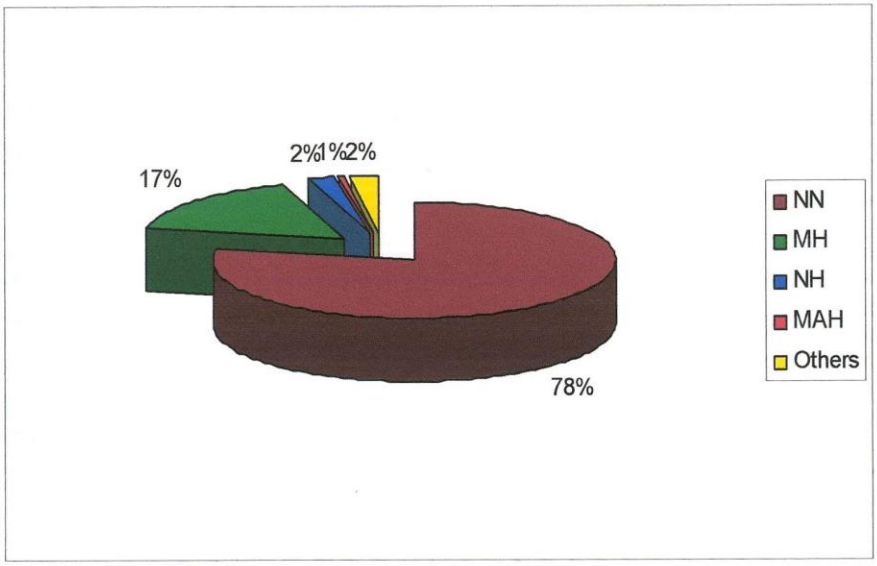


Figure 2. Red cell morphology of congestive heart failure patients
Key

NN – Normocytic normochromic

MH – Microcytic Hypochromic

NH – Normocytic Hypochromic

MAH – Macrocytic Hypochromic

4.1.5. Iron studies

A total number of 126 (89.3%) of patients examined had serum Ferritin estimation .As shown in table 6, majority of patients (92%) had normal serum Ferritin and 10% had above normal levels. Among these patient two (1.4%) had below normal Ferritin levels yet their haematocrit and hemoglobin was meeting the diagnostic criteria for ferropenic anemia.

It was found that 27.8% of the patients were having a serum Ferritin level of below 50ng/l. 90.00% Patient with serum Ferritin above 400ng/dl were having anemia followed by 88.6% 0f patients with serum Ferritin level less than 50ng/dl, however the difference within the groups when comparing serum Ferritin of anemic versus non anemic was not statistically significance p=0.115.These results indicate that serum Ferritin does not relate to presence of anemia in

chronic heart failure. The results are as shown in table no 4

Table 4. Serum Ferritin of the patient with congestive heart failure in relation to status of anemia

Variable	Whole group N=126	Non anemic N=26	Anemic N=100	P-value*
<50ng/dl	35(27.8%)	4(11.4%)	3(88.6%)	
50 – 100	33(26.2%)	6(18.2%)	27(81.8%)	
101 – 400	48(38.1%)	15(31.3%)	33(68.7%)	
>400	10(7.9%)	1(10.0%)	9(90.0%)	0.115

Normal range (13ng/l – 400ng/l)

Data are mean (SD) for continuous variable serum Ferritin

*Anemic versus non-anemic groups

4.1.6. NYHA functional classification

When these patients were classified according to severity of heart failure, it was found that 3(2.1%) were in NYHA class I, 15(10.7%) were in NYHA class II, 59(42.1%) were in NYHA class III and 63(45.0%) were in NYHA class IV. Proportionally it was found that majority of the patients (85.71%) with anemia were in NYHA class IV, follower by NYHA class III 76.3%, class II 53.3% and 33.3% were in NYHA class I. p=0.013

The Risk of having anemia increases with severity of heart failure (measured by NYHA classification).A patient in NYHA class IV had 12 times likelihood of becoming anemic as the one in class I, OR 0.5, CI (0.04 – 5.51) and OR 6.0 CI (2.96- 12.15) for class I and IV respectively) class II OR1.1, CI (0.41 – 3.15).class III OR 3.21 CI (1.76-5.85),chi square for trends was found to be statistically significance with p=0.0018.

Hemoglobin was found to decrease as the patients are having severe form of heart failure. Mean hemoglobin was 13.5±1.5 in patients with NYHA class I, and 10.47± 2.2 in NYHA class IV, the difference between mean hemoglobin between the NYHA classification was not statistically significant by ANOVA p=0.060 .This findings could suggest that anemia was equally prevalent in NYHA class II.III and IV.

