Medical Science

*25(112), June, 2021*

# Prevalence of anemia among heart failure patients with reduced left ventricular ejection fraction, single center study, Saudi Arabia

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**To Cite:**
Alraheili RA, Alsarhan BK, Alsarhan LK, Alruwaili AS, Albishi FM, Alraheili AA, Almehmadi FM, Alqhtani MM, Alotaibi TF, Smaisem FS, Alhenaki GA, Alghamdi SM, Almuzaini JI, Almuraykhi RA. Prevalence of anemia among heart failure patients with reduced left ventricular ejection fraction, single center study, Saudi Arabia. *Medical Science*, 2021, 25(112), 1469-1476

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**Peer-Review History**
Received: 08 May 2021
Reviewed & Revised: 10/May/2021 to 11/June/2021
Accepted: 12 June 2021
Published: June 2021

**Peer-review Method**
External peer-review was done through double-blind method.



## ABSTRACT

*Background*: Heart Failure (HF) has become a significant health problem. It can cause anemia by different pathophysiological mechanisms. The presence of anemia is associated with more symptoms and impaired life functional capacity. *Methods*: This is a cross-sectional study that included 1607 patients who had been admitted at Madinah cardiac center with a diagnosis of HF with reduced left ventricular Ejection Fraction (HFrEF) during the period from March 2011 to January 2019. Anemia is defined when Hemoglobin (Hb) level <13 and <12 g/dl in males and females, respectively. According to the World Health Organization (WHO) criteria of anemia, mild anemia was defined when Hb level is 12.9-11 g/dl in males and 11.9-11 g/dl in females; moderate anemia when Hb level is 10.9-8 g/dl and severe anemia when Hb level is<8 g/dl. *Results:* Of the total 1607 patients included in the analysis, 67% were males, 51% were hypertensive, 52% were diabetic, and 39% had stage III Chronic Kidney Disease (CKD). About 56% of patients were anemic, 66% of them had mild anemia, 24% had moderate anemia, and 10% had severe anemia. Mean ± SD of age was 68±11 years in anemic patients compared to 63±11 years in non-anemic patients (p<0.001). Anemic patients were significantly females (p<0.001), Hypertensive (HTN) (p<0.001), had Diabetes Mellitus (DM) (p<0.001), or advanced CKD stage (p=0.020). *Conclusion*: The prevalence of anemia was 56%. Approximately 66% of patients had mild anemia, 24% had moderate anemia, and 10% had severe anemia. Female genders, presence of HTN, DM, or advanced CKD stage were the factors associated with anemia among HFrEF patients.

**Keywords:** Anemia, Heart failure with reduced left ventricular ejection fraction, Hemoglobin

## 1. INTRODUCTION

Heart Failure (HF) has become a significant health problem due to its increasing prevalence, healthcare costs and the higher rates of associated morbidity, and mortality (Beverborg et al., 2018). More than half of HF patients had HF with reduced left ventricular Ejection Fraction (HFrEF) (Sánchez-Torrijos et al., 2007). Causes of anemia in HF patients are complex and multifactorial. HF and anemia share multiple risk factors. HF can cause anemia by different pathophysiological mechanisms (Tang et al., 2008). HF patients usually have inadequate levels of Erythropoietin (EPO), particularly in patients with renal dysfunction. Moreover, HF patients often have iron deficiency and bone marrow unresponsiveness accompanying by excessive elevation of EPO level, resulting in unfavorable outcomes (Lipsic et al., 2004; Beverborg et al., 2016). Activation of the renin angiotensin aldosterone system leads to fluid and salt retention and volume overload resulting in pseudo anemia (Adlbrecht et al., 2008). Medication prescribed in HF such as Angiotensin Converting Enzyme Inhibitors (ACEIs) and carvedilol can result in iatrogenic anemia (Beverborg et al., 2018). In most cases, the origin of anemia in HF patients is uncertain and anemia of chronic illness is diagnosed (Komajda et al., 2006).

