



ST. PAUL'S HOSPITAL MILLENNIUM MEDICAL COLLEGE

PREVALENCE OF ANEMIA AND ASSOCIATED FACTORS AMONG ADULT PATIENTS WITH HEART FAILURE AT CARDIAC FOLLOW UP CLINIC OF ST. PAUL'S HOSPITAL MILLENNIUM MEDICAL COLLEGE, ADDIS ABABA, ETHIOPIA FROM MAY 1 TO JULY 30 ,2021

BY: ERMIA LIMENEH (MD, INTERNAL MEDICINE RESIDENT)

A RESEARCH PAPER SUBMITTED TO THE DEPARTMENT OF INTERNAL MEDICINE AND PUBLIC HEALTH, SPHMMC, IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR SPECIALTY CERTIFICATE IN INTERNAL MEDICINE

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Table of Contents

Acknowledgment	iii
Table of Contents.....	iv
Acronyms	vi
List of figures and tables	viii
List of figures.....	viii
List of tables.....	viii
Abstract	9
1. Introduction.....	11
1.1. Background.....	11
1.2. Statement of the problem.....	12
1.3 Significance of the study.....	13
2. Literature Review	14
3. Objectives.....	19
3.1. General objective	19
3.2. Specific objectives	19
4. Methods and Materials	20
4.1. Study area and period.....	20
4.2 Study design.....	20
4.3 Population	20
4.3.1. Source population:.....	20
4.3.2. Study population:	20
4.4. Inclusion and exclusion criteria	21
4.4.1. Inclusion criteria.....	21
4.4.2. Exclusion criteria.....	21
4.5. Sample size determination and sampling technique	21
4.5.1. Sample size determination:	21
4.5.2 Sampling technique:	22
4.6 Data collection tools and techniques.....	22
4.7 Study variables.....	22
4.7.1 Dependent variables	22

4.7.2 Independent variables.....	22
4.8 Operational Definition	23
4.9 Data quality management	24
4.10 Data processing and analysis	24
4.11 Ethical considerations	24
4.12 Dissemination of result	25
5. Results.....	26
5.1 socio-demographic and clinical variables.....	26
5.1.1 socio-demographic variables	26
5.1.2 clinical characteristics of study participants.....	28
5.2 Prevalence of anemia	30
5.3 Factors associated with anemia in HF patients	33
6.Discussion	36
7. Strength and limitation of the study.....	39
8. Conclusion.....	39
9. Recommendation	40
10.References	41
11.ANNEXES.....	44
11.1 Annex I: Information sheet and consent form	44
11.2 Annex II: Data collection tools (questionnaires)	47
11.3Annex III: Assurance of Investigator.....	52

Acronyms

ACEI: Angiotensin Converting Enzyme inhibitors

AOR: Adjusted odds ratio

ARB: Angiotensin Receptor Blockers

CBC: Complete blood count

CI: Confidence Interval

COR: Crude odds ratio

CRVHD: Chronic rheumatic valvular heart disease

CHARM: Candesartan in heart failure assessment of reduction in mortality and morbidity

DC: Data Collector

DBP: Diastolic blood pressure

DM: Diabetes mellites

ESA: Erythropoietin Stimulating Agents

ESC: European society of cardiology

EF: Ejection Fraction

eGFR: Estimated glomerular filtration rate

EPO: Erythropoietin

Hgb: Hemoglobin

HF: Heart failure

HFmrEF: Heart failure with minimally reduced ejection fraction

HFpEF: Heart failure with preserved ejection fraction

HFrfEF: Heart failure with reduced ejection fraction

HHD: Hypertensive heart disease

HR: Hazard ration

IHD: Ischemic heart disease

IN CHF: Italian Network for Congestive Heart Failure

MAGGIC: Meta-Analysis Global Group in Chronic Heart Failure

MDRD: Modification of Diet in Renal Disease

KCCQ: Kansas City cardiomyopathy
questioner -12 points

LV: Left ventricle

NCD: non communicable diseases

NT-BNP: N-terminal brain natriuretic
peptide

NYHA: New York Heart association

OR: Odds ration

PI: Principal investigator

RBC-Red blood cells

RFT: Renal function test

6MD; 6-minute distance

RCT: Randomized control trial

SBP: Systolic blood pressure

SPHMMC: Saint Paul's Hospital
millennium medical college

WHO: World Health Organization

List of figures and tables

List of figures

Figure 1: Prevalence of anemia among adult outpatient HF patients at SPHMMC, Addis Ababa, Ethiopia 2021. (n=260).....	30
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List of tables

Table 1: Socio-demographic characteristics of study participants at SPHMMC, Addis Ababa, Ethiopia, 2021 (n=260).....	27
Table 2: Distribution of the clinical profiles of study subjects at SPHMMC, Addis Ababa, Ethiopia, 2021 (n=260)	29
Table 3: Distribution of anemia in different variables among adult outpatient HF patients at SPHMMC, Ethiopia 2021 (n=260)	31
Table 4: Bivariable and multivariable binary logistic regression predicting anemia among outpatient HF patients at SPHMMC, Addis Ababa, Ethiopia 2021 (n=260).	34

Abstract

Background: Anemia is a common comorbidity in heart failure (HF) patients and its presence is associated with decreased functional capacity, poor quality of life and increased mortality. Previous studies showed the overall prevalence of anemia in HF patients ranges from 10-50% and in outpatient HF patients 25%. Older age, renal dysfunction, diabetes mellitus, male sex and worse New York heart association (NYHA) functional status were reported to be independently associated with anemia. Anemia is a prevalent problem in the in Ethiopian setting affecting 23% of reproductive age women, 18% of adult men. But data is lacking about its prevalence and factors associated with it in outpatient HF patients in our set up.

Method: A hospital based cross-sectional study was conducted to assess the prevalence of anemia among outpatient HF patients at SPHMMC from May1-July 30, 2021. Systematic random sampling (k=6) was used to recruit study participants which were calculated to be 273. Interviewing and chart review were made using questionnaires containing socio-demographic characteristics, clinical and medication profiles, complete blood count (CBC), renal function test (RFT), ejection fraction (EF) and Kansas City cardiomyopathy questionnaire- 12 points (KCCQ-12). STATA version 13 software was used to get descriptive statistics results and to see the association of variables which was assessed using bivariate and multivariate binary logistic regression model.

Results: Among respondents, 68(26.2%) patients had anemia. The majority (91%) had $\geq$ mild anemia (Hgb 10-11.9g/dl for females and 10-12.9 g/dl for males). The mean Hgb in the anemic group was 11.4 ± 1 g/dl as compared to 14.6 ± 1.5 g/dl in the non-anemic group. The mean age of respondents was 55.68 ± 17 years and majority were females (52.7%). In multivariable binary logistic regression analysis, the odds of having anemia in those HF patients with NYHA functional class III was 6 times higher than those with NYHA class I (AOR=6.05, P=0.004, 95% CI 1.8-20.33). Compared to those HF patients who had diabetes mellitus, those who didn't have were about 79% less likely to develop anemia (AOR=0.21, P=0.002, 95% CI, 0.08-0.56). The odds of having anemia in those patients with estimated glomerular filtration rate (eGFR) 60-89 mL/min/1.73 m² was 6.6 times higher than those with eGFR ≥ 90 (AOR=6.61, P< 0.001, 95% CI, 2.74-25.93). And those HF patients with eGFR 30-59 mL/min /1.73 m² had the odds of having anemia 13.5 times as compared to those with eGFR 90 and above (AOR 13.5(3.7-49.4), P <0.001).

Conclusion: Anemia is common in outpatient HF patients in our setup. The presence of higher NYHA functional class, lower eGFR and diabetes mellitus were strong predictors of anemia in HF patients. But there was no significant association between age, sex, etiology of HF, use of angiotensin converting enzyme inhibitors /angiotensin receptor blockers (ACEI /ARBs), duration of illness and hospital admission between the anemic and non-anemic patients in this study.

