Transthoracic echocardiographic changes in patient with Iron deficiency anemia

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سم الله الرحمن الرحيم

وَأَنَّ الْفَضْلَ بِيَدِ اللَّهِ يُؤْتِيهِ مَن يَشَاءُ ۚ وَاللَّهُ ذُو الْفَضْلِ الْعَظِيمِ

صدق الله العظيم

سوره الحديد, الايه 29

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Dedication

To all people who had been there for me...

My family, especially my parents and my best friend saraa salah

Abbreviations

Hb	Hemoglobin
PCV	Packed cell volum
MCV	MEAN CORPUSCULAR VOLUME
LV	Left ventricular
LVH	Left ventricular hypertrophy
$LVID_D$	Left ventricular internal diameter at end diastole
$LVID_S$	Left ventricular internal diameter at end systole
SWT_D	Septal wall thickness at end diastole
PWT_D	Posterior wall thickness at end diastole
EF	Ejection fraction
LVMass	Left ventricular mass
IDA	iron deficiency anemia

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Abstract

Back ground

Anemia is defined as a reduction in the number of circulating red blood cells, the hemoglobin concentration, or the volume of packed red cells (hematocrit) in the blood. In the laboratory, anemia is identified when a patient's hemoglobin (Hb)/hematocrit (Hct) values fall below the lower end of a normal range of values for age- and sex-matched subjects.

Aim: to assess Echocardiographic changes in relation to microcytic anemia and in relation to severity of anemia.

Patients and methods

cross sectional study was Performed during a period between October 2018 to March 2019 at AL-IMMAMIAN ALKADYMIAN MEDICAL CITY , BAGHDAD, IRAQ. included randomly selected 30 participants who were diagnosed to have iron deficiency anemia based on CBC (HB ,MCV and PCV) and serum ferritin then followed by echo study (include $LVID_D$, $LVID_s$, PWT_D , SWT_D , EF and ventricular mass) , Patient were grouped according to HB level in to mild , moderate and sever .

Conclusion

- Low hemoglobin level was associated with change in cardiac chambers ($LVID_S$), increase septal and posterior wall thickness and increased LV mass in the subjects without cardiovascular risk factors or overt cardiovascular disease.
- Echocardiographic feature of anemia may preceded changes in EF.
- severe anemia is more correlated with SWT_D .

(1)Introduction

(2-1) Anemia

(1-1-1) Definition:

According to World Health Organization criteria, anemia is defined as blood hemoglobin (Hb) concentration <130 g/L (<13 g/dL) or hematocrit (Hct) <39% in adult males; Hb <120 g/L (<12 g/dL) or Hct <37% in adult female . [1] Severity of anemia can be classified according to hemoglobin level as shown in table (1).

Table 1 : hemoglobin levels to diagnose anemia at sea level (g/d).[2]

Population	Non-anaemia	Mild Anaemia	Moderate Anaemia	sever Anaemia
Non pregnant woman 15 year and above)	120 or higher	110-119	80-109	Lower than 80
pregnant woman	110 or higher	100-109	70-99	Lower than70
Men (15 year and above)	130 or higher	110-129	80-109	Lower than80

(1-1-2) Etiology :

1. DECREASE OR INEFFECTIVE MARROW PRODUCTION THIS INCLUDE :

a. nutrient deficiency ; iron , vitamin B12 ,folate
b. hypoplasia for example aplastic anemia
c. invation by malignant cells for example lymphoma
d. anemia of chronic disease : this include anemia of chronic renal failure, hypothyroidism, hyperparathyroidism ,crons disease and diabetes mellitus, also joint disease : SLE, rheumatoid arthritis .[3]

2. PERIPHERAL CAUSES :

a. blood loss

Blood loss from any cause may result in anemia, which may be acute, chronic, or acute on chronic. Chronic blood loss anemia is most often the result of chronic gastrointestinal bleeding such as Loosing of blood from bleeding

hemorrhoid, an ulcer, cancer and regular use of some over-the-counter pain relievers, especially aspirin, malaria, hook infestation or due heavy menstrual bleeding. Acute blood loss anemia is associated with acute or subacute GI bleeding, trauma, or surgery.[5] [6]

b. hemolysis

CONGENITAL HAEMOLYSIS

Inherited red cell defects of structure or metabolism may result in a chronic hemolytic state. The principal pathologies are red cell membrane defects (hereditary spherocytosis or elliptocytosis), glucose-6-phosphate dehydrogenase (G6PD) deficiency and the hemoglobinopathies such as Thalassemia and sicle cell anemia.