The presence of anemia is associated with more symptoms and impaired life functional capacity, elevated levels of serum B-type natriuretic peptide, and increased New York heart association class (Iftekhar et al., 2018; Van Veldhuisen et al., 2011). Recently, the studies of anemia among HF patients have been increased because of its high prevalence and significant prognostic implications (Sánchez-Torrijos et al., 2007). Anemia has been identified as a significant prognostic factor of morbidity and mortality for HF patients (Kaldara-Papatheodorou et al., 2010). Independently on the mechanism, the presence of anemia in patients with HF leads to a bad prognosis (Sánchez-Torrijos et al., 2007). Rehospitalization is often associated with constitute an excessive healthcare burden and increased mortality rate (Emami et al., 2016). Some intervention studies observed a beneficial effect of correction of anemia on decreasing HF related rehospitalization. However, the information regarding the prevalence of anemia among patients with HFis still limited (Sánchez-Torrijos et al., 2007). This study aimed to determine the prevalence of anemia among HFrEF patients in Madinah Cardiac Center (MCC).

## 2. METHODS

**Study Design, Study Setting, and Study Period**

This is a cross sectional study conducted at MCC. The study included HF patients registered in the Health Management Information Systems (HMIS) database during the period from March 2011 to January 2019.

**Study Population**

The electronic medical records from HMIS were reviewed. A total of 2683 patients were identified to have a documented clinical diagnosis of HF. Patients with HFrEF were included in the study. HFrEF was defined when Ejection Fraction (EF) ≤ 40% as determined by echocardiography. Patients with EF >40% were excluded. Those with coeliac disease, chronic liver disease, chronic GI bleeding related to any underlying cause, autoimmune connective tissue diseases, and pregnant women were excluded as well. Of the remaining 1656 patients, we excluded 49 patients with missing data, yielding 1607 patients for analysis (figure 1).

**Measurements**

Anemia was defined as a baseline Hemoglobin (Hb) <13 g/dl and <12 g/dl in males and females, respectively. According to the World Health Organization (WHO) criteria of anemia, mild anemia was defined when Hb level is 12.9-11 g/dl in males and 11.9-11 g/dl in females; moderate anemia when Hb level is 10.9-8 g/ dl and severe anemia when Hb level is<8 g/dl (Alraheili et al., 2020). Glomerular Filtration Rate (GFR) was estimated depending on the equation made by the Chronic Kidney Disease (CKD) epidemiology collaboration as the following: $eGFR = 141 \times \min(S_{cr} / \kappa, 1)^{\alpha} \times \max(S_{cr} / \kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black] where: $S_{cr}$ is serum creatinine in mg/dL, $\kappa$ is 0.7 for females and 0.9 for males, $\alpha$ is -0.329 for females and -0.411 for males (Stevens et al., 2011). All patients were divided according to the current national kidney foundation kidney disease outcomes quality initiative recommendations into five renal function categories with eGFR (mL/min/ 1.73 m2): Stage I (eGFR ≥90, normal function), Stage II (eGFR 60–89, mild dysfunction), Stage III (eGFR 30–59, moderate dysfunction), Stage IV (eGFR 15–29, severe dysfunction) and Stage V (eGFR <15, end stage renal disease) (Löfman et al., 2016).