Key words: Anemia, Heart failure, prevalence, SPHMMC, Ethiopia

1. Introduction

1.1. Background

Heart failure is one of the most common non communicable diseases (NCDs) worldwide. It affects 6.2 million adults ≥ 20 years or 2.2% of the population in united states of America (USA) alone. More than >20 million people worldwide live with HF. (1) There are no HF prevalence data in most African countries in the community setting but HF accounts for 3-5% of medical admissions in these countries and studies have shown that 75% of the etiologies of HF are non-ischemic in nature although the contribution of ischemic heart disease is rising recently. (2) There are no adequate data about prevalence of HF in Ethiopian setting but valvular heart disease accounts for most of admission with HF in hospital based studies .(3)

Anemia, one of the common comorbidities in heart failure, affects 1.62 billion or 24.8% of the population worldwide. (4) In Ethiopia anemia affects 56% of children under 5 year of age, 23 % of reproductive age group women and 18% of adult men (15-49 years). (5)

Anemia is associated with variety of adverse outcomes in heart failure patients including decreased functional capacity and increased mortality as a result of different pathophysiologic mechanism. Anemia causes reduced oxygen delivery to metabolizing tissues and triggers a host of hemodynamic, neuro hormonal and renal alteration, leading to increased myocardial workload, which results in left ventricular (LV) remodeling and hypertrophy. (6)

A low number of circulating red blood cells (RBCs) reduces systemic vascular resistance by decreasing whole-blood viscosity, and low hemoglobin enhances nitric oxide-mediated vasodilation. The resulting decrease in arterial blood pressure causes baroreceptor-mediated neuro hormonal activation. Increased sympathetic and renin angiotensin activity decreases renal blood flow and glomerular filtration rate (GFR), resulting in renal retention of salt and water with the expansion of extracellular and plasma volumes. (6)

The etiology of anemia in HF is multifactorial. Deficiency of iron, folate and vitamin B12 account for relatively small portion anemia in HF, in most studies. (7) The most common etiologies of anemia in HF identified are renal dysfunction, inadequate production and

blunted response to erythropoietin (EPO), activated proinflammatory state and anemia of chronic inflammation. Plasma volume expansion and hemodilution can result in pseudo anemia. The use of ACEI and ARB is also associated with anemia as a result of impaired EPO synthesis and decreased marrow proliferation. (6)(7)

1.2. Statement of the problem

Anemia is one of the common comorbidities associated with HF affecting more than one third of patients with heart failure. The prevalence of anemia is estimated to be 25% in outpatients with stable HF and 41% in hospitalized patients according to the Swedish HF registry.(8) But different studies have reported prevalence rate that varies from 10 to 50% depending on the definition of anemia used, severity of HF, the patient demography and the study type.(6)(9)

The presence of anemia is associated with poor functional capacity, decreased 6 min walking distance, and poor quality of life as assessed by standard quality of Life questioners such as the Kanas City cardiomyopathy questioner (KCCQ). (7)(10)

The KCCQ, a 23-item questioner, is a well validated international tool for assessing the quality of life of patients who have heart failure. Because it relatively long and cumbersome a 12-item version, KCCQ-12, was derived and validated for use in heart failure patients to asses health related quality of life. (11)

Anemic patients compared with non-anemic patients also have increased rate of hospital admission and re admission after discharge and frequent emergency visit. (12)

Anemia is an independent predictor of short- and long-term mortality both in hospitalized patients and in the community setting. The risk of death becomes higher with progressively lower Hgb. After adjusting for demographic and clinical factors, each 1% lower hematocrit was associated with a 2% greater 1-year mortality. Compared with patients with a hematocrit 42%, those with a hematocrit 27% had a 40% greater 1-year mortality. This high mortality was consistent in all spectrums of ejection fraction. (13)

The presence of older age, renal failure and worse NHYA functional class were consistently shown to be independently associated with anemia. Among these factors renal failure is more strongly associated with anemia. (13) The association of gender with

anemia is not consistent in all studies although male sex was more strongly associated in most of these studies. (8)(14)(15) .Diabetes, IHD as etiology of HF, lower SBP and wide pulse pressure were reported to be predictors of anemia in some of the studies.(13)(14) It has also been seen that Hgb and EF are inversely related and anemia is more prevalent in those with HFpEF compared to patients with HFrEF. But anemia is important predictor of all-cause mortality in both HFrEF and HFpEF. (8)(14)(15)

Given its association with poor functional status and increased mortality in HF, anemia was considered as a novel target of treatment in HF. Treating correctable causes of anemia like deficiency of iron, folate, vitamin B12, and anemia of chronic blood loss should always be considered first and is guideline recommended. (16) Anemia of chronic disease is the most common cause in heart failure. But treating this type of anemia with erythropoietin stimulating agents although increased the Hgb level, didn't lead to decreased mortality and was associated with thromboembolic complications. (17)(18)

1.3 Significance of the study

Anemia is one of the common comorbidities in HF resulting decreased functional performance as well as increased mortality. Anemia of chronic disease is considered as the most common cause of anemia in HF patients in western set up, and treating this type of anemia with ESA has so far, no beneficial role.

But there is little data on the prevalence and associated factors of anemia in HF patients in Ethiopian setting. The possible etiologies of anemia in our setup might be different from the western patients and treating the reversible causes of anemia could have a beneficial impact on heart failure outcome .This study is expected to provide data on the prevalence and associated factors of anemia among outpatient HF patients in our set up and it might be used as the bases for future studies that looks into the etiologies and outcome of treating this important comorbidity. So SPHMMC can use this result as a foundation for improving its services regarding management of anemia in heart failure patients and expand its influence to other health service areas.

2. Literature Review

The normal Hgb concentration varies with age, sex and physiologic status but the world health organization (WHO) uses Hgb cut off points of <13g/dl for men and <12g/dl for women to define anemia. (4) In the following literature review, anemia is defined based on the above criteria unless otherwise specified in respective studies.

In the Swedish HF registry, 49,985 patients with HF with all spectrums of EF were analyzed. Among these patients 23% had heart failure with preserved EF (HFpEF), 21% had heart failure with minimally reduced EF (HFmrEF), and 55% had heart failure with reduced EF (HFrEF). As many as 24,707 (57%) patients were in-patients and 18,278 (43%) were out-patients. The mean age of the patient was 75 years and of 60% of them were males. The overall prevalence of anemia was 34%. Prevalence of anemia in in-patients was 41% whereas it was 25% in out-patients. Anemia was more prevalent in HFpEF being 41% as compared to 35 % in HFmrEF and 32% had HFrEF. Higher EF was independently associated with higher likelihood of concomitant anemia. Important predictors of anemia across the EF spectrum were male sex, older age, worse NYHA and renal function, lower systolic blood pressure (SBP), higher NT- BNP, diabetes. History of ischemic heart disease, coronary revascularization, and peripheral artery disease were predictors of concomitant anemia in HFmrEF and HFrEF but not in HFpEF. Over long-term follow-up, anemia was independently associated with increased risk of death or HF hospitalization and of death alone in both HFpEF, HFmrEF and HFrEF. Over a median follow-up of 2.2 years, the composite outcome of HF hospitalization and all-cause mortality occurred in 56% with anemia vs. 45% without anemia. The association between anemia and outcomes was independent of several potential confounders, and importantly of CKD. The adjusted HR (95%CI) for mortality or HF hospitalization was 1.24 (1.18–1.30) in HFpEF, 1.26 (1.19–1.34) in HFmrEF and 1.14 (1.10–1.19) in HFrEF; and for mortality 1.28 (1.20–1.36) in HFpEF, 1.21 (1.13–1.29) in HFmrEF, and 1.30 (1.24–1.35) in HFrEF. (8)

Justin A. Ezekowitz and et al. performed an analysis on 12,605 patients with HF in population-based cohort of new onset HF patients from database of 138 acute care hospitals in Alberta, Canada from 1993-2001. Among the 12,605 patients, 17% had anemia (21% iron deficiency, 8% other deficiency, 13% other identifiable causes, and