ACQUIRED HAEMOLYTIC ANAEMIA

A. AUTOIMMUNE HAEMOLYTIC ANAEMIA

This results from increased red cell destruction due to red cell autoantibodies. The antibodies may be IgG or M, or more rarely IGE or IGA.

B. ***NON-IMMUNE HAEMOLYTIC ANAEMIA*****:**

1. Physical trauma.
2. Infection.
3. Chemicals and drugs .[3] [4]

Iron deficiency is the commonest nutritional deficiency world wide and most common type anemia , affecting more than one-third of the population .iron is an important building block for hemoglobin , the part of red blood cells that carry in most developed countries , iron deficiency is the main cause of of anemia during pregnancy.in developing countries in addition to poor intake of heme iron from animal sources ,hookworm infection is prevalent in many tropical areas. Hookworm casue upper gastrointestinal blood loss, which contributed directly to iron deficiency anemia . breast feeding woman ,malnutrition , heavy menstrual bleeding, malabsorption disease like celiac ,frequent blood donation ,dialysis ,gastrointestinal loss due to polyp , ulcer cancer ,and blood loss may consider as cause of iron deficiency anemia .

(1-1-3) cardiac pathophysiological changes in relation to anemia

The amount of oxygen delivered to an organ depends on three factors: blood flow and its distribution; the oxygen-carrying capacity of the blood, i.e. haemoglobin concentration; and oxygen extraction. Non-haemodynamic and haemodynamic mechanisms operate to compensate for anaemia. Non-haemodynamic mechanisms include increased erythropoietin production to stimulate erythropoiesis, and increased oxygen extraction (displacement of the haemoglobin–oxygen dissociation curve). This decreased affinity of oxygen for haemoglobin is mediated by increased 2,3-diphosphoglycerate concentrations.

Increased cardiac output is the main haemodynamic factor, mediated by lower afterload, increased preload, and positive inotropic and chronotropic effects. Decreased afterload is due to vasodilatation and reduced vascular resistance as a consequence of lower blood viscosity, hypoxia-induced vasodilatation, and enhanced nitric oxide activity.[7]

Based on the physiological significance of oxygen transported to myocardial tissue, anemia may be a cause of more severe cardiovascular diseases or a sign of other severe diseases that occur in the body. The physiologic response to anemia is a compensatory increase in cardiac output in order to maintain adequate oxygen delivery · It has reported that myocardial contractility would decrease when hemoglobin was below 7 g/dL.[8]

(1-1-4) CLASSIFICATION:

according toMEAN CORPUSCULAR VOLUME (MCV):
the average volume of erythrocytes expressed in cubic micrometers or femto-liter per red cell measured directly during using an automate hemoglobin analysis , normal value (78-98 fL) .

1. Low MCV (microcytic anemia)

-Iron deficiency anemia

-thalassemia
-sideroblastic anemia (rare)
-anemia of chronic disease

2. Normal MCV (normocytic anemia)

-acute blood loss
-anemia of chronic disease (eg: renal diseases)
-bone marrow failure
-hypothyroidisim (or may increase)

3. High MCV

-B12 or folate deficiency.
-alcohol excess or liver disease.
-reticulocytosis .
-myeloid dysplastic syndrome. [8]

(1-1-5) Symptoms and signs

The general symptoms and signs of anemia are:

1. Nonspecific symptoms:

Tiredness, Lightheadedness, Breathlessness, Ankle swelling and Worsening of any previous coexisting disease such as angina

2. Nonspecific signs:

Mucous membrane pallor, Tachypnea, Raised jugular venous pressure, Flow murmurs, Ankle edema, Postural hypotension and Tachycardia .[9]

(1-2) echocardiograph

(1-2-1) definition

Echocardiography is none invasive tool uses high-frequency sound waves (ultrasound) to penetrate the body, reflect from relevant structures, and generate an image. [9]

Any provoked alteration involve either the anatomy or the functionality of heart can easily be detected and imaged by echocardiography which represents a real time ,quick, reproducible ,cheap , and wide spread method. [10]

(1-2-2) indication

Used for evaluation of cardiac structure and function

i) anatomical approach ,which include measurement of heart cavities

ii) Functional approach, which include assessment indices of function [10]

(1-2-3) parameter

Regarding left ventricular echocardiograph, 2D or M-mode measurements should be taken at end diastole and perpendicularly to the axis in left parasternal view. Short axis data overestimate Lv dimension, as shown in figure 1.