Anemia was found to be more prevalent in those with symptoms for more than six month, however the difference did not reach significant level (p=0.094). Other baseline characteristics of the patients are as it is shown in table 2

Patients with severe form of heart failure (NYHA IV) were found to have low haematocrit compared to other groups. Mean haematocrit was found to decrease from 38.16±10.7 in NYHA I to 32.56±2.5 in patients with NYHA class IV. The difference between the groups by ANOVA was statistically significant p=0.031.

4.1.7. Echocardiography findings of the patients

4.1.8. Left ventricular ejection fraction

Left ventricular ejection fraction (EF) was found to be less than 45% in 88(63 %) of the patients, among those 76.1% were having anemia. EF of more than 45% was found in 52(37%) of the patients, among those 78.85% were having anemia, and the difference between the two groups of ejection fraction was not statistically significant, p= 0.712.

The mean LVEF was 32.7±8.3 (95%CI 31-34) in patients with reduced EF ≤45 versus EF of 60± 10.7 (95% CI 57.8-63.7) and the difference was statistically significant with t test p=0.0001

When LVEF was compared within each NYHA functional classification, it was found that 52.3 % patients with LVEF ≤ 45% were in NYHA class IV, compared to 32.7 % of patients with LVEF >45% .The difference seen was statistically significant with p=0028 Mean LVEF was found to decrease with the increase in severity of NYHA from 61(SD ±7) in NYHA class I to 39.14(SD±14) in NYHA class IV p= 0.015.

4.1.9. Other Echocardiography findings

Figure 3 shows the Echocardiography findings. Hypertensive heart disease was found in 28 % of the patients, followed by hypertensive dilated cardiomyopathy 20%, dilated cardiomyopathy was diagnosed in 28 % and rheumatic heart disease was found in 17 %. Massive pericardial effusion with features of TB was seen in 3% of the patients; other echocardiography findings include 4% of patients with anterior mitral leaflets prolapse, co-pulmonale, and aortic dilatation and Ebstein anomaly. From this findings Hypertension was the most common possible etiology to the development of heart failure with prevalence of 48 %(both HHD and Hypertensive DCM).

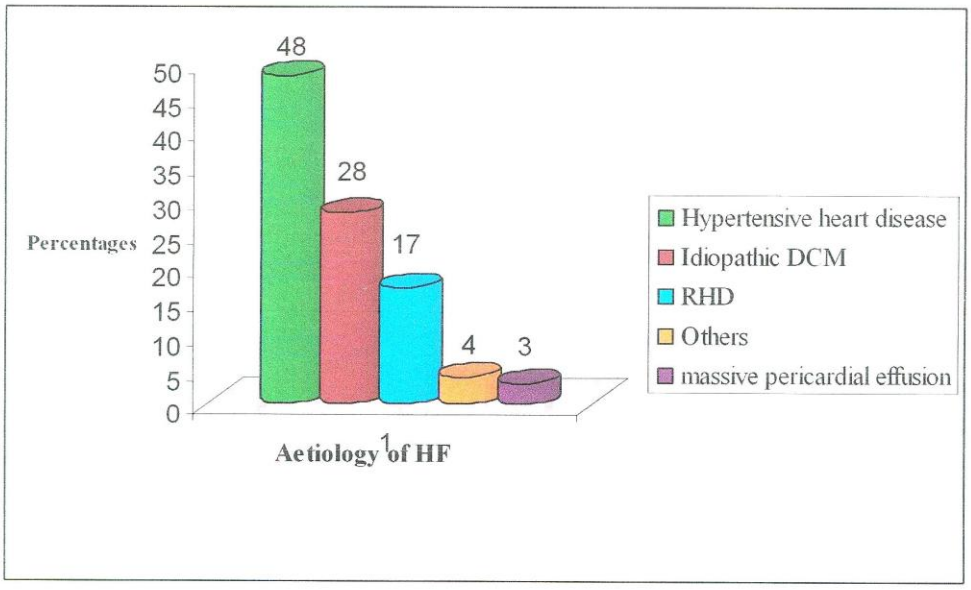


Figure 3. Echocardiography findings of patients with Congestive cardiac failure n=140

4.1.10. Co-morbidities of Congestive heart failure patients

Hypertension was the most common found condition in 61.5%, among those 68(79.1%) was found to have anemia. this was followed by Diabetes, A combination of Hypertension and diabetes was found in 12 (8.6%) and all of these were having low hemoglobin as per definition of anemia. Other conditions are as shown in table 5, the difference between the anemic and non anemic patients were not statistically significant. No co-morbidity featured significantly as risk for anemia in CHF.