58% had anemia of chronic disease). The median age of the patients was 78 years. After adjustment for clinical and demographic variables, patients with anemia were more likely to be older (OR 1.01 per year) and female (OR 1.2) and to have a history of chronic renal insufficiency (OR 3.2), or hypertension (OR 1.3). Hazard ratios for mortality, adjusting for covariates, were 1.34 (1.24 to 1.46) in anemic patients, and 1.36 (1.23 to 1.50) in those patients with anemia of chronic disease. On subsequent follow up, the 1-year and 5-year mortality rates were 38% and 59% in those with anemia, respectively, compared with 27% and 50% for those without anemia.(14)

In the individual data analysis from Meta-Analysis Global Group in chronic heart failure (MAGGIC) data base, 13,295 patients with HF from 19 studies (9887 with HFrEF*(defined in this study as EF<50%) and 3408 with HFpEF*(defined in this study as EF>=50%) were included. The mean age of the patients was 68 years .Unlike other studies the prevalence of anemia was similar among those with HFrEF and HFpEF (42.8 and 41.6% respectively).Compared with patients with normal Hgb values, those with anemia were older, were more likely to have diabetes, ischemic etiology, NYHA class IV symptoms, lower estimated GFR and were more likely to be taking diuretic and less likely to be taking a beta-blocker. Patients with anemia had higher all-cause mortality (adjusted HR 1.38, 95% CI 1.25–1.51), independent of EF group: adjusted HR 1.67 (1.39–1.99) in HFpEF and adjusted HR 2.49 (2.13–2.90) in HFrEF. There was no interaction between anemia and gender for either EF group. (15)

In systemic review and meta-analysis of 34 studies involving anemia and heart failure published up to 2007, among the 153,180 HF patients, 37.2% were anemic. After a minimal follow-up of 6 months, 46.8% of the anemic patients died compared with 29.5% of non-anemic patients. Crude mortality risk of anemia was odds ratio 1.96 (95% CI: 1.74 to 2.21, P= 0.001). Lower baseline hemoglobin values were associated with increased crude mortality rates ($r = -0.396$, $p = 0.025$). (9)

In the Candesartan in heart failure assessment of reduction in mortality and morbidity (CHARM) program (which encompasses CHARM-Preserved, CHARM-Added, CHARM- Alternative studies) 7599 patients were randomized to either candesartan or placebo. Among these baseline Hgb was available for 2653 patients. The overall prevalence of anemia was 26%. Anemic patients were more often elderly and black and

had worse renal function and NYHA functional class and lower body mass index. Renal dysfunction was one of the strongest independent predictors of lower Hgb, and mean eGFR was lower in anemic than in non-anemic individuals. In the multivariable model, female gender, lower diastolic BP, black ethnicity, and lower eGFR and higher mean EF were the most powerful predictors of low Hgb. The independent predictors of reduced Hgb were similar in patients with reduced and preserved LVEF. Anemia was an independent predictor of both the composite of cardiovascular death or HF hospitalization and all-cause mortality. Diabetes remained an independent predictor of anemia, after taking renal function into account. Anemic patients had more evidence of congestion.(19)

In the Italian network for chronic heart failure (IN CHF) heart failure registry which involves 2411 consecutive outpatients with HF followed in 133 cardiologic centers, 15.5% had anemia. In this registry, 1-year all-cause mortality was significantly higher in anemic patients (25.9%) than in patients without anemia (13.2%) (P .0001). The association of anemia with mortality was confirmed by the multivariable analysis (hazard ratio [HR] 1.54, 95% CI 1.20–1.97). Patients with anemia were older, with more severe functional impairment, lower systolic blood pressure, and with a lower body mass index than patients without anemia. Anemic patients had a higher frequency of ischemic etiology of HF and higher creatinine levels. Multivariable analysis showed that higher functional class, low body mass index, high creatinine levels, and ischemic etiology were independently associated with the diagnosis of anemia. Prescription of ACE-inhibitors was significantly associated to anemia in IN-CHF.(20)

In the analysis that was performed on 3731 (90%) of 4133 hospitalized HF patients with $EF \leq 40\%$ enrolled in the EVEREST trial (that randomized HFrEF patients <48 hours of admission to oral tolvaptan, a vasopressin-2 receptor antagonist, or placebo), comparing the clinical characteristics and outcomes (all-cause mortality and cardiovascular mortality or HF hospitalization) of patients with and without anemia on admission or discharge/day7. Overall, 1277 patients (34%) were anemic at baseline, which persisted through discharge in 73% and resolved in 27%; 6% of patients without baseline anemia developed anemia by discharge or day 7. Patients with anemia were older, with lower blood pressure, and higher creatinine and natriuretic peptide levels compared with those

16

without anemia (all $P < 0.05$). Neither baseline nor discharge anemia was associated with long-term cardiovascular mortality plus HF hospitalization (>100 days) on adjusted analysis (both $P > 0.1$). (21)

A study from the polish cohort of 2 European society of cardiology (ESC)- Heart Failure Registries included 1,394 Caucasian patients hospitalized for HF, with known hemoglobin concentration on hospital admission. Anemia at hospital admission was present in 33% of patients with 2% of patients having severe anemia ($\text{Hgb} < 9\text{mg/dl}$). Independent predictors of anemia included older age, diabetes, greater NYHA functional class at hospital admission and renal dysfunction. During 1-year follow up, 21% of anemic and 13% of non-anemic patients died ($p < 0.0001$). Combined primary end point of all-cause death occurred in 45% of anemic and in 33% of non-anemic patients ($p < 0.0001$). Anemia was strongly predictive of all the pre specified clinical end points (all-cause death at 1 year, a composite of all-cause death and re hospitalization for HF at 1 year) in univariate analyses but not in multivariate analyses. Changes in hemoglobin concentration during hospitalization had no effect on 1-year outcomes.(22)

In a review of 6,159 consecutive ambulatory patients seen at the Cleveland Clinic internal medicine or cardiology outpatient clinics with a documented clinical diagnosis of heart failure, patients were seen and investigated at baseline, short-term (3-month) follow-up, and long-term (6-month) follow-up between 2001 and 2006. The overall prevalence of anemia was 17.2%. Diabetes, B-natriuretic peptide, LVEF, and estimated GFR were independent predictors of baseline anemia. At 6 months follow up, new onset anemia developed in 16% of patients without prior anemia, whereas 43% patients with anemia at baseline had resolution of their Hgb levels. Higher total mortality rates were evident in patients with persistent anemia (58% vs. 31%, $p < 0.0001$) or with incident anemia (45% vs. 31%, $p < 0.0001$) compared with those without anemia at 6 months.(23)

In a cross-sectional study conducted in Cameron on 109 patients in HF, the prevalence of anemia was 49.5%. Severe anemia with $\text{Hgb} < 8\text{mg/dl}$ was present in 5.6% of the patients.(24)

In a retrospective cohort of 379 admitted patients with HF in Gondar university from 2010-2016, the mean age of the participants was 54.56 (± 17.49) years with significant difference among the groups. The prevalence of anemia was 41.90% and majority of the participants were females (64.59%). The mean Hgb in anemic patients was 10.11 ± 2.17 . HF patients with anemia tend to be older age, had lower sodium level and higher creatinine value. There was no difference between the two groups based on NYHA functional class as well as etiology of HF except for cor pulmonale (8.84% vs. 0.65%, $P = < 0.001$). On median follow up of 18 months, mortality was 21.94% in HF patients with anemia (34 patients) and 9.78% in patients without anemia (21 patients). Even though, anemia is a significant risk marker, it is not an independent predictor of mortality in this study.(25)

Among 169 patients admitted to Tikur Anbessa Specialized Hospital with acute HF, baseline Hgb data was available for 158 patients. The mean Hgb was 12.8 and 38% patients have $Hgb < 12$. Anemia was the third most common precipitating factor documented for HF (in 24.4% of the patients) preceded by pneumonia and atrial fibrillation. In the chi-squared test there was no significant association documented between anemia and in hospital mortality.(26)

3. Objectives

3.1. General objective

- To assess the magnitude of anemia and associated factors among adult patients with heart failure at cardiac follow up clinic of SPHMMC, Addis Ababa, Ethiopia, from May1 to July 30 ,2021

3.2. Specific objectives

- To determine the prevalence of anemia among adult cardiac patients who are on follow up in the study period
- To identify the factors associated with anemia in adult heart failure patients
- To compare the quality of life between anemic and non-anemic patients using the validated Kanas City cardiomyopathy questioner-12(KCCQ-12)

4. Methods and Materials

4.1. Study area and period

This study was conducted from May 1 to July 30, 2021 at cardiac follow up clinic of SPHMMC, the second-largest governmental tertiary care hospital located in Gulele sub-city, Addis Ababa, Ethiopia.