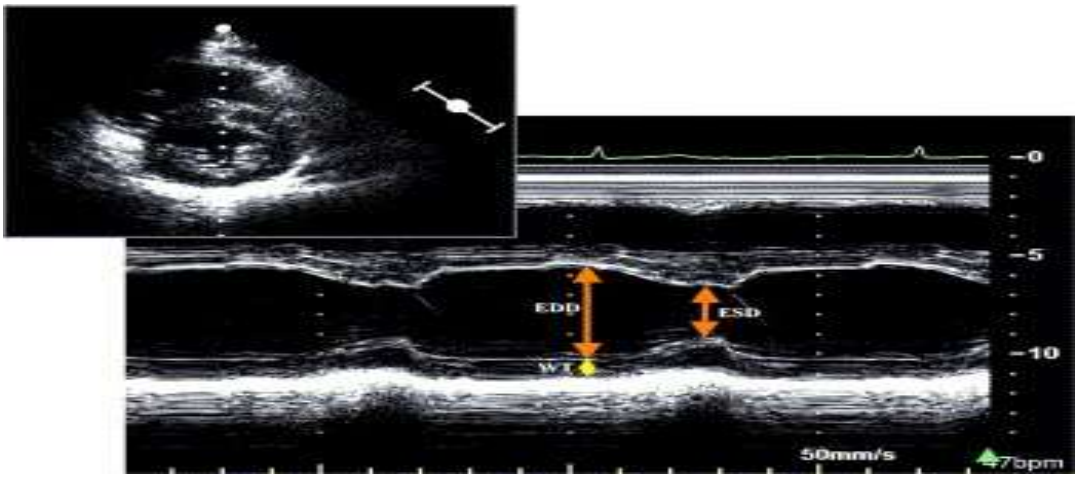

Figure 1 Measurement of left ventricular end-diastolic diameter (*EDD*) and end-systolic diameter (*ESD*) from M-mode, guided by parasternal short-axis image (*upper left*) to optimize medial-lateral beam orientation. [11]

3D echocardiography provides more accurate data and is well correlated with MRI. LVH is Considered when Septal and posterior wall thickness is above normal .Normal left ventricular parameters are shown in table 2 : [11]

Table 2: normal range for Echocardiographic parameter in male and femal .(cm)

parameter	Male	Female
$LVID_d$ (cm)	4.2-5.9	3.9-5.3
LVIDs(cm)	1.2-3.0	1.2-3.0
SWT_d (cm)	0.6-1.0	0.6-0.9
PWT_d (cm)	0.6-1.0	0.6-0.9
LVIDd :Left ventricular internal diameter at end diastole , SWT_d:Septal Wall thickness at end diastole , PWT_d **:** posterior wall thickness at end diastole . [11]		

as shown in figure 2

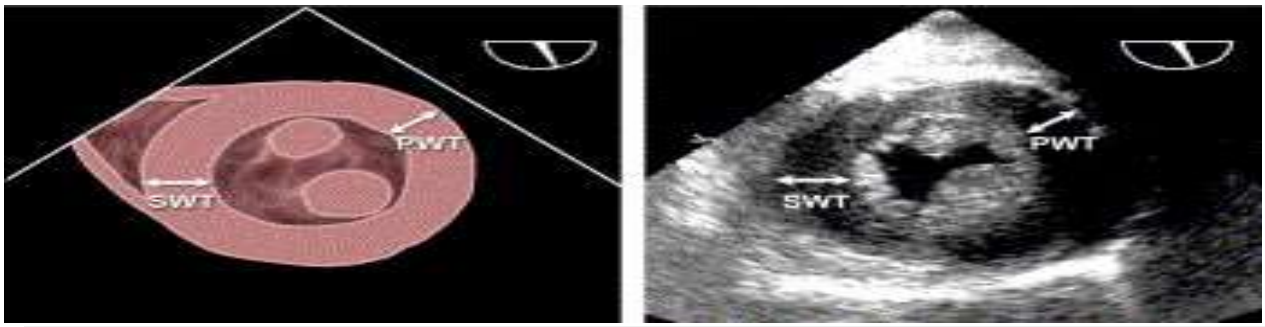

Figure 2 : Transesophageal echocardiographic measurements of wall thickness of left ventricular (LV) septal wall (*SWT*) and posterior wall (*PWT*) from transgastric short-axis view of LV, at papillary muscle level, usually best imaged at angle of approximately 0 to 30 degrees. [11]

The conventional way to assessing left ventricular systolic function with echocardiography is via left ventricular ejection fraction, determined by applying Simpson method of discs. [12]

The development of left ventricular diastolic dysfunction may precede hypertrophy and may be one of the earliest changes associated with heart disease, Notably, diastolic dysfunction may not be accompanied by symptoms and is usually a chance finding during a Doppler echocardiographic examination.[13]

Ejection fraction (EF) refers to how well the left ventricle (or right ventricle) pumps blood with each heart beat. Most times, EF refers to

the amount of blood being pumped out of the left ventricle each time it contracts. The left ventricle is the heart's main pumping chamber.