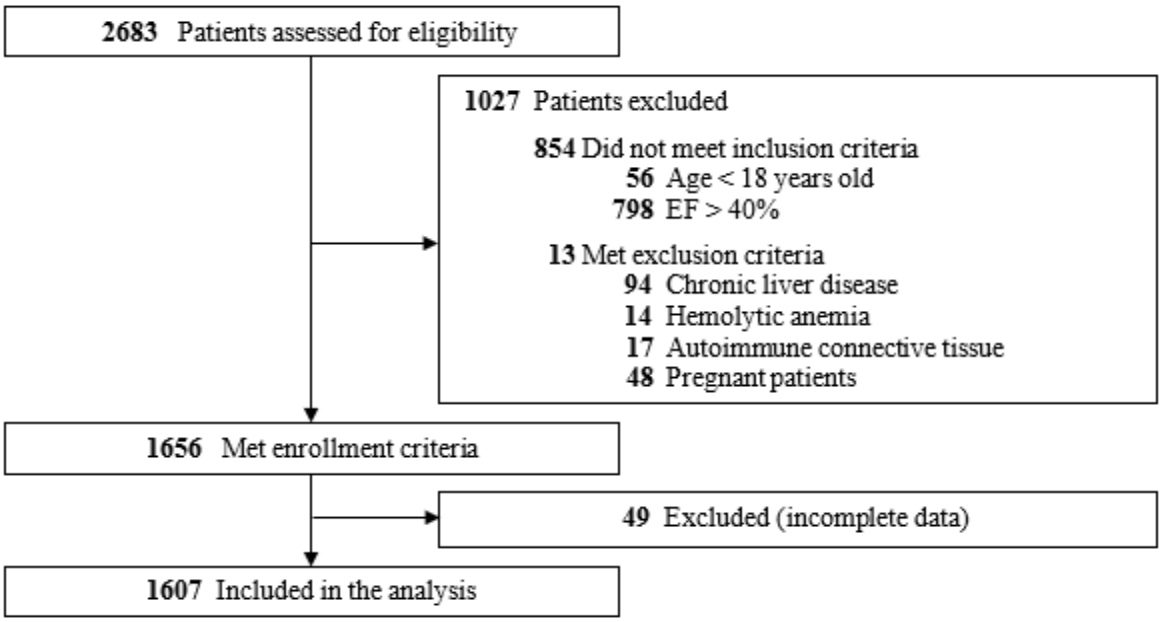


**Figure 1** Flow chart of the study population

**Ethical Approval**

The research ethics committee of Madinah cardiac center approved this study protocol (approval number: IRB00010413). All study parts were conforming to the declaration of Helsinki Ethical Principles for medical research involving human subjects as revised in 1975.

**Statistical Analysis**

Data were analyzed using the Statistical Package for Social Science software version 23. Continuous data were presented as mean ± Standard Deviation (SD) as they were normally distributed when tested by the Shapiro-Wilk test, while the categorical data were presented as frequencies and percentages. Baseline demographic and clinical variables were compared between two groups by using the Pearson chi-squared test for categorical variables. To assess whether the continuous variables differed among the study two groups, we used the independent sample t-test. P-value was considered significant if it is ≤ 0.05.

## 3. RESULTS

Out of 1607 patients included in the analysis, 1078 (67.1%) were males, 127 (7.9%) had a history of Myocardial Infarction (MI), 356 (22.2%) had valvular heart disease, 597 (37.1%) had Coronary Artery Diseases (CADs), 146 (9.1%) underwent Percutaneous Coronary Interventions (PCI) and 95 (5.9%) underwent Coronary Artery Bypass Grafting (CABG). 825 (51.3%) were hypertensive, 835 (52.0%) were anemic, 289 (18.0%) were smokers, and 629 (39.1%) had stage III CKD. 1418 (88.2%) were on angiotensin converting enzyme inhibitors and 994 (61.9%) were on aspirin (Table 1).

**Table 1** Sociodemographic and clinical characteristics of the study population

| Variables | Number (n=1607) | (%) |
|---|---|---|
| Gender | | |
| Female | 529 | (32.9) |
| Male | 1078 | (67.1) |
| Cardiac History | | |
| Myocardial Infarction | 127 | (7.9) |
| Atrial Fibrillation | 215 | (13.4) |
| Arrhythmias | 98 | (6.1) |
| Valvular Heart Disease | 356 | (22.2) |