SPHMMC was established through a decree of the Council of Ministers in 2010, although the medical school opened in 2007 and the hospital was established in 1968 by the late Emperor Haile Selassie. It is governed by a board under the Federal Ministry of Health and is in the process of building its capacity quickly in a short period of time, expanding teaching facilities. The college has more than 3000 clinical, academic and administrative and support staffs that provide medical specialty services to patients who are referred from all over the country, teaching medicine and post graduate programs and doing basic and applied researches. While the inpatient capacity is more than 700 beds, the College sees an average of 1200 emergency and outpatient clients daily

The cardiology unit, one of the subunits of internal medicine, has started fellowship program by 2016 and currently has 4 cardiology fellows and 8 senior cardiologists. It has a cardiac follow up clinic three times per week and on average 50 patients are seen on each day with average appointment of 3 months. It also has a Cath lab at St. Peter specialized hospital, Addis Ababa, Ethiopia.

4.2 Study design

A hospital based cross-sectional study design was used for this study

4.3 Population

4.3.1. Source population:

All adult heart failure patients seen in in the cardiac follow up clinic of SPHMMC

4.3.2. Study population:

All adult heart failure patients having follow up during the study period and who fulfill the inclusion criteria during the study period

4.4. Inclusion and exclusion criteria

4.4.1. Inclusion criteria

All adult patients (age ≥ 18 years) with clinical diagnosis of heart failure seen over the study period who were willing to participate in the study were included

4.4.2. Exclusion criteria

- ✓ Patients who were critically ill, and not able to communicate
- ✓ Patients who didn't have the basic required laboratory parameters (CBC, RFT) and echocardiography done (based on the timing of indications) were excluded from the study

4.5. Sample size determination and sampling technique

4.5.1. Sample size determination:

Sample size was determined using the formula, $(n = Z^2 p (1-p)/d^2)$

Where: n= sample size

- $Z = Z\text{-score at } 95\% \text{ confidence interval} = 1.96$
- $P = 25\%$ (prevalence of anemia in outpatients from the Swedish HF registry. (12))
- $d = \text{marginal error} = 0.05 (5\%)$

Therefore, n becomes:

- $n = (1.96)^2 \times (0.25 \times 0.75) / (0.05)^2$
- $n = 288$
- Note: The average number of cardiac patients seen per day is 50, Having 3 days of cardiac clinic per week, estimated 1800 cardiac patients were seen over 3 months of the study period according to HMIS report. Since the estimated source population is $<10,000$, we use reduction formula $n/(1+n/N) = 248+25 (10\% \text{ Non-response rate})$. **Final Sample size was 273.**

4.5.2 Sampling technique:

Systematic random sampling technique was used to recruit the study participants. From the estimated cardiac patients seen over the study period (1800), sampling was done by taking 1 in every 6th patient (1800/273 makes, k=6) after taking the first patient randomly, until the sample size was reached.

4.6 Data collection tools and techniques

Data was collected by interviewing patients with structured questionnaires developed from related literatures and Amharic version of KCCQ-12 points. In addition, charts of patients who had follow up in the study period was reviewed. The questionnaire had the required socio-demography, clinical, biochemical and echo parameters of the selected patients

The data was collected by four junior internal medicine residents and two nurses working at the follow up clinic after trained by the investigator.

4.7 Study variables

4.7.1 Dependent variables

- Anemia among HF patients

4.7.2 Independent variables

- Age, sex, marital status, educational status, occupational status, dietary habit, residence area, aetiology of heart failure, EF, RFT, presence of diabetes, NYHA functional class, medication profile, duration of illness, admission in the past 6-month, smoking, alcohol history
- The quality of life as assessed with KCCQ-12-points questioner

4.8 Operational Definition

Anemia: WHO uses Hgb cut off points of <13g/dl for men and <12g/dl women to define anemia and classified as mild (Hgb 10.0–11.9 g/dL for females and 10-12.9g/dl for males), moderate (Hgb 7.0–9.9 g/dL), and severe (Hgb <7.0 g/dL).(4)

Heart failure: is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.(16) Patients in this study are considered to have heart failure based on the current clinical diagnosis put forward by the treating physician.

NHYA function class: HF symptom assessment tool used to describe the severity of symptoms and exercise intolerance. (16)

KCCQ-12 points: is a well validated international tool for assessing health related quality of life in patients with CHF.(11)

LVEF: the ratio of stroke volume to end-diastolic volume as measured by echocardiography.(16) Expressed in the following classification.

HFpEF: EF $\geq$ 50%

HFmrEF: EF from 40-49%

HFrEF: EF <40%

eGFR: is a calculation that determines how well the blood is filtered by the kidneys. Measures kidney function and helps to classify chronic kidney disease (CKD) into 5 stages. Determined by Modification of Diet in Renal Disease (MDRD) formula

Stage1 eGFR $\geq$ 90 mL/min/1.73 m²

Stage2 eGFR 60-89 mL/min/1.73 m²

Stage3 eGFR 30-59 mL/min/1.73 m²

Stage4 eGFR 15-29 mL/min/1.73 m²

Stage5 eGFR <15 mL/min/1.73 m²

4.9 Data quality management

Data quality was managed through training the data collectors, and filling the structured questionnaires with the appropriate data from patient charts and interviewing the patients. The questionnaires were first prepared in English and then translated to Amharic. There was supervising personnel for the quality of data other than the collectors. Pretest was done two weeks before the actual data collection at SPHMMC with 5% of sample size to check its clarity, time required for completion and appropriateness and the necessary correction was done accordingly.

4.10 Data processing and analysis

The data collected was coded, entered, cleaned and further analysis done using STATA version 13 Statistical software. Descriptive statistics were presented as mean $\pm$ standard deviation for continuous variables, and as frequencies and percentage for categorical variables. Tables and figures were used for data presentation. Binary logistic regression analysis was used to assess statistical association between the dependent and independent variables. Bivariate analysis was done to check the existence of crude association of individual independent variables with the dependent variable. Variables which had a P-value of ≤ 0.2 were then entered in to multivariable binary logistic regression models for final analysis. The summary measures of estimated crude and adjusted odds ratios with 95% CI were presented and P-value of < 0.05 was used to declare statistical significance.

4.11 Ethical considerations

Ethical clearance was obtained from the Institutional Review Board (IRB) of SPHMMC, and then permission was sought from the school administration through the academic vice provost of the school to carry out the study. Patients was informed about the aim, benefit and possible inconvenience of the study. They were assured the information they gave was confidential and the right of withdrawal at any time if the need arises. The collected data were not used for any other purpose and all the collected patient information was stored anonymous.

4.12 Dissemination of result

Finally, the results of this research will be submitted to the departments of internal medicine, cardiology unit and public health of SPHMMC so that all clinicians will understand significance of the problem. Attempts will be made to disseminate it through publication in scientific peer reviewed journal.