Table 5. Co-morbidities of congestive heart failure patients in relation to anemia status

Variable	Whole group N=140	Non anemic N=32	Anemic N=108	P-value*
Single Coomobidities				
Hypertension	86(61.45%)	18(20.93%)	68(79.07 %)	0.493
Diabetes	13(9.29%)	1(7.69%)	12(92.31 %)	0.172
Chronic Kidney Disease	9(6.43%)	0(0%)	9(100%)	Ns
Extra pulmonary tuberculosis	5(3.53%)	1(20.0%)	4(80.00 %)	Ns
Multiple Coomobidities				
Hypertension & Diabetes	12(8.57%)	0(0.0%)	12(100.0 %)	Ns
Hypertension & Chronic kidney	9(6.42%)	0(0.0%)	9(100%)	Ns
Hypertension & Diabetes & Chronic Kidney	2(1.43%)	0(0.0%)	2(100%)	Ns

Data are percentage * χ^2 test Anemic versus non-anemic groups

µmol/l in female

GFR was estimated by the Cockcroft-Gault equation, 12.9% had renal failure as defined by eGFR less than 15mls/minutes. 7.1% had severely decreased GFR. Normal GFR was found in 23.6% .Anemia was found in 89.3% of the patients with moderate to severe reduction in GFR. Figure 4 shows the frequency of anemia by GFR levels comparing the patients with moderate to severe renal impairment to those with GFR ≥ 60mls/min, the formal were more likely to be hypertensive and in NYHA class III and IV. Other clinical Characteristics of the anemic patients with and without moderate to severe renal insufficient eGFR <60mls/min clinical are as in table 6.

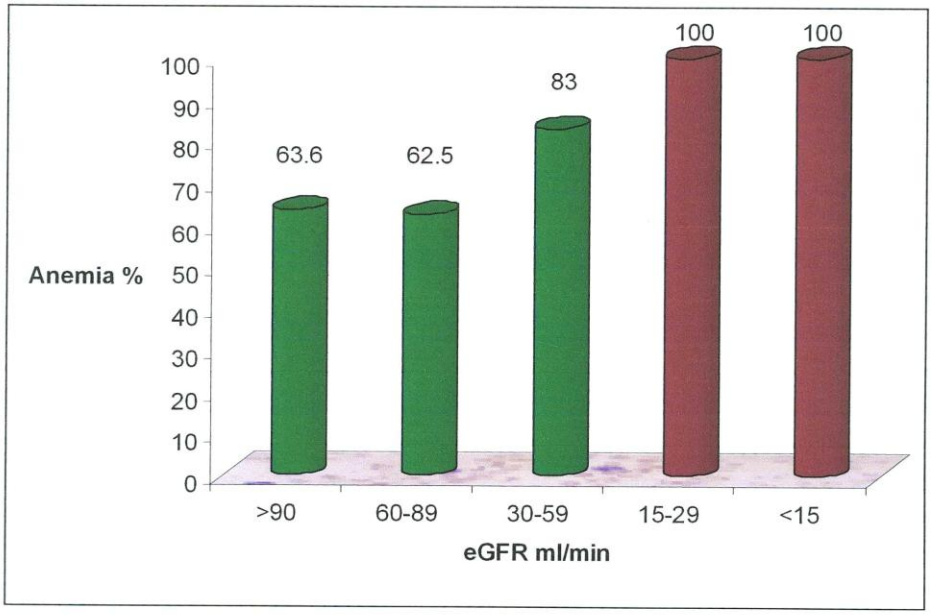


Figure 4. Prevalence of anemia in patients with CHF grouped according to eGFR calculated by the Cockcroft – Gault equation n=140

Table 6. Clinical Characteristics of congestive HF patients with anemia according to their eGFR <60mls/min n=108

Characteristics	Without renal insufficient GFR ≥ 60mls/min n=41	With moderate/severe renal insufficient GFR <60mls/min n= 67	*P value
Gender			
Male	23(56%)	33(49%)	0.489
Female	18(44%)	34(51%)	
Duration of heart failure			
Less than 6 months	9(22%)	10(15%)	
Above 6 months	32(78%)	57(85%)	0.352
Risk for HF			
Hypertension	17(41%)	51(76%)	0.0003
Diabetes	5 (12%)	7(10%)	0.779
RHD	10(24%)	10(15%)	0.219
LVEF			
EF ≤ 45%	23(56%)	44(66%)	
EF >45	18(44%)	23(34%)	0.320
NYHA Classification			
Class I	1(2%)	0(0%)	
Class II	5(12%)	3(4%)	0.250
Class III	15(37%)	30(45%)	
Class IV	20(49%)	34(51%)	

Data are percentages *eGFR ≥ 60mls/min vs. eGFR <60mls/min

CHAPTER FIVE

5. DISCUSSION

The main finding of the present study was that anemia in patients with CHF was relatively common and significantly correlated with severity of the disease. Anemia (hemoglobin <13 in male and <12g/dl in female) was present in 108 of 140 patients (77.14%).The Mean hemoglobin level decreased with increasing severity of NYHA class, and there were significantly more patients with anemia in NYHA class III and IV than in NYHA class I and II.