| | | |
|---|---|---|
| Coronary Artery Diseases | 597 | (37.1) |
| Percutaneous Coronary Interventions | 146 | (9.1) |
| Coronary Artery Bypass Grafting | 95 | (5.9) |
| Cardiac Device | 98 | (6.1) |
| Cardiac Arrest | 52 | (3.2) |
| Noncardiac History | | |
| Anemia | 902 | (56.1) |
| Current Smoker | 289 | (18.0) |
| Hypertension | 825 | (51.3) |
| Diabetes Mellitus | 835 | (52.0) |
| Stroke | 103 | (6.4) |
| Chronic Kidney Disease Stages | | |
| Stage 1 (eGFR > 90 mL/min) | 242 | (15.1) |
| Stage 2 (eGFR 60-89 mL/min) | 501 | (31.2) |
| Stage 3 (eGFR 30-59 mL/min) | 629 | (39.1) |
| Stage 4 (eGFR 15-29 mL/min) | 182 | (11.3) |
| ESRD (eGFR < 15 mL/min) | 53 | (3.3) |
| Medications | | |
| Aspirin | 994 | (61.9) |
| Clopidogrel | 229 | (14.3) |
| Angiotensin Converting Enzyme Inhibitors | 1418 | (88.2) |
| Beta Blockers | 272 | (16.9) |
| Digoxin | 565 | (35.2) |
| Anticoagulants | 99 | (6.2) |
| Diuretics | 530 | (33.0) |
| Statin | 591 | (36.8) |
| Ferrous sulfate | 631 | (39.3) |
| eGFR; estimated Glomerular Filtration Rate, ESRD; End-Stage Renal Disease | | |

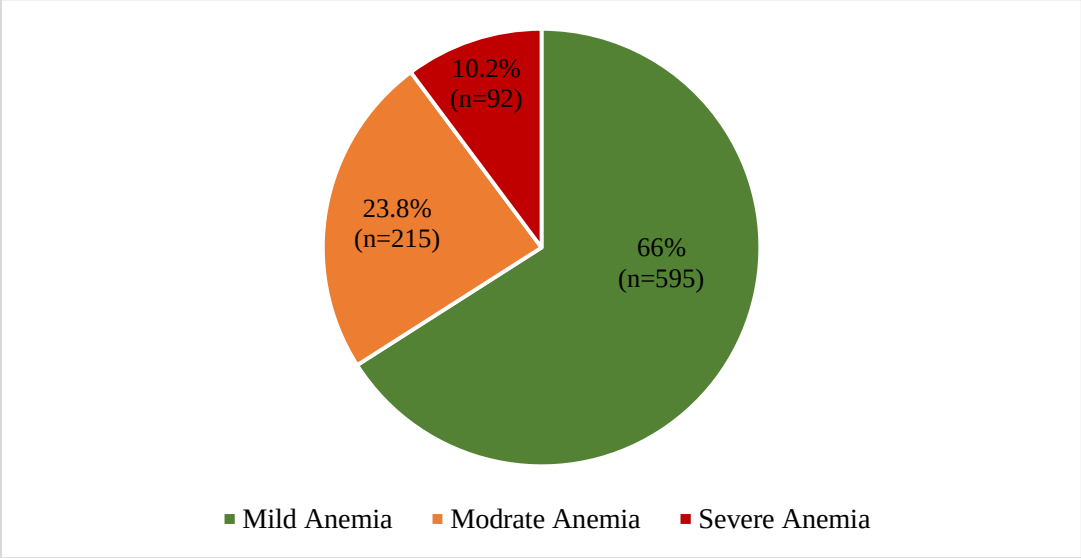


**Figure 2** Prevalence of anemia according to WHO criteria of anemia

About 56.1% of HFrEF patients were anemic. According to the WHO criteria of anemia, about 595 (66.0%) of the patients had mild anemia, 215 (23.8%) had moderate anemia, and 92 (10.2%) had severe anemia (Figure 2). Anemic patients were significantly older. Mean ± SD of age was 68±11 years in anemicpatients compared to 63±11 years in non-anemic patients (p<0.001). Anemic patients were significantly females (p<0.001), Hypertensive (HTN) (p<0.001), had Diabetes Mellitus (DM) (p<0.001), stroke (p=0.012), CKD (p=0.020), underwent PCI (p<0.001), or CABG (p=0.013). There was no significant association in the history of MI, CAD, atrial fibrillation, arrhythmias, or smoking.