EF is expressed as a percentage. An EF that is below normal can be a sign of heart failure. If you have heart failure and EF lower-than-normal (reduced) [14].EF can help the doctor know how severe your condition is as shown in table 3 .

Table 3: refrence value and grading scale for left ventriculare (Lv) function and Ejection fraction (EF)[14] :

LV Function	LVEF (%)
Normal	≥55
Mildly reduced	45 - 54
Moderately reduced	30 - 44
Severely reduced	<30

Left ventricular mass (LVM) is a well-established measure that can independently predict adverse cardiovascular events and premature death [16]. LV Mass estimate by using linear measurements of interventricular septal thickness, left ventricular (LV) internal dimensions, and LV posterior wall thickness at end-diastole using cube formula as shown in figure 3:

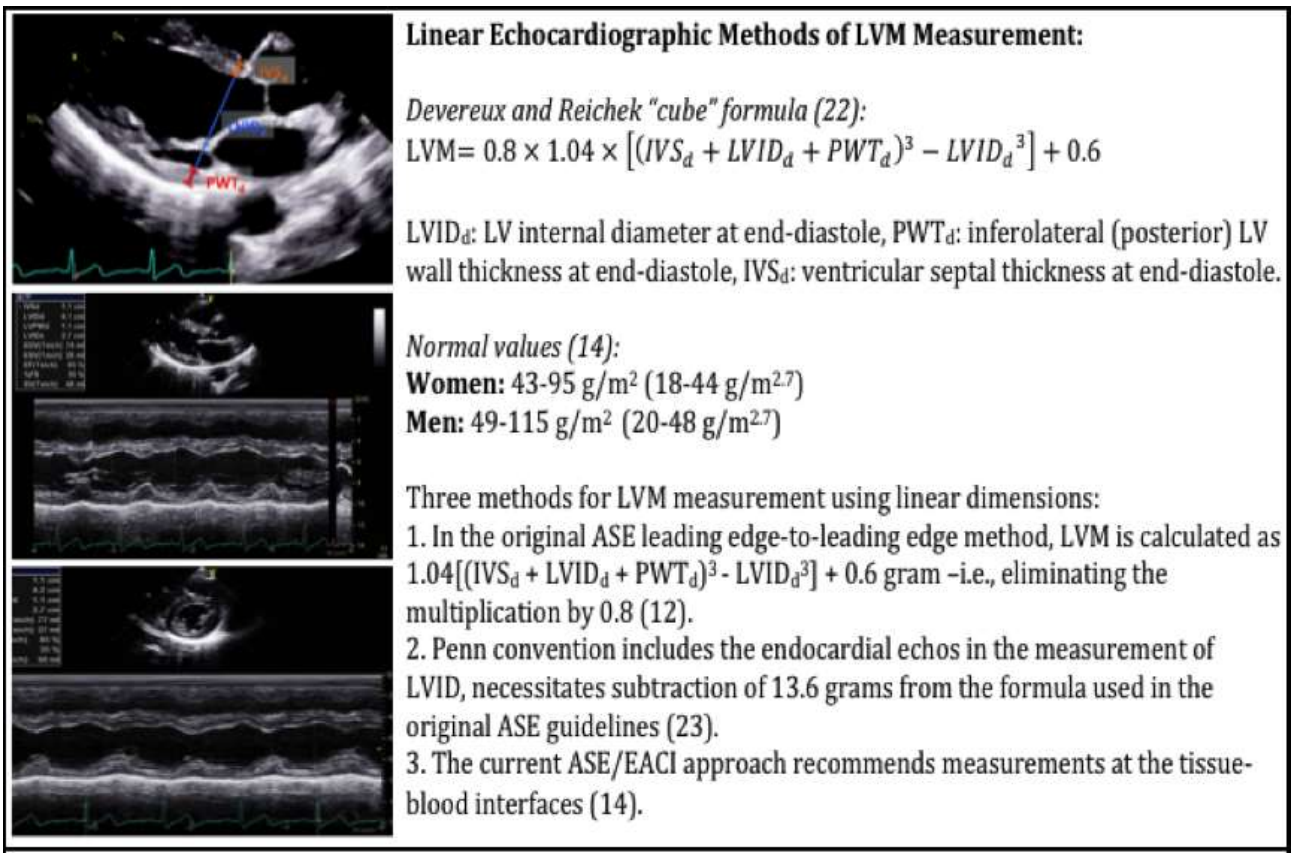

figure 3: Linear Echocardiographic Methods of LVM Measurement [17].