5. Results

5.1 socio-demographic and clinical variables

5.1.1 socio-demographic variables

From the 273 samples, information was collected from 260 HF patients making the response rate 95.23%. Of those, 137 (52.7%) of the patients were females and 123 (47.3%) were males. The mean age of study was 55.68 ± 17 years with the majority number of patients being in the age group of 70 and above years 63(24.23%) followed by 50-59 years 57(21.92%). Most of the participants 209(80.38%) were from urban area. And as to the marital status 181(69.62%) were married, and 48(18.46%) were single. Concerning the dietary habit, only 20(7.69%) of the patients were strict vegetarian and others were taking mixed type of feeding. (**Table1**)

Table 1: Socio-demographic characteristics of study participants at SPHMMC, Addis Ababa, Ethiopia, 2021 (n=260)

Socio- demographic characteristics		Frequency	N (%)
Age	18-19	9	3.46
	20-29	10	3.85
	30-39	34	13.08
	40-49	32	12.31
	50-59	57	21.92
	60-69	55	21.15
	≥70	63	24.23
sex	Male	123	47.31
	Female	137	52.69
Marital status	single	48	18.46
	Married	181	69.62
	Divorced	15	5.77
	Widowed	16	6.15
Educational status	No education	54	20.77
	Primary education	81	31.15
	Secondary education	61	23.46
	College graduate	46	17.69
	University graduate	16	6.15
	Others	2	0.77
Occupation	Civil servant	57	21.92
	Merchant	35	13.46
	Farmer	23	8.85
	Housewife	57	21.92
	Unable to work	49	18.85
	Others	39	15
Residency area	urban	209	80.38
	Rural	51	19.62
Dietary habit	Strict vegetarian	20	7.69
	Mixed	240	92.31

5.1.2 clinical characteristics of study participants

The most common cause of HF was HHD 81(31.2%) followed by IHD 78(30%) and CRVHD 48 (18.5%). Most of the patients 196(75.4%) had HFpEF defined by $EF \geq 50\%$. Most of the patients 122(46.9%) had NYHA functional class II HF. And only 20% patients had admission for the past 6 months. Regarding the medication profile, 157(60.38%) and 91(35%) of the patients were taking ACEI/ARB and antiplatelet respectively but only 12(4.62%) participants were taking anticoagulant. Most of the patients were nonsmokers 215(82.69%) and non-alcoholic 232(89.23%). Diabetes mellitus was found in 44(16.92%) of the patients. More than half of the patients (53.85%) had $eGFR \geq 90 \text{ ml/min/1.73 m}^2$ and the mean $eGFR$ was 92.11 ± 24.22 . The mean EF was 53.9 ± 13.1 . When we see the duration of illness, 138 (53.08%) patients had 1-5 years and 122 (46.92%) had more than five years. (**Table2**)

Table 2: Distribution of the clinical profiles of study subjects at SPHMMC, Addis Ababa, Ethiopia, 2021 (n=260)

Variables			Frequency	N (%)
Etiology of HF	HHD		81	31.15
	IHD		78	30
	CRVHD		48	18.46
	Congenital HD		10	3.85
	Cor pulmonale		6	2.31
	Others		37	14.23
NYHA class	Class I		75	28.85
	Class II		122	46.92
	Class III		63	24.23
	Class IV		0	0
Duration of illness	1-5 years		138	53.08
	More than 5 years		122	46.92
Previous admission in the past 6 months	Yes		52	20
	No		208	80
Presence of DM	Yes		44	16.92
	No		214	83.08
Smoking	No		215	82.69
	Previous history		38	14.62
	Current smoker		7	2.69
Alcohol	No/less than standard		232	89.23
	Standard		24	9.23
	More than standard		4	1.54
Medication profile	ACEI/ARB	Yes	157	60.38
		No	103	39.62
	Antiplatelet	Yes	91	35
		No	169	65
	Anticoagulant	Yes	12	4.62
		No	248	95.38
eGFR	≥ 90		140	53.85
	60-89		93	35.77
	30-59		26	10
	15-29		0	0
	<15		1	0.38
LV EF	≥50		196	75.38
	40-49		18	6.92
	<40		46	17.69

5.2 Prevalence of anemia

From the respondent HF patients, 68 (**26.2%**) patients had anemia and the remaining participants (192) were non-anemic. The mean Hgb in the anemic group was 11.4 ± 1 g/dl as compared to 14.6 ± 1.5 g/dl in the non-anemic group. There was no severe anemia and only 6(2.3%) of these patients had Hgb<10. Anemia is more common in males as compared to females (33.3% vs 19.7%) and it is common in the age group of 70 and above years (34.9%). The mean MCV was 87.2 ± 5.8 fl and it was 85.6 ± 6.4 fl in the anemic group compared to 87.7 ± 5.5 fl in the non-anemic group.

The mean eGFR in anemic patients was lower compared to non-anemic patients 80.6 ± 27.15 vs 96.2 ± 21.75 mL/min/1.73 m², and the mean EF was $50 \pm 14\%$ in anemic patients and $53.3 \pm 12.5\%$ in non-anemic patients.

When we see the prevalence of anemia with respect to different clinical variables, it was higher in those with IHD, higher NYHA functional class, DM, lower eGFR, above standard alcohol drinks, and those who were taking antiplatelet drugs and those patients with LVEF 40-49% compared to the respective other variables. (**Table 3**)

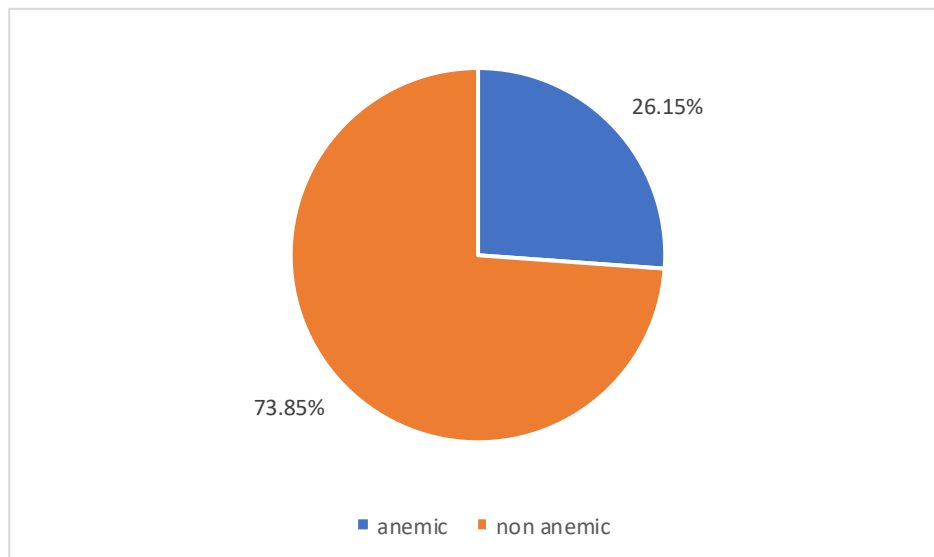


Figure 1: Prevalence of anemia among adult outpatient HF patients at SPHMMC, Addis Ababa, Ethiopia 2021. (n=260)

Table 3: Distribution of anemia in different variables among adult outpatient HF patients at SPHMMC, Ethiopia 2021 (n=260)