Medical therapy using differed between anemic and non-anemic patients. Using aspirin, digoxin, diuretics, statins, and ferrous sulfate was markedly lower in anemic patients (p<0.000). Also, clopidogrel using was higher in anemic patients compared to non-anemic patients. Clopidogrel was used in 161 (70.3%) and 68 (29.7%) in anemic and non-anemic patients, respectively (p<0.001). Detailed clinical characteristics are shown in (Table 2).

**Table 2** Baseline clinical characteristic stratified by presence or absences of anemia (n=1607)

| Clinical Variable | Anemic (n=902) (56.1%) | | Non anemic (n=705) (43.9%) | | OR (95% CI) | | P value |
|---|---|---|---|---|---|---|---|
| | Number (%) / Mean ± SD | | | | | | |
| Age | 68±11 | | 63±17 | | | | <0.001 |
| Gender | | | | | | | |
| Female | 335 | (63.3) | 194 | (36.7) | 1.556 | (1.257-1.927) | <0.001 |
| Male | 567 | (52.6) | 511 | (47.4) | | | |
| Cardiac History | | | | | | | |
| Myocardial Infarction | 70 | (55.1) | 57 | (44.9) | 0956 | (0.664-1.377) | 0.811 |
| Atrial Fibrillation | 89 | (41.4) | 126 | (58.6) | 0.503 | (0.376-0.673) | 0.054 |
| Arrhythmias | 40 | (40.8) | 58 | (59.2) | 0.518 | (0.342-0.784) | 0.072 |
| Valvular Heart Disease | 158 | (44.4) | 198 | (55.6) | 0.544 | (0.429-0.690) | 0.123 |
| Coronary Artery Diseases | 395 | (66.2) | 202 | (33.8) | 1.940 | (1.573-2.393) | <0.001 |
| PCI | 102 | 69.9) | 44 | (30.1) | 1.915 | (1.325-2.768) | <0.001 |
| CABG | 65 | (68.4) | 30 | (31.6) | 1.747 | (1.120-2.725) | 0.013 |
| Cardiac Device | 45 | (45.9) | 53 | (54.1) | 0.646 | (0.429-0.973) | 0.036 |
| Cardiac Arrest | 31 | (59.6) | 21 | (40.4) | 1.159 | (0.660-2.035) | 0.607 |
| Noncardiac History | | | | | | | |
| Current Smoker | 149 | (51.6) | 140 | (48.4) | 0.799 | (0.619-1.031) | 0.084 |
| Diabetes Mellitus | 525 | (62.9) | 310 | (37.1) | 1.774 | (1.454-2.165) | <0.001 |
| Hypertension | 606 | (73.5) | 219 | (26.5) | 4.543 | (3.677-5.614) | <0.001 |
| Stroke | 70 | (68.0) | 33 | (32.0) | 1.713 | (1.119-2.624) | 0.012 |
| Chronic Kidney Diseases Stages | | | | | | | |
| Stage 1 (eGFR > 90 mL/min) | 148 | (61.2) | 94 | (38.8) | | | 0.020 |
| Stage 2 (eGFR 60-89 mL/min) | 288 | (57.5) | 213 | (42.5) | | | |
| Stage 3 (eGFR 30-59 mL/min) | 356 | (56.6) | 273 | (43.4) | | | |
| Stage 4 (eGFR 15-29 mL/min) | 83 | (45.6) | 99 | (54.4) | | | |
| ESRD (eGFR < 15 mL/min) | 27 | (50.9) | 26 | (49.1) | | | |
| Medications | | | | | | | |
| Aspirin | 527 | (53.0) | 467 | (47.0) | 0.716 | (0.584-0.879) | <0.001 |
| Clopidogrel | 161 | (70.3) | 68 | (29.7) | 2.035 | (1.504-2.755) | <0.001 |
| ACEIs | 805 | (56.8) | 613 | (43.2) | 1.246 | (0.919-1.688) | 0.156 |
| Beta Blockers | 156 | (57.4) | 116 | (42.6) | 1.062 | (0.816-1.382) | 0.655 |
| Digoxin | 257 | (45.5) | 308 | (54.5) | 0.514 | (0.417-0.632) | <0.001 |
| Anticoagulants | 46 | (46.5) | 53 | (53.5) | 0.661 | (0.440-0.994) | 0.045 |
| Diuretics | 230 | (43.4) | 300 | (56.6) | 0.462 | (0.374-0.571) | <0.001 |
| Statin | 285 | (48.2) | 306 | (51.8) | 0.602 | (0.491-0.739) | <0.001 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ferrous sulfate | 310 | (49.1) | 321 | (50.9) | 0.626 | (0.512-0.767) | <0.001 |
| Hospitalization History | | | | | | | |
| Number of hospitalizations | 1.63 ± 1.193 | | 1.79 ± 1.660 | | | | 0.098 |
| Total length stays | 11.86 ± 20.415 | | 13.61 ± 28.062 | | | | 0.103 |
| Death | 46 | (22.8) | 156 | (77.2) | 0.189 | (0.134-0.267) | <0.001 |
| PCI; Percutaneous Coronary Interventions, CABG; Coronary Artery Bypass Grafting, eGFR; estimated Glomerular Filtration Rate, ESRD; End-Stage Renal Disease ACEI; Angiotensin Converting Enzyme Inhibitors | | | | | | | |