The values for LV mass vary according to gender, age, body size , obesity, and region of the world. Therefore, uniform reference values are difficult to define and roughly estimated as shown in table 4 . LV mass is higher in men and increases with body size.[11]

Table 4: reference range of LV Mass in male and female [15]:

	Female	Male
reference Range	43-95	49-115
Mildly Abnormal	96-108	116-131
Moderately Abnormal	109-121	132-148
Severely Abnormal	≥122	≥149

(2)Aim: to assess Echocardiographic changes in relation to microcytic anemia and in relation to severity of anemia.

(3)Patients and methods

(3-1) study design :

a cross sectional study was berformed during aperiod between October 2018 to March 2019 at AL-IMMAMIAN ALKADYMIAN MEDICAL CITY , BAGHDAD, IRAQ.

(3-2) population :

This study included randomly selected 30 participants who were diagnosed to have iron deficiency anemia base on CBC (HB ,MCV and PCV) and serum feritin. At hematological ward, out patient clinic and gynecological word. Patients were informed about the study to get approval for participation. Data of each patient were collected from the case sheet include age and gender ,CBC (HB ,MCV and PCV) and serum ferritin, then followed by echo study (include $LVID_D$, $LVID_s$, PWT_D , SWT_D , EF and ventricular mass) that performed by specialist at echo department in ALKADYMIA hospital , exclude patient have chronic heart failure ,anemia due to chronic disease and those who have hemoglobinopathy or other type of anemia .

(3-1) Statistical analysis

For each variable the frequency and percentage were analyzed using Microsoft office Excel 2010 and express as mean ± SD, percentage % and frequency .

Patient were grouped according to HB level in to mild , moderate and sever [2] .

(4) RESULTS:

The total number of patient enrolled in this study was 30.
there gender distribution consist of female predominance ,26 female(86.66%) 3 of them are pregnant as shown in figure 4.