Variables		Anemic	Non anemic	Total	%
Age	18-19	1 (11.1%)	8 (88.9%)	9	3.5
	20-29	2 (20%)	8 (80%)	10	3.8
	30-39	10 (29.4%)	24 (70.6%)	34	13.1
	40-49	9 (28.1%)	23 (71.9)	32	12.3
	50-59	11 (19.3%)	46 (80.7%)	57	21.9
	60-69	13 (23.6%)	42 (72.4%)	55	21.1
	≥70	22 (34.9%)	41 (65.1%)	63	24.2
sex	Male	41 (33.3%)	82 (66.7%)	123	47.3
	Female	27 (19.7%)	110 (80.3%)	137	52.7
Marital status	single	14 (29.2%)	34 (70.8 %)	48	18.5
	Married	44(24.3%)	137(75.7%)	181	69.6
	Divorced	5 (33.3%)	10 (66.7%)	15	5.8
	Widowed	5 (31.3%)	11 (68.7%)	16	6.2
Educational status	No education	13 (24.1%)	41 (75.9)	54	20.8
	Primary education	22 (27.2)	59 (72.8)	81	31.2
	Secondary education	15 (24.6)	46 (75.4)	61	23.5
	College graduate	15 (32.6)	31 (67.4)	46	17.7
	University graduate	3 (18.8)	13 (81.2)	16	6.2
	Others	0	2 (100)	2	0.08
Occupational status	Civil servant	16 (28.1)	41(71.9)	57	21.9
	Merchant	8 (22.9)	27(77.1)	35	13.5
	Farmer	8 (34.8)	15(65.2)	23	8.85
	Housewife	19 (33.3)	38(66.7)	57	21.9
	Unable to work	9 (18.4)	40(81.6)	49	18.8
	others	8 (20.5)	31(79.5)	39	15
Residency area	urban	56 (26.8%)	153 (73.2%)	209	80.4
	Rural	12 (23.5%)	39 (76.5%)	51	19.6
Dietary habit	Strict vegetarian	3 (15%)	17 (85%)	20	7.7
	Mixed	65 (27.1%)	175 (72.9%)	240	92.3
Etiology of HF	HHD	14 (17.3%)	67 (82.7%)	81	31.2
	IHD	30 (38.5%)	48 (61.5%)	78	30
	CRVHD	11 (22.9%)	37 (77.1%)	48	18.5
	Congenital HD	0	10 (100%)	10	3.8
	Cor pulmonale	2 (33.3%)	4 (66.7%)	6	2.3
	Others	11 (29.7%)	26 (70.3%)	37	14.2

NYHA class	Class I		8 (10.7%)	67 (89.3%)	75 28.8
	Class II		28 (22.9%)	94 (77.1%)	122 46.9
	Class III		32 (50.8%)	31 (49.2%)	63 24.2
	Class IV		0	0	0 0
Duration of illness	1-5 years		38 (27.5%)	100 (72.5%)	138 53.1
	More than 5 years		30 (24.6%)	92 (75.4%)	122 26.9
Previous admission in the past 6 months	Yes		18 (34.6%)	34 (65.4%)	52 20
	No		50 (24%)	158 (76%)	208 80
Presence of DM	Yes		21 (47.7%)	23 (52.3%)	44 16.9
	No		47 (21.8%)	169 (78.2%)	216 83.1
Smoking	No		50 (23.3%)	165 (76.7%)	215 82.7
	Previous history		15 (39.5%)	23 (60.5%)	38 14.6
	Current smoker		3 (42.9%)	4 (57.1%)	7 2.7
Alcohol	No/less than standard		57 (24.6%)	175 (75.4%)	232 89.2
	Standard		7 (29.2%)	17 (70.9%)	24 9.2
	More than standard		4 (100%)	0	4 1.5
Medication profile	ACEI/ARB	Yes	42 (26.8%)	115 (73.2%)	157 60.4
		No	26 (25.2%)	77 (74.8%)	103 39.6
	Antiplatelet	Yes	33 (36.3%)	58 (63.7%)	91 35
		No	35 (20.7%)	134 (79.3%)	169 65
	Anticoagulant	Yes	2 (16.7%)	10 (83.3%)	12 4.6
		No	66 (26.6%)	182 (73.4%)	248 95.4
eGFR	≥ 90		16 (11.4%)	124 (88.6%)	140 53.8
	60-89		38 (40.9%)	55 (59.1%)	93 37.8
	30-59		13 (50%)	13 (50%)	26 10
	15-29		0	0	0 0
	<15		1 (100%)	0	1 0.4
Mean eGFR	Anemic		80.6±27.15	96.2±21.75	
LVEF	≥50		44 (22.5%)	152 (77.5%)	196 73.4
	40-49		7 (38.9%)	11 (61.1%)	18 5
	<40		17 (37%)	29 (63%)	46 17.7
Mean LV EF			50±14%	53.3±12.5%	
Mean MCV			85.6±6.4	87.4±5.5	
Mean KCCQ-12 score			40 ± 9	46 ±8.6	

5.3 Factors associated with anemia in HF patients

In bivariate binary logistic regression analysis, age, sex, NYHA functional class, the presence of diabetes mellitus, eGFR, LVEF, etiology of HF, taking antiplatelet and previous admission for the past 6 months and smoking had strong association with anemia in HF patients ($P\text{-value} \leq 0.2$).

On independent T-test anemic patients had a lower mean KCCQ-12 points score compared with non-anemic patients (40 ± 9 vs 46 ± 8.6), $P\text{-value} < 0.001$, which implies poor quality of life.

The Multivariable binary logistic regression analysis showed only NYHA functional class, the presence of diabetes mellitus and eGFR had significant association with anemia ($P < 0.05$). The odds of having anemia in those HF patients with NYHA functional class III was 6 times higher than those with NYHA class I (AOR=6.05, $P=0.004$, 95% CI 1.8-20.33). Compared to those HF patients who had diabetes mellitus, those who didn't have were about 79% less likely to develop anemia (AOR=0.21, $P=0.002$, 95% CI, 0.08-0.56). The odds of having anemia in those patients with eGFR 60-89 mL/min/1.73 m² is 6.6 times higher than those with eGFR ≥ 90 (AOR=6.61, $P < 0.001$, 95% CI, 2.74-25.93). And those HF patients with eGFR 30-59 mL/min /1.73 m² had the odds of having anemia 13.53 times higher as compared to those with eGFR 90 and above (AOR 13.5(3.7-49.4), $P < 0.001$). (**Table4**)

Table 4: Bivariable and multivariable binary logistic regression predicting anemia among outpatient HF patients at SPHMMC, Addis Ababa, Ethiopia 2021 (n-260).

Variables	Anemic	Non anemic	COR (95% CI)	P-value	AOR (95% CI)	P-value
Age (years)						
18-19	1 (11.1%)	8 (88.9%)	1.00		1.00	
20-29	2 (20%)	8 (80%)	2(0.15-26.73)	0.600	2.3(0.06-87.9)	0.656
30-39	10 (29.4%)	24 (70.6%)	3.33(0.37-30)	0.285	10.31(0.6-182)	0.112
40-49	9 (28.1%)	23 (71.9)	3.1(0.34-28.7)	0.313	5.8(0.3-123.6)	0.257
50-59	11 (19.3%)	46 (80.7%)	1.9(0.22-16.9)	0.560	4.2(0.21-82.9)	0.347
60-69	13 (23.6%)	42 (72.4%)	2.5(0.29-21.7)	0.413	1.77(0.1-32.7)	0.700
≥70	22 (34.9%)	41 (65.1%)	4.29(0.5-37.8)	0.183	5.3(.29-97.1)	0.263
Sex						
Male	41 (33.3)	82 (66.7%)	1.00		1.00	
Female	27 (19.7%)	110 (80.3%)	0.49 (0.3-0.86)	0.013	0.47(0.2-1.12)	0.090
Etiology						
CRVHD	11 (22.9%)	37 (77.1%)	1.00		1.00	
HHD	14 (17.3%)	67 (82.7%)	0.70(0.29-1.7)	0.435	0.62(0.16-2.4)	0.483
IHD	30 (38.5%)	48 (61.5%)	2.1(0.93-4.74)	0.073	0.69(0.12-3.8)	0.669
Congenital HD	0	10 (100%)	1		1	
Cor pulmonale	2 (33.3%)	4 (66.7%)	1.68(0.3-10.4)	0.577	0.51(0.05-4.9)	0.561
Others	11 (29.7%)	26 (70.3%)	1.42(0.54-3.8)	0.478	1.9(0.44-8.36)	0.391
NYHA class						
Class I	8 (10.7%)	67 (89.3%)	1.00		1.00	
Class II	28 (22.9%)	94 (77.1%)	2.49(1.1-5.81)	0.034	1.45(0.53-4)	0.473
Class III	32 (50.8%)	31 (49.2%)	8.65(3.6-20.9)	0.<001	6.05(1.8-20.3)	©0.004
Class IV	0	0				
Admission past 6 months						
Yes	18 (34.6%)	34 (65.4%)	1.00		1.00	
No	50 (24%)	158 (76%)	0.59(0.31-1.3)	0.123	1.47(0.56-3.9)	0.433
DM						