5.1. Prevalence of anemia

Overall prevalence of anemia in CHF of 77% was high. In this study anemia was present in 84.9% of males and 70.3% of females. The prevalence decreased with increasing severity of anemia with Normocytic normochromic anemia being the most prevalent RBC morphological type.

The prevalence of anemia in this study was notably higher than what was previously reported (33.3%) by Makule et al [51] even though the study used a lower Hemoglobin (<9.9g/dl) cut off point to define anemia.

The prevalence of anemia in this study was also higher compared to the two reported studies in Africa.[52] these two studies used the same WHO criteria for defining anemia. The observed difference between this study and the two studies conducted in Africa could be explained by the fact that the reported prevalence in the study by Inglis and colleagues [52] was from a selected group of patients with relatively milder degree of cardiac failure NYHA class II and class III in which anemia was generally less frequent, also these patients were first timer attendees at cardiac unit, our study included patients with different etiology and risk factors for heart failure, and the majority had symptoms for more than 6 months.

In this study, the study patients were relatively young .The median age among patients with anemia was 42 years with statistically significant difference in median age between males (48 years) and females (35 years) (P<0.001). This finding was not very different from that was reported in Uganda with a prevalence of 64.3% [5] and a reported a median age of 45 years among a cohort of patients admitted with heart failure at Mulago Hospital. Their study was almost similar to this study in the set up and used almost similar hemoglobin cut off point; their definition of anemia was hemoglobin ≤ 12g/dl in men and hemoglobin of ≤11.9 in women.

The prevalence of anemia reported in western world heart failure studies applying WHO definition of anemia ranged from 15.9 to 57 %. [13, 25, 45, 54] In these studies anemia was often reported to be associated with older age, in our study the patients were not as older as in the above studies. Higher age has been associated with more frequent anemia as reported by Tanner [42] at least in part due to incidence of hyperproliferation often caused by chronic disease or iron deficiency and less often vitamin deficiency or bone marrow infiltrations. Age rate was shifted to younger patients in our study. Moreover, iron, vitamin deficiency, chronic infections, parasitic infections and gastrointestinal blood loss were not excluded, and this could explain higher prevalence found in our set up.

This study found mild anemia in 45.0%, moderate anemia in 27.9% and severe anemia in 4.3%, these findings which were almost similar to those reported in Ugandan study.[5] There was no statistically significant difference found between mean hemoglobin of male 10.9 (SD 2.5) and female 10.7 (SD2) this was in contrast to the report findings by Marshal and colleagues [49] which found that mean hemoglobin level of women was about 1g/dl lower than men. The difference in anemia between men and women in this study could be explain by the fact that men were older than female and presented with severe form of heart failure and anemia compared to women.

Microcytic hypochromic anemia was found in 17.1% suggesting that iron deficiency was an important cause, however functional iron deficiency could not be excluded; further studies are needed to exclude whether iron deficiency has an influence on anemia in the population of heart failure patients as nutrition deficiency as the cause of anemia is common in our clinical set up.

The presence of ferropenic anemia as suggested by the presence of serum Ferritin< 15ng/dl, Hb < 12g/dl and Hematocrit <36 was of low prevalence. In this study, two (2) patients (1.4%) qualified for the diagnosis of ferropenic anemia despite a higher prevalence of anemia in our study population. These findings would suggest that Ferritin level could have no influence on anemia in Heart failure. Similar findings have been reported by Nanas et al [1].

5.2. NYHA functional classification

The prevalence of anemia in CHF patients in this study was 85.7% in patients in NYHA class IV compared to 76.3% in NYHA class III; these findings were slightly higher than the findings in Uganda [5] where 72.4% were in NYHA class IV and 57.4% in NYHA class III. The difference in the findings between the two studies could be explained by the difference in age between men and women found in this study i.e. women were younger in their reproductive age with 9% of female population having peripartum cardiomyopathy, menstruation and lactation history was not asked. All these could contribute to the severity of anemia in our study. In contrast to the findings by Julius K et al in Uganda and Israel study [54] the prevalence of anemia in CHF did not increase with increasing patient age.

Silverberg and others [25] reported the prevalence of anemia to increase with severity of CHF and reaches almost 80% in those patients with NYHA functional class IV, this finding was similar to this study which found the prevalence of anemia to increase with severity of heart failure and reached 87.7% in patients in NYHA class IV. Our study patients seem to present late and in severe forms of HF as also reflected in the majority having symptoms for more than six months.