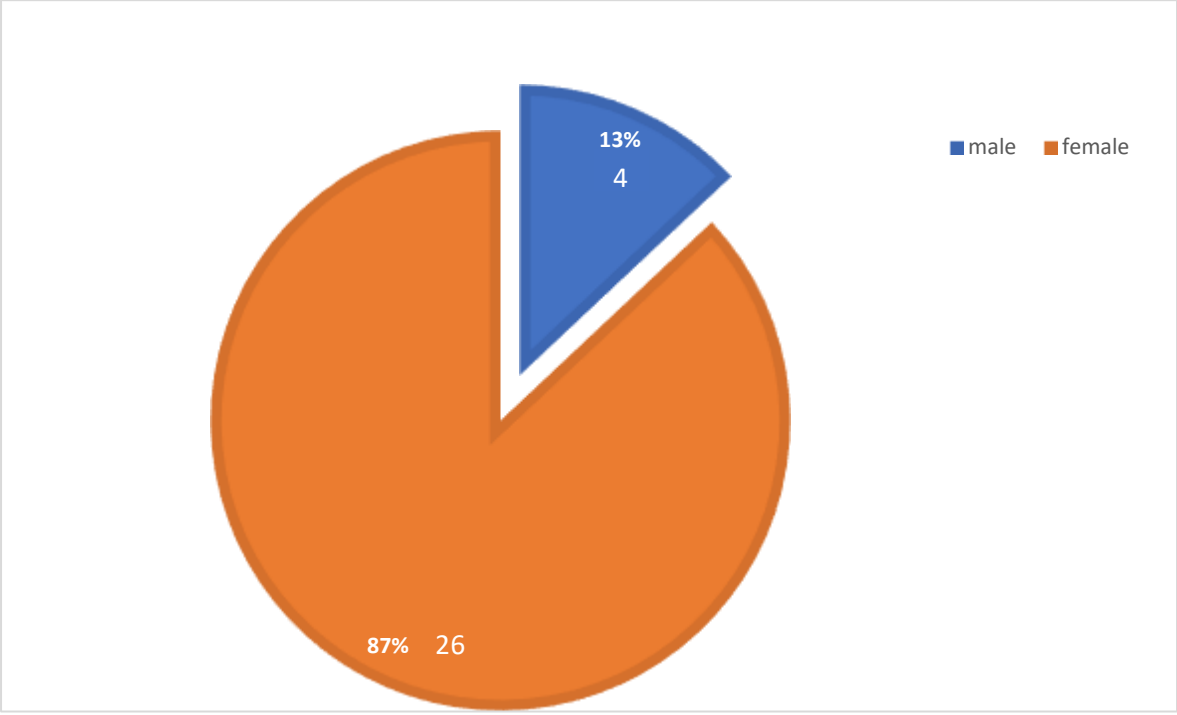

Figure 4 : distibution of gender in patient sample .

Concerning The age it is ranged from (15 -65years old) with a mean age 40.63± 14.32 year ,The study showed that all age group were similarly equivalent with slight predominant age between 45 to54 years, 8 (26.66%) as shown in figure 5:

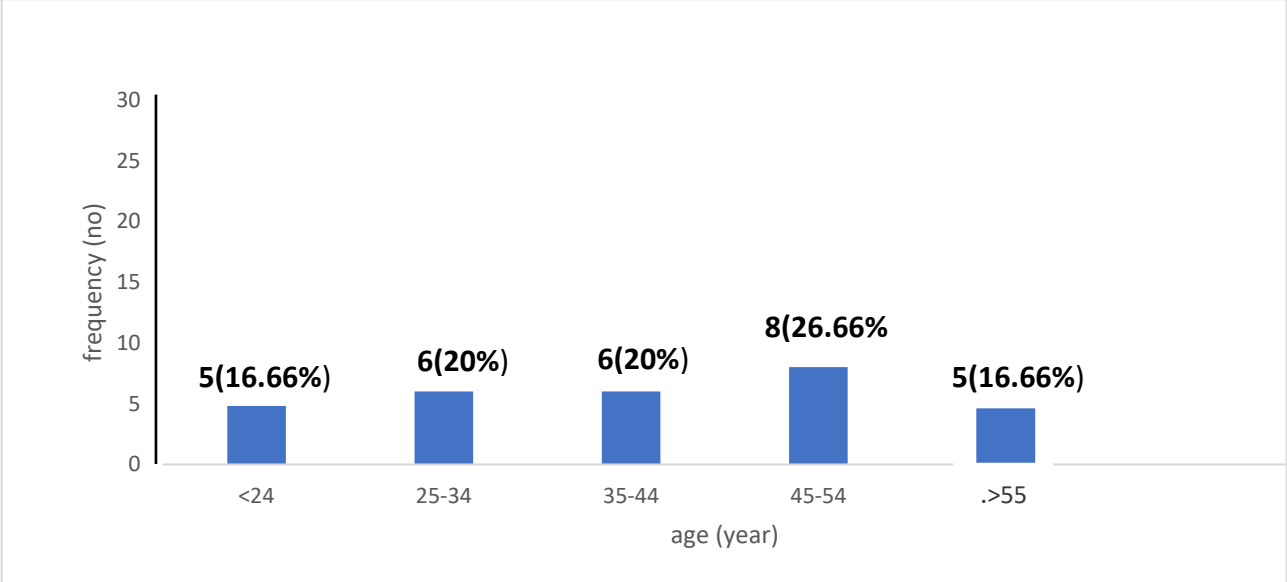

Figure 5: distubution of age in patient study.

laboratory parameter of this study revel HB range (1.7_11.1) with amean 8.39± 2.23 as shown in table 5:

Table 5: laboratory parameter of study population

parameter	Range	Mean ± SD
HB (g/dl)	(1.7-11.1)	8.39 ± 2.23
PCV (%)	(7.2-36.7)	28.26 ± 6.59
MCV(fl)	(60-78.6)	67.4 ± 6.85
Serum ferritin (ng/ml)	(3-24)	8.84 ± 5.15

Concerning severity of anemia , moderate anemia is predomenant 16 (53.33%) with mean Hb equal 9.39 ±0.82 SD as shown in figure 6:

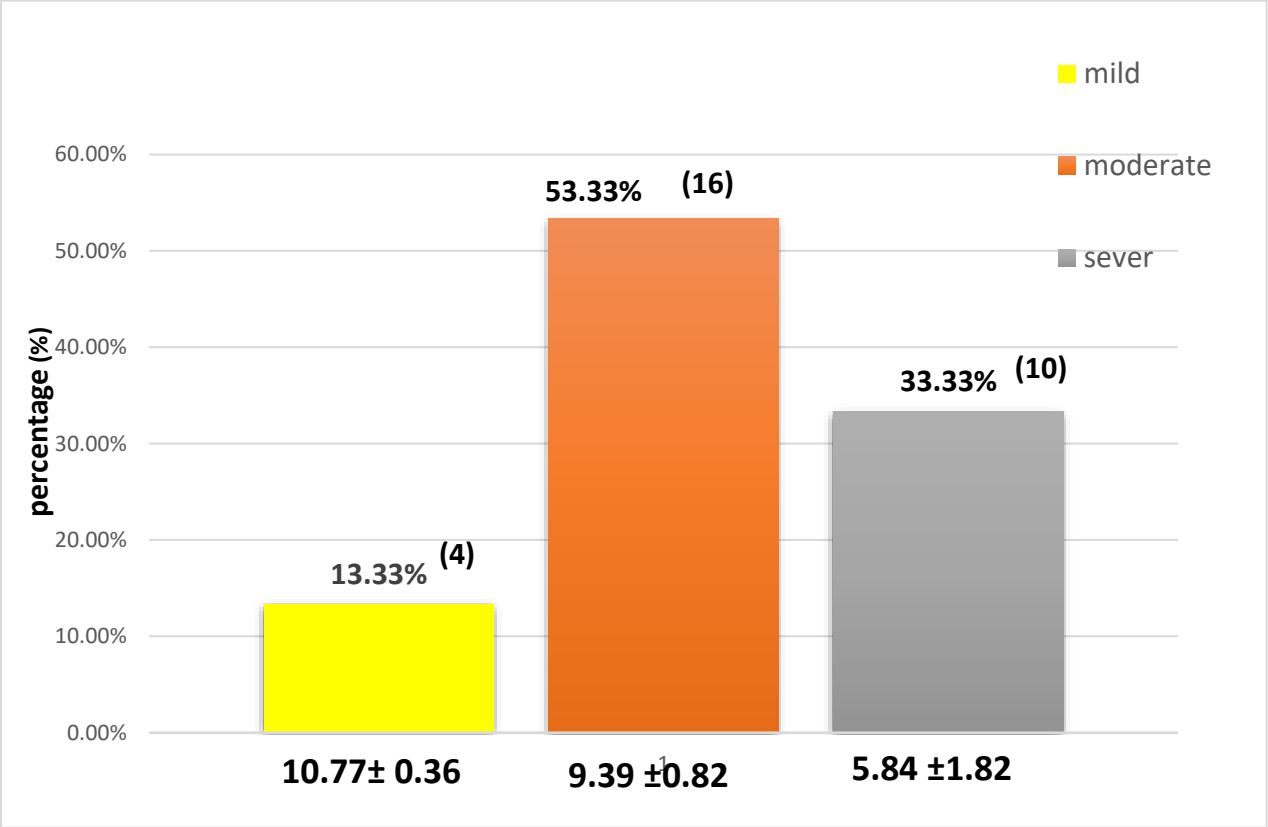

Figure 6 : severity of anemia in study population .

Regarding relationship between severity of anemia and blood parameter , shows that sever anemia have lowest PCV value (21.4 ± 6.44) , lowest MCV

value (62.83 ±7.39) and lowest serum Ferritin value (8.26 ±7.30) as shown in table 6 :

Table 6: laboratory parameter in relation to anemia severity in form of mean ± SD

parameter	mild	moderate	sever
PCV(%)	32.75 ± 0.53	31.43 ±34.42	21.4 ± 6.44
MCV(FL)	74.08 ±5.16	66.28 ± 10.92	62.83 ±7.39
Ferritin (ng/ml)	11.5 ± 0*	10.60± 7.47	8.26 ±7.30

Regarding echocardiographic parameter of study population shows that $LVID_s$ are severely elevated for both male (3.73±0.21) and female (3.73±0.5) , [15], LV MASS are severely elevated for both male (174.25±48.94)and female (177.38 ± 78.45) as shown in table 7:

Table 7 : echocardiographic parameter of study population

parameter	Male(Mean ± SD)	Normal range	female(Mean ± SD)	Normal range
$LVID_D$ (cm)	4.93±0.37	4.2-5.9	4.93±0.73	3.9-5.3
$LVID_s$ (cm)	3.73±0.21	1.2-3.0	3.37 ±0.5	1.2-3.0
PWT_D (cm)	0.95±0.1	0.6-1.0	0.89±0.2	0.6-0.9
SWT_D (cm)	0.98±0.19	0.6-1.0	1.01 ±0.23	0.6-0.9
EF (%)	62.25±7.76	55-70	64.92 ± 5.34	55-70
LV MASS (g)	174.25±48.94	49-115	177.38 ± 78.45	43-95