The mean Hb level was 10.22±2.18 g/dl in diabetic patients compared to 13.10±2.21 g/dl in nondiabetic patients (p <0.001). Anemic patients exhibited significantly worsening kidney function tests. Mean eGFR was 56.78±24.87 mL/min in anemic patients compared to60.09±33.49 mL/min in non-anemic patients (p <0.001). Higher levels of creatinine and blood urea nitrogen were also observed in anemic patients. Detailed laboratory data are shown in (Table 3).

**Table 3** Continuous characteristics of the study population stratified by presence or absences of anemia

| Variables | Anemic (n=902) (56.1%) | Non anemic (n=705) (43.9%) | P value |
|---|---|---|---|
| | Mean ± SD | | |
| Complete Blood Count | | | |
| Hemoglobin (g/dl) | 10.22±2.18 | 13.10±2.21 | <0.001 |
| HCT% | 37.19±6.19 | 39.89±6.10 | <0.001 |
| RBC $\times 10^{12}/\mu L$ | 4.36±0.81 | 4.60±0.75 | <0.001 |
| MCV fL | 85.96±7.01 | 87.10±8.23 | 0.170 |
| WBC $\times 10^{3}/\mu L$ | 10.02±5.60 | 9.43±6.00 | 0.238 |
| Platelet Count $\times 10^{3}/\mu L$ | 266.87±103.34 | 257.73±107.64 | 0.132 |
| Kidney Function Tests | | | |
| eGFR (mL/min) | 56.78±24.87 | 60.09±33.49 | 0.081 |
| Creatinine (μmol/L) | 145.38±93.67 | 130.12±64.30 | 0.002 |
| BUN (mmol/L) | 11.02±8.19 | 9.92±6.59 | 0.005 |
| Sodium (mEq/L) | 135.72±6.17 | 137.61±8.87 | <0.001 |
| Troponin (mcg/L) | 3.33±9.80 | 4.36±11.03 | 0.110 |
| Lipid Profile | | | |
| LDL (mmol/L) | 2.23±1.02 | 2.30±1.09 | 0.036 |
| HDL (mmol/L) | 0.96±0.47 | 0.96±0.39 | 0.707 |
| Triglycerides (mmol/L) | 1.22±0.67 | 1.25±0.71 | 0.691 |
| Total cholesterol (mmol/L) | 3.74±1.25 | 3.84±1.33 | 0.121 |
| HCT%; Hematocrit, RBC; Red Blood Cells, MCV; Mean Corpuscular Volume, WBC; White Blood Cells, eGFR; estimated Glomerular Filtration Rate, BUN; Blood Urea Nitrogen, LDL; Low Density Lipoprotein, HDL; High Density Lipoprotein. | | | |