Mean hemoglobin decreased with increasing severity of NYHA from 13.5 (SD1.5) in NYHA class I to 10.5 (SD2.3) in NYHA class IV. This was in contrast to what was reported in another study by Tanner and others [32] who reported a similar hemoglobin in all the four NYHA groups, The difference could be due to the difference in the age and sex distribution in our study and the detected high prevalence of co-morbidities .The other important thing was the difference between mean Hemoglobin concentration of the two studies; Hemoglobin concentration in their study was higher compared to what was found in this study. Our findings suggested the presence of other possible causes for anemia in our study population.

5.3. Co-morbidity

This study found that the presence of co-morbidity was associated with the occurrence of anemia. This finding was similar to those reported by Tanner and Anand.[31,32] The most important contributing factor for anemia in the study by Tanner and others [32] appeared to be renal insufficient. Anand also found that in patients with chronic anemia renal blood flow and glomerular filtration rate were reduced [55]. In our study the significant co-morbidities were chronic renal insufficiency due to hypertension, and hypertensive heart disease

In this study median serum creatinine was found to increase with increasing severity of heart failure $p < 0.01$, 285(SD97)μmol/l in NYHA class IV a level higher than what was reported by Tanner and colleagues (131(SD43) μmol/l). [32]

The median serum creatinine varied significantly according to sex $p<0.05$.Serum creatinine was 252±326 μmol/l in males and 158±186.6 μmol/l in female. This finding could explain higher prevalence of anemia in Men than in women. These findings were similar to that of Inglis and colleagues in a South Africa [52] who reported the value of serum creatinine to vary significantly between men and women (106.5 ±33.2 for male vs. 87.7±26.4 for females $p= 0.001$) There was a statistical significant difference between mean serum creatinine of the group with a anemia versus those without anemia ($p <0.005$). Serum creatinine was found to be higher in anemia group 234.9 ±293.8 than in non anemic group 93.7±33.9. These findings

were also reported by other studies above by Tanner and Anand and this supported the presence of renal insufficiency in these patients the CHF patients with anemia. [31, 55]

In our study significant renal dysfunction was defined as calculated eGFR <60mils/min. The prevalence of renal dysfunction in the study population was 53.6% vs. 46.4% in those without renal dysfunction. This was higher than that reported in South Africa (10.5%). Patients with anemia and renal dysfunction were found in 67/108(62%). This is the classical finding; the complex association among patients with HF, anemia and renal dysfunction among our relatively young populations deserve particular attention and calls for intervention strategies. This finding was comparable to other studies [33, 55, 56, 57] who reported that more than 50% of patients with Heart failure had GFR below 60mls/min compare to only 30% of those without anemia.

Potentials contributing factors included medications and presence of hypertension. Unfortunately many patients medication was not documented and patients could not identify them. Whatever the etiological factors, presence of impaired renal function in the population of HF patients is independently associated with increased morbidity and mortality [56]

The relationship between HF, anemia and Cardio renal syndrome is responsible for faster progression of cardiac and renal diseases[20] .Presently, mechanisms that lead to anemia in patients with HF are being studied to find treatments that can correct this complication and improve prognosis of these patients. Malnutrition, malabsorption and chronic gastrointestinal bleeding are frequent causes of anemia in HF patients. Reduced hemoglobin concentration, in these cases, can also be caused by hemodilution resulting from the activation of the renin-Angiotensin Aldosterone system (RAAS), which worsens prognosis [21, 22].

Anemia was equally prevalent in both patients with reduced left ventricular ejection fraction as well as those with preserved LVEF. This could suggest a common pathophysiological basis, in the two types of HF, a finding which was similar to a study by Berry and

colleagues.[58]However, mean LVEF was found to decrease with increasing NYHA functional classification ($p<0.05$).

In our study diabetes alone was reported in 13(9%) of the patients while diabetes and hypertension was found in 12(8.6%) and 2(1.43%) had diabetes and chronic kidney disease. This was lower than that reported in other studies which report prevalence of 20-30% [59] This lower prevalence could be explained by the fact that most diabetic patients in MNH attended a special diabetic clinic which was not included in the study site, and the above patients were those admitted due to decompensate heart failure.

On analysis of the cause of heart failure found on echocardiography, Hypertension (48%), DCM (28%) and RHD (17%) were the most prevalent conditions. There was no statistical significance association between anemia and hypertensive heart disease ($p>0.05$).This finding was in contrast to the findings in Uganda [5] who reported an association between hypertension and anemia. In the Ugandan study, the commonest cause of HF from echocardiography findings was reported to be RHD followed by DCM then HHD. The difference between these two studies could be explained by the fact that the 5% of study group included other causes of heart failure which were Ebstein anomaly, aortic dilatation co-pulmonale and anterior mitral valve leaflet Prolapsed, and the fact that there was 28% of DCM which was of unknown etiology The presence of chronic infections could not be ruled out.

The underlying real cause of anemia in this study remained unknown. This study was not able to identify weather low hemoglobin observed in some patients is indicative of hemodilution. The confounding factors which were not asked especially in females included, history of peripartum cardiomyopathy and the duration post delivery and lactation history.