Yes	21 (47.7%)	23 (52.3%)	1.00		1.00	
No	47 (21.8%)	169 78.2%	0.31(0.16-0.6)	0.001	0.21(0.08-0.56)	© 0.002
Smoking						
No	50 (23.3%)	165(76.7%)	1.00		1.00	
Previous hx of smoking	15 (39.5%)	23 (60.5%)	2.15(1.04-4.44)	0.038	1.470.52-4.18)	0.472
Current smoker	3 (42.9%)	4 (57.1%)	2.5(0.54-11.4)	0.246	0.37(0.03-3.9)	0.409
Alcohol						
No/ less than standard	57 (24.6%)	175(75.4%)	1.00			
Standard drink	7 (29.2%)	17 (70.9%)	1.26(0.53-0.2)	0.49		
More than standard	4 (100%)	0	1			
ACEI/ARB						
Yes	42 (26.8%)	115 73.2%)	1.00			
No	26 (25.2%)	77 (74.8%)	0.92(0.52-1.6)	0.787		
Antiplatelet						
Yes	33 (36.3%)	58 (63.7%)	1.00		1.00	
No	35 (20.7%)	134 (.3%)	0.46(0.26-0.8)	0.007	0.32(0.09-1.2)	0.088
Anticoagulant						
Yes	2 (16.7%)	10 (83.3%)				
No	66 (26.6%)	182 (73.4%)	1.81(0.39-8.5)	0.450		
eGFR (mL/min /1.73 m ²)						
>= 90	16 (11.4%)	124 (88.6%)	1.00		1.00	
60-89	38 (40.9%)	55 (59.1%)	5.35(2.8-10.4)	0.<001	6.6(2.75-15.9)	© 0.<001
30-59	13 (50%)	13 (50%)	7.75(3.1-19.6)	0.<001	13.5(3.7-49.4)	© 0.<001
15-29	0	0				
<15	1 (100%)	0	1		1	
LV EF (%)						
>=50	44 (22.5%)	152 (77.5%)	1.000		1.00	
40-49	7 (38.9%)	11 (61.1%)	2.2(0.8-6)	0.125	0.63(0.15-2.7)	0.538
<40	17 (37%)	29 (63%)	2.02(1.01-4)	0.044	0.42(0.14-1.3)	0.142
KCCQ-12			8.8 (2.2-35.9)	0.002	0.5(0.01-24)	0.738

Note: - © indicates statistically significant association whereas the constant is represented by 1.00.

6. Discussion

Anemia is a common comorbidity in patients with chronic heart failure (CHF) and has been proposed as a novel therapeutic target in this patient population. Institutional based cross-sectional descriptive study was conducted to evaluate the prevalence of anemia and associated factors among outpatient heart failure patients at SPHMMC. The study showed the prevalence of anemia in outpatients HF patients was 26.2% which was comparable to the study from the larger Swedish HF registry, which was 25%.(8) and to the overall global prevalence of anemia which was 24.8%.(4) But higher than a study done at Cleveland Clinic internal medicine, cardiology outpatient clinics which was found to be 17.2%. (23) When it is compared to local studies, it was significantly lower than a prevalence of 41.9% reported from a similar hospital-based study in hospitalized HF patients from Gondar university Hospital (25) and Cameron which was 49.5%.(24) This might be due to the fact that hospitalized patients are more critical and can have other potential causes of anemia like malaria, leishmaniasis etc.

Generally, the prevalence of anemia in our outpatient HF patients seems to reflect the overall prevalence of anemia in the general population which is 18-23%.(5)

In the CHARM program (which encompasses CHARM-Preserved, CHARM-Added, CHARM- Alternative studies). The overall prevalence of anemia was 26%. Anemic patients were more often elderly and black and had worse renal function and NYHA functional class. Renal dysfunction was one of the strongest independent predictors of Hgb, and mean eGFR was lower in anemic than in non-anemic individuals. In the multivariable model, female gender, black ethnicity, and lower eGFR and higher mean EF were the most powerful predictors of low Hgb. Diabetes remained an independent predictor of anemia.(19) This study goes in line with our study which showed higher NYHA functional class, lower eGFR and the presence of Diabetes mellites independently predicts anemia in HF patients. But unlike this study and most of the literatures, our study showed anemia was prevalent in patients with lower EF. This might be due to possible etiologies of anemia in our setup might be different from the westerns and needs further etiologic studies.

In Swedish HF registry and analysis of the MAGGIC database important predictors of anemia across the HF patients were male sex, older age, worse NYHA and renal function, lower systolic BP, higher NT- BNP, diabetes, history of ischemic heart disease, coronary revascularization, and peripheral artery disease. Anemic HF patients are at higher risk of increased hospitalization and mortality.(8)(15) The above study was in line with our study in terms of worse NYHA functional class ($P=0.004$, AOR 6(1.8-20.33)), renal dysfunction ($P<0.001$, 6.6-13.5(2.7-49)) and diabetes mellites ($P=0.002$) which independently predicts anemia in our setup too. In bivariate analysis, ischemic heart disease, hospital admission, male sex and older age had association with anemia but the multivariate analysis didn't show significance of the association. This might be because the mean age of our patients was lower than the above studies with a wide variation in terms of age and, most of the patients (80%) had no recent admission.

In the IN CHF heart failure registry which involved 2411 consecutive outpatients with HF followed in 133 cardiologic centers, 15.5% had anemia. Multivariable analysis showed that higher functional class, low body mass index, high creatinine levels, and ischemic etiology were independently associated with the diagnosis of anemia. Prescription of ACE-inhibitors was significantly associated to anemia in IN-CHF. (20) This was true for our study in terms of higher functional class and high creatinine level but taking ACEI/ARBs had no significant association in our study. Body mass index was not measured in this study which was one of its limitations.

According to Val-HeFT study, after adjusted analysis older age, lower systolic blood pressure and body mass index, high creatinine levels, and advanced NYHA class were significantly associated with anemia but the number of anemic patients was similar in patients allocated to valsartan or placebo in this study.(20) which was consistent with our study except blood pressure, body mass index which was not measured and age had no significant association in this study.

On independent T-test anemic patients had a lower mean KCCQ-12 points score compared with non-anemic patients (40 ± 9 vs 46 ± 8.6), P -value <0.001 , which implies poor quality of life associated with anemia but when adjusted for other variables in multivariate analysis it didn't show significant association. This was against the finding

of the ASIAN HF study which showed the lower quality of life measured by KCCQ and higher mortality in anemic HF patients.(27) This might be due to the fact that KCCQ-12 points questionnaire was not locally validated.

7. Strength and limitation of the study

Strength of the study: To the best of my knowledge, there was no study conducted in Ethiopia that assessed the prevalence of anemia and its associated factors in outpatient HF patients. So, this will give an insight for further study

The primary data was included and was collected by the department health professionals so it gives the advantage of keeping the quality of data.

Limitation of the Study: The study design was cross-sectional and it was difficult to establish a cause and effect relationship between the dependent and independent variables because of the nature of the study.

Nutritional assessment was not done which might contribute significantly as cause of anemia in a set up like ours.

The confidence interval of the AORs were wide which might be due to the low sample size.

KCCQ-12 was not locally validated.

8. Conclusion

Anemia is a common comorbidity in outpatient HF patients in our set up and almost similar to a study done in a large Swedish HF registry, and to the global prevalence of anemia at large.

In general, according to this study, the presence of worse NYHA functional class, lower eGFR, and diabetes mellites strongly predicts anemia in outpatient HF patients. But there was no significant association between age, sex, etiology of HF, use of ACEI /ARBs, duration of illness and hospital admission with anemia.