## 4. DISCUSSION

In the current study, we demonstrated the prevalence of anemia among HFrEF patients at MCC. We found that about 56% of HFrEF patients were anemic. The prevalence of anemia was 63% among female patients compared to 52% among male patients. According to the WHO criteria, 66% of patients had mild anemia, 23.8% had moderate anemia, and 10.2% had severe anemia. A retrospective study carried out in Riyadh enrolled 1256 patients with HFrEFwas found that about 27% of the patients were anemic (Odeh et al., 2012). The study undertaken by Urrutia *et al., (2004)* showed that the prevalence of anemia was 30%. Grigorian *et al., (2005)* found that the prevalence of anemia was 44% in a series of patients admitted to hospital for HF in whom the WHO definition of anemia was applied. However, Villacorta *et al., (2010)* observed that about 20% of HF patients presented with anemia.

Recent studies found that the prevalence of Iron Deficiency Anemia (IDA) among HF patients is high. Co-morbidities such as anemia, CKD, DM, HTN, and chronic obstructive pulmonary disease play a crucial prognostic role in HF. IDA is present in approximately 50% of patients with HF. Sandhu et al., (2010) found that the prevalence of IDA reached up to 74%, with absolute IDA being the most common subtype. In accordance with the previous study results, Cohen-Solal *et al*., (2007) reported rates of IDA of about 70% in a cohort of 832 patients with HF, with absolute IDA being the most prevalent form.

The prevalence among HF patients varies from study to study. It may be explained by the different diagnostic criteria. In a retrospective study with a hospital population, it was found that 45% of HF patients had anemia, as a cut of 12 g/dL was used independently on gender (Silva et al., 2007). In another study, in which the cut value was Hb <13 g/dL for females and <12 g/dL for males, the prevalence of anemia reached 63% (Sales et al., 2004). Iftekhar *et al., (2018)* showed that the prevalence of anemia was 29% in patients presenting with congestive HF in which 7% of patients had hospital mortality, 81% of patients were rehospitalized while 12% of patients died in 3 months period. Anemia can lead to exacerbating HF symptoms, chronic volume overload, increased cardiac workload, and possible further deterioration of heart function and prognosis (Beverborg et al., 2018). Collectively, all these pathologic changes possibly responsible for the higher number of rehospitalization in anemic HFrEF patients as reported in HF-ACTION study and have been observed in other studies (O'Connor et al., 2009). Kajimoto *et al., (2006)* reported that anemia correction in patients with HFrEF reduces HF related hospitalizations. The Study of anemia in HF trial demonstrated that even an increase of only 1.0 g/dL or more in Hb resulted in the reduction of HF related hospitalization (Beverborg et al., 2018).

In a univariate analysis, anemia was associated with the female gender, HTN, DM, and advanced CKD stage. Though the objective of this study was not to establish the mechanisms involved in anemia genesis, these data suggest that the presence of HTN, DM, and advanced CKD stage plays an important role as anemia cause in patients with HF.

## 5. CONCLUSION

About 56.1% of HFrEF patients were anemic. According to the WHO criteria, 66.0% of them had mild anemia, 23.8% had moderate anemia, and 10.2% had severe anemia. Anemia was associated with the female gender. The presence of HTN, DM, and advanced CKD stage plays an important role as anemia cause in patients with HF.

**Informed consent**

Oral informed consent was obtained from all individual participants included in thestudy.

**Ethical approval**

The research ethics committee of Madinah cardiac center approved this study protocol (approval number: IRB00010413).

**Author's contributions**

All authors contributed to the research and/or preparation of the manuscript.

**Conflict of interest**

The authors have no conflict of interest to declare.

**Funding**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Data and materials availability**

All data associated with this study are present in the paper.

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