Previous medications used by the patients before referral to MNH were not identified as it was neither included in the referral notes nor remembered by the patients. It was not possible to identify the previous hemoglobin values of these patients, whether or not they were having low hemoglobin even before the heart failure, was impossible document .The presence of

parasitic infestation and nutrition deficiencies which are considered higher in this setting was not considered. So anemia found in this population of patients was different to that reported in western heart failure studies where low hemoglobin might be influenced by underlying atherothrombotic events, in particular chronic disease which reflected systemic organ dysfunction due to deterioration of heart failure syndrome finding which might the contradictory in this set up.

CONCLUSION

- Anemia is common in patients with CHF attending MNH with a prevalence of 77.1%
- Normocytic normochromic was the major type of anemia 78%
- Patients with anemia are more found to be in NYHA class III & IV
- Anemia was equally prevalent in both patients with reduced left ventricular ejection fraction as well as those with preserved LVEF
- Serum Ferritin has no co-relation to presence of anemia in CHF patients
- Renal dysfunction(moderate to severe eGFR: of <60mils/min) was the most prevalent co morbid condition 62%

RECOMMENDATIONS

- Improve awareness that anemia is common in CHF and should be addressed as a important co morbidity
- Efforts should be made to detect anemia in non hospital based studies
- There is also a need for interventional studies in anemia of congestive heart failure
- There is a need for a large follow up study including all patients with heart failure to asses the contribution of co-morbidities in CHF patients with anemia

STUDY LIMITATIONS

- Screening method used could to leads to underestimations of CHF patients
- There were 21% dropout from 11 patients discharged before complete investigations, and 27 patients from outpatients department who did not turn up for investigations
- Haemoglobin levels were assessed at a single point in time, hence cannot comment on the importance of changing Hb over time
- The results can not be generalized as it is a Hospital based study

REFERENCES

1. Nanas JN, Matsouka C, Karageorgopoulos D, Leonti A, Tsolakis E, et al. Etiology of anemia in patients with advanced heart failure. J Am Coll Cardiol. 2006 Dec 19; 48(12):2485-9.

2. Drakos SG, Anastasiou-Nana MI, Malliaras KG, Nanas JN. Anemia in chronic heart failure. Congest Heart Fail. 2009 Mar-Apr;15(2):87-92

3. Komajda M, Anker SD, Charlesworth A, Okonko D, , et al prevalence of anemia in patients with chronic heart failure and their clinical characteristics Journal of Cardiac Failure Vol. 10 No. 1 Suppl. 2004.S1- S4

4. Tang YD, Katz SD. Anemia in chronic heart failure: prevalence, etiology, clinical correlates, and treatment options. Circulation.2006;113(20):2454–2461

5. Julius KK, Emmanuel S, Juergen F, Anemia among patients with congestive cardiac failure in Uganda – its impact on treatment outcomes, S Afr Med J 2009; 99: 876-880

6. Tanner H, Moschovitis G, Kuster GM, Hullin R, Pfiiffner D, Hess OM, et al. The prevalence of anemia in chronic heart failure. Int J Cardiol. 2002 Nov;86(1):115-21.

7. Karaye KM, Sani MU. Factors associated with poor prognosis among patients admitted with heart failure in a Nigerian tertiary medical centre: a cross-sectional study. BMC Cardiovascular Disorder. 2008; 8:16.

8. Olubodun JO. Nutritional factors and heart failure in Nigerians with hypertensive heart disease. Int J Cardiol. 1992 Apr; 35(1):71-6.

9. Oyoo GO, Ogola EN. Clinical and socio demographic aspects of congestive heart failure patients at Kenyatta National Hospital, Nairobi. East Afr Med J. 1999 Jan; 76(1):23-7.

10. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, et al. The Euro Heart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J. 2003 Mar; 24(5):442-63.

11. Al-Ahmad A, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol. 2001 Oct; 38(4):955-62.

12. Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol. 2000 Jun; 35(7):1737-44.

13. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. J Am Coll Cardiol. 2002 Jun 5;39(11):1780-6

14. Androne A-S, Katz SD, Lund L, LaManca J, Hudaihed A, Hryniewicz K, et al. Hemodilution is common in patients with advanced heart failure. Circulation 2003; 107:226–9.

15. Wisniacki N, Aimson P, Lye M. Is anemia a cause or a consequence of heart failure in the elderly? Heart 2001; 85(Suppl I):P4.