9. Recommendation

For SPHMMC cardiology unit:

Patients with concomitant diabetes and/or renal dysfunction should be seen closely and should make sure that the underlying disease is treated well with possible multidisciplinary approach

For fellow researchers:

Further studies that look into the etiologies including iron study, ferritin, hematinic vitamins (Vitb12& folate) & C-reactive protein is recommended so that treatment can be tailored accordingly to improve quality of life of HF patients.

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11.ANNEXES

11.1 Annex I: Information sheet and consent form

Information Sheet for Study Subjects

My name is _____. I am working with the research team of SPHMMC. We would like to assure you that your name will not be mentioned in the questionnaire and the information that you will give us will be kept confidential and used only for research purpose. You have the full right to refuse to take part or to interrupt the interview at any time. But the information that you will give us is quite useful to achieve the objective of the study. You are kindly invited to participate in this study.

Purpose: To assess the prevalence of anemia and associated factors among adult patients with heart failure at cardiac follow up clinic of SPHMMC, Addis Ababa, Ethiopia, so as to further improve the services given in our institution in particular, and in the country in general.

Duration: the study will be conducted from May1-July 30, 2021.

Procedures to be carried out: It only involves an interview for data collection using a standardized questionnaire by a trained interviewer.

Expected benefits: the findings of this research will be useful for the health personnel, stake holders, institutional and national policy makers involved in improving quality of health services based on evidence-based practice. No reward was provided for participating in this study.

Confidentiality: all your personal information will be kept confidential.

Termination of the study: participation in the study is absolutely voluntary, and refusal to participate involves no penalty or loss of benefits to which you are otherwise entitled. The study participants have a right to keep hold information, or decline to cooperate in the study and to refuse provision of data. I would also like to inform you that this study was approved by the Department of Internal medicine and IRB of SPHMMC. If you have any questions about the study, the name and contact information of the principal investigator (PI) is given below.

Name of PI: **Dr. Ermias Limeneh** **Tel: +251913909925/+251911540653**

Individual Consent Form

SPHMMC Department of Internal medicine individual consent form for the study on the prevalence of anemia and associated factors among adult patients with heart failure at cardiac follow up clinic of SPHMMC, Addis Ababa, Ethiopia 2021.

My name is _____. I am working with the research team of SPHMMC. We would like to assure you that your name will not be mentioned in the questionnaire and the information that you will give us will be kept confidential and used only for research purpose. You have the full right to refuse to take part or to interrupt the interview at any time. But the information that you will give us is quite useful to achieve the objective of the study and to improve our services

Are you willing to participate in the study? A- Yes B - No

If the answer is yes, thanks! Conduct the interview. If the answer is no, Thanks!

Don't force or reinforce an individual to participate in the survey

Interviewer's: name ----- signature -----

Date of interview ----- date -----month/2021.

Checked on ----- date-----month/2021

Complete 1 Incomplete 2 other (specify) -----

የፈቀደኝነት መግለጫ ቅጽ

ስሜ _____ ይባላል። ከቅዱስ ጳውሎስ ሆስፒታል ሚሴንዮም ሕክምና ኮሌጅ የጥናት ቡድን ጋር ተባብሮ ነው የምሰራው። የዚህ ጥናት ዋና አላማ በቅዱስ ጳውሎስ ሆስፒታል የልብ ሕመም ክትትል የሚያደርጉ ታካሚዎች ምን ያህሎቹ የደም ማነስ እንዳለባቸው እና ተያያዥ ነገሮችን ለማወቅ የሚዳስስ ሲሆን በዚህ መጠይቅ ውስጥ የእርሶ ስም እንደማይጠቀስ እና የሚሰጡን መልስ እና መረጃዎች ሁሉ በሚስጥር እንደሚጠበቁ እና ለዚህ ጥናት ዓላማ ብቻ እንደሚውሉ እናረጋግጥሎታለን።

በዚህ መጠይቅ ውስጥ ላለመሳተፍ ወይም ፈቅደው ከጀመሩ በኋላ በማንኛውም ሰዓት አቋርጠው የመሄድ ነጻነትዎ የተጠበቀ ነው። ነገር ግን የሚሰጡን መልስ የጥናቱን ዓላማ ግብ ለመምታትና አገልግሎታችንን ለማሻሻል ከፍተኛ አስተዋጽኦ ይኖረዋል።

በዚህ ጥናት ለመሳተፍ ፈቃደኛ ኖት? 1. አዎ 2. አይደለሁም

1. መልስዎ አዎ ከሆነ እናመሰግናለን። (መጠይቁ ይጀመር)
2. መልሳቸው ፈቃደኛ አይደለሁም ከሆነም እናመሰግናለን።

ሰዎች በመጠይቁ እንዲሳተፉ አታስገድዱዋቸው፤ አታበረታቱዋቸውም።

የጠያቂው ስም _____ ፊርማ _____

መጠይቁ የተደረገበት ቀን _____ ወር _____ ዓ.ም _____

- ☐ ተጠናቋል
- ☐ አልተጠናቀቀም
- ☐ ሌላ (ይጥቀሱ) _____

11.2 Annex II: Data collection tools (questionnaires)

Instruction to data collector

1. Circle the appropriate answer for Multiple-Choice questions
2. Write in the Space provided for open-ended questions

Questionnaire number _____

Card number _____

Part one: - Socio-demographic status

Variables	Category	Code	Skip to;
Age	Write in number	[__ __] years	
Sex	Male	1	
	Female	2	
Residency area	Urban	1	
	rural	2	
Marital status	Single	1	
	Married	2	
	Divorced	3	
	Married	4	
Educational status	No education		
	Primary education		
	Secondary education		
	College graduate		
	University graduate		
	©Others (specify)		
Occupational status	Civil servant		
	Merchant		
	Farmer		
	Housewife		
	Unable to work		
	©©Others (specify)		
What is your dietary habit	Strict Vegetarian	1	
	Mixed	2	

Note: - ©Others include informal learning

©©Others includes student, pensioners

Part two: - Clinical Parameters

Variables	Category		Code	skip
Duration of illness	1-5 years		1	
	More than 5 yr.		2	
Etiology of HF	CRVHD		1	
	Congenital HD		2	
	IHD		3	
	Cor pulmonale		4	
	HHD		5	
	®Others (Specify)		6	
Diabetes present	Yes		1	
	No		2	
NYHA functional class	Class I		1	
	Class II		2	
	Class III		3	
	Class IV		4	
Previous admission in the past 6 months	Yes		1	
	No		2	
Smoking	No		1	
	Previous hx		2	
	Current smoker		3	
Alcohol	No /less than standard		1	
	Standard		2	
	More than standard		3	
Medication profile	ACEI/ARB	Yes	1	
		No	2	
	Antiplatelet	yes	1	
		No	2	
	Anticoagulant	yes	1	
		No	2	

Note: - ®others includes, degenerative valvular heart disease (DVHD),

Idiopathic, tachycardia induced and alcohol induced DCMP

Bradyarrhythmia

Part three: - Laboratory and Echo findings

Variables	Category		Code	Skip
CBC	Hgb	Baseline (no.)		
			g/dl	
		Current	g/dl	
	MCV:	Baseline	femtoliters	
		Current	femtoliters	
Renal function test	Cr:	Baseline	Mg/dl	
		Current	Mg/dl	
	BUN:	Baseline	Mg/dl	
		Current	Mg/dl	
	eGFR	Baseline	ml/min/1.73 m ²	
		Current	ml/min/1.73 m ²	
Left ventricular EF	Baseline		%	
	Current		%	

Key eGFR - as determined by the MDRD formula

[illegible]

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Thanks!

Date of Interview-----

Interviewer Name-----

Supervisor-----

11.3Annex III: Assurance of Investigator

I the undersigned resident agree to accept all responsibilities for the scientific, ethical and technical conduct of the research project and for provision of required progress reports as per terms and conditions of the Research and Publication Directorate and /or Department of Public Health of SPHMMC.

Name of the Resident: _____

Signature: _____

Date: _____

Approval of Advisors

Name of Public Health Advisor: _____

Signature:_____

Date:_____

Name of Clinical Advisor:_____

Signature:_____

Date: _____