16. Young JB, Abraham WT Albert NM, Gattis Stough W, et al; OPTIMIZE-HF Investigators and Coordinators. Relation of low hemoglobin and anemia to morbidity and mortality in patients hospitalized with heart failure (insight from the OPTIMIZE-HF registry). Am J Cardiol. 2008 Jan 15;101(2):223-30

17. Kevin M, Sullivan et al Hemoglobin Adjustment to define anemia ,Tropical medicine and international healthy,2008,13(10):p.1267 - 1271

18. Cromie N, Lee C, Struthers AD. Anemia in chronic heart failure: what is its frequency in the UK and its underlying causes? Heart 2002; 87:377–8.

19. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12 065 patients with new-onset heart failure. Circulation. 2003 Jan 21; 107(2):223-5.

20. Anand IS. Anemia and chronic heart failure implications and treatment options. J Am Coll Cardiol 2008; 52:501-11.

21. Adlbrecht C, Kommata S, Hulsmann M, Szekeres T, Bieglmayer C, Strunk G, et al. Chronic heart failure leads to an expanded plasma volume and pseudoanaemia, but does not lead to a reduction in the body's red cell volume. Eur Heart J. 2008 Oct; 29(19):2343-50.

22. Komajda M, Anker SD, Charles worth A, Okonko D, Metra M, Di Lenarda A, et al. The impact of new onset anaemia on morbidity and mortality in chronic heart failure: results from COMET. Eur Heart J. 2006 Jun;27(12):1440-6

23. Felker GM, Adams FK Jr. Gattis WA, and Christopher M.O'ConnorJ. Anemia as a risk factor and therapeutic target in Heart Failure. J Am. Coll. Cardiol. 2004; 44: 959-66

24. Witte KK, Nikitin NP, De Silva R, Cleland JG, Clark AL. Exercise capacity and cardiac function assessed by tissue Doppler imaging in chronic heart failure. Heart. 2004 Oct;90(10):1144-50

25. Silverberg DS, Wexler D, Sheps D, Blum M, Keren G, Baruch R, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. J Am Coll Cardiol. 2001 Jun 1; 37(7):1775-80.

26. Herbert, V., S. Shaw, and E. Jayatilleke, Evidence of a new assay, % saturation of Ferritin, is the most reproducible and reliable measure of the whole range of body iron stores. Blood Rev, 1995. 86(suppl 1): p. 584.

27. Herzog, C., H. Muster, and S. Li, Impact of congestive heart failure, chronic kidney disease, and anemia on survival in the Medicare population. J Card Fail, 2004. 10: p. 467–72

28. Volpe M, Tritto C, Testa U, Rao MA, Martucci R, Mirante A, et al. Blood levels of erythropoietin in congestive heart failure and correlation with clinical, hemodynamic, and hormonal profiles. Am J Cardiol. 1994 Sep 1;74(5):468-73

29. Van der Meer P, Voors AA, Lipsic E, Smilde TD, van Gilst WH, van Veldhuisen DJ. Prognostic value of plasma erythropoietin on mortality in patients with chronic heart failure. J Am Coll Cardiol. 2004 Jul 7;44(1):63-7

30. Brucks S, Little WC, Chao T, Rideman RL, Upadhya B, Wesley-Farrington D, et al. Relation of anemia to diastolic heart failure and the effect on outcome. Am J Cardiol. 2004 Apr 15;93(8):1055-7

31. Anand I, McMurray JJ, Whitmore J, Warren M, Pham A, McCamish MA, et al. Anemia and its relationship to clinical outcome in heart failure. Circulation. 2004 Jul 13;110(2):149-54

32. Tanner H, Moschovitis G, Kuster GM, Hullin R, Pfiiffner D, Hess OM, et al. The prevalence of anemia in chronic heart failure. Int J Cardiol. 2002 Nov;86(1):115-21.

33. Anand IS, Kuskowski MA, Rector TS, et al. Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from Val-HeFT. Circulation. 2005;112:1121–1127

34. Redondo-Bermejo B,Pascual-Figal DA,Hurtado-Martínez JA, et al . Clinical determinants and prognostic value of hemoglobin in hospitalized patients with systolic heart failure Rev Esp Cardiol .2007 Jun;60(6):597-606

35. McClellan WM, Flanders WD, Langston RD, Jurkovitz C, Presley R. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. J Am Soc Nephrol. 2002 Jul;13(7):1928-36

36. Ishani A, Weinhandl E, Zhao Z, et al. Angiotensin-converting enzyme inhibitor as a risk factor for the development of anemia, and the impact of incident anemia on mortality in patients with left ventricular dysfunction. J Am Coll Cardiol. 2005;45(3):391–399

37. Torre-Amione G, Bozkurt B, Deswal A, Mann DL. An overview of tumor necrosis factor alpha and the failing human heart. Curr Opin Cardiol 1999;14:206-10

38. Sharma R, Anker SD. Cytokines, apoptosis and cachexia: the potential for TNF antagonism. Int J Cardiol 2002; 85:161–71.

39. Deswal A, Petersen NJ, Feldman AM, Young JB, White BG, Mann DL. Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the Vesnarinone trial (VEST). Circulation. 2001 Apr 24;103(16):2055-9

40. Sánchez-Torrijos J ,Gudín-Uriel MN ,et al Prognostic value of discharge hemoglobin level in patients hospitalized for acute heart failure: Rev Esp Cardiol. 2006 Dec;59(12):1276-82

41. Kosiborod M, Smith GL, Radford MJ, Foody JM, Krumholz HM. The prognostic importance of anemia in patients with heart failure. Am J Med. 2003 Feb 1; 114(2):112-9.

42. Erslev AJ. Anemia of chronic disease. In: Beutler E, Lichtman MA, Caller BS, Kipps TS, eds. Williams Hematology. 5th Ed. New York, NY: McGraw-Hill; 1995:518–24

43. Sears DA. Anemia of chronic disease. Med Clin North Am. 1992 may;76(3):567–79

44. Go AS, Yang J, Ackerson LM, Lepper K, Robbins S, Massie BM, et al. Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure: the Anemia in Chronic Heart Failure: Outcomes and Resource Utilization (ANCHOR) Study. Circulation. 2006 Jun 13;113(23):2713-23.

45. Felker GM, Gattis WA, Leimberger JD, Adams KF, Cuffe MS, Gheorghiade M, et al. Usefulness of anemia as a predictor of death and rehospitalization in patients with decompensated heart failure. Am J Cardiol. 2003 Sep 1;92(5):625-8

46. Levin A, Thompson CR, Ethier J, Carlisle EJ, Tobe S, Mendelssohn D, et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. Am J Kidney Dis. 1999 Jul;34(1):125-34

47. Kengne AP, Dzudie A, Sobngwi E. Heart failure in sub-Saharan Africa: a literature review with emphasis on individuals with diabetes. Vasc Health Risk Manag. 2008; 4(1):123-30.

48. Iverson, P., P. Worldbaek, and T. Tonnessen, Decreased hematopoiesis in bone marrow of mice with congestive heart failure. Am J Physiol,, 2002. 282: p. R166-R172

49. Marshal, T, Fox et al., Anemia, Chronic Heart Failure, and the Impact of Male vs. Female Gender. CHF, 2005. 11: p. 129-132.

50. Malenganisho W, Magnussen P, Vennervald BJ, Krarup H, Kaestel P, Siza J, et al. Intake of alcoholic beverages is a predictor of iron status and hemoglobin in adult Tanzanians. J Nutr. 2007 Sep;137(9):2140-6

51. Makule A. Causes of admission in patients with Heart Failure in the department of Internal Medicine. Dar es Salaam: University of Dar es Salaam; 2003

52. Sally C. Inglis, Simon Stewart et al Anemia and renal function in heart failure due to idiopathic dilated cardiomyopathy European Journal of Heart Failure 9 (2007) 384–390

53. de Silva R, Rigby AS, Witte KK, Nikitin NP, Tin L, Goode K, et al. Anemia, renal dysfunction, and their interaction in patients with chronic heart failure. Am J Cardiol. 2006 Aug 1;98(3):391-8

54. Wexler D, Silverberg D, Sheps D, et al. Prevalence of anemia in patients admitted to hospital with a primary diagnosis of congestive heart failure. Int J Cardiol 2004; 96: 79-87.

55. Anand IS. Pathogenesis of anemia in cardiorenal disease. Rev Cardiovascular Med. 2005; 6 Suppl 3:S13-21.

56. O'Meara E, Clayton T, McEntegart MB, McMurray JJ, Lang CC, Roger SD, et al. Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. Circulation. 2006 Feb 21;113(7):986-94

.

57. Silverberg D, Wexler D, Blum M, Schwartz D, Iaina A. The use of androgens in anemia resistant to erythropoietin and i.v. iron in patients with heart and renal failure. Nephrology Dial Transplant. 2004 April 1, 2004;19(4):1021-25

58. Berry C, Hogg K, Norrie J, Stevenson K, Brett M, McMurray J. Heart failure with preserved left ventricular systolic function: a hospital cohort study. Heart. 2005 Jul;91(7):907-13

59. Ulf Dahlstro¨m, Frequent non-cardiac co morbidities in patients with chronic heart failure, The European Journal of Heart Failure 7 (2005) 309– 316

60. Mozaffarian D, Regina N, Wayne CL, Anemia predicts mortality in severe heart failure The prospective randomized amlodipine survival evaluation (PRAISE) Am Coll Cardiol, 2003; 41:1933-1939

61. Smith, G., J. Lichtman, and M. Bracken, Renal impairment and outcomes in heart failure: systematic review and meta-analysis. J Am Coll Cardiol, 2006. 47: p. 1987-96.

62. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia Report of a WHO/IDF Consultation,2006