Regarding echocardiographic parameter in relation to anemia severity Which is shown that all anemic patient for both gender and all severity group have normal $LVID_D$,high $LVID_s$ and severly elevated LV Mass [15] .

for female :

sever anemia have highest PWT_D value (0.96 ± 0.16), both sever and moderate anemia have SWT_D value above the normal (1.07 ± 0.11) and (1.05± 0.25) respectively , sever anemia have lowest Ef value (62.2 ± 8.38) but still with in normal range as shown in table 8.

Table 8: echocardiographic parameter in relation to anemia severity in form of mean ± SD for female and male.

parameter	mild *	moderate	sever	Normal range
Female				
$LVID_D$ (cm)	4.7 ± 0.55	5.04± 0.7	4.81± 0.92	3.9-5.3
$LVID_s$ (cm)	3.2 ± 0.73	3.39± 0.44	3.43± 0.6	1.2-3.0
PWT_D (cm)	0.85 ± 0.06	0.86± 0.24	0.96± 0.16	0.6-0.9
SWT_D (cm)	0.75 ±0.17	1.05± 0.25	1.07±0.11	0.6-0.9
EF (%)	65 ±2.87	66.2± 3.3	62± 8.68	55-70
LV Mass (g)	126 ±40.36	183.06±93.04	194.57 ±49.45	43-95
male				
$LVID_D$ (cm)		5.2 ±0	4.86 ±0.40	4.2-5.9
$LVID_s$ (cm)		3.6 ±0	3.30±0.173	1.2-3.0
PWT_D (cm)		1.0 ±0	0.93 ±0.16	0.6-1.0
SWT_D (cm)		1.0 ±0	0.97 ±0.23	0.6-1.0
EF (%)		61 ±0	62.66 ±9.45	55-70
LV Mass (g)		194 ±0	167.68 ± 57.74	49-115
*Due to small sample no male patient have mild anemia				

(5) Discussion

This study showed female predominance , 26 females (87%) and those results correspond to Qiao Zhou etal. Result in there study at Hospital of Dalian Medical University; Dalian-China in 2017 , who included 83pateint , females formed71 (85.5%) females. Also correspond to In-Jeong Cho etal results in there study done at Yonsei University College of Medicine, Seoul, Korea in 2014 the sample include 34 pateint ,females formed 32(94%) females , females are more susseptable to blood loss during menstrual cycle ,increase demand during pregnancy and lactation ,and nutritional deficiency due to improper diet [4] .

Regarding the age disterbution it is found that mean age 40.63± 14.32 SD which is approximate to mean age of Hakkı Simsek etal study done at Yuzuncu Yil University Van, Turkey in 2010 which equal to 37.48 ± 11.9 and consistent with another study done by In-Jeong Cho etal with mean age 35 ± 11 .

Regarding the hb level , it ranged between (1.7-11.1) which differe from In-Jeong Cho etal study in which hb ranged between (4.7 -10.0 g/d), the level of HB is lowest than what populated by In-Jeong Cho etal (1.7 vs 4.7) which indicate more severe anemia with delay presentation which attributed to luck of medical eduction in addition to chronic anemia.

Regarding the severity of anemia, moderate anemia is predominant type 16(53.33%) in compare to In-Jeong Cho etal which demonstrate that sever anemia is predominant , this difference is due to fact that ,most of cases is referral cases and same take medication with improve hb level and decrease in severity at time of study.

Regarding the mean of HB it is found that mean HB 8.39 ± 2.23 which is approximate to mean of Hakkı Simsek etal study with mean hb 7.9 ±1.6 . differ from study done by In-Jeong Cho etal in which mean Hb 5.8 ± 1.4 ,this different explain by that majority of patient in this study have moderate anemia with mean equal 9.39 ±0.82

Regarding the the mean of PCV in this study 28.26 ± 6.59 which is a proximate to study of Hakkı Simsek etal with mean of PCV 25.3 ± 4.9.

Regarding the mean of serum Ferritin this study show highest level of ferritin than study done by In-Jeong Cho etal equale (8.84 vs 4.3), this different related to that most of sample in this study have moderate anemia in compare to sever anemia predominant in other study and same take medication with improve serum Ferritin level at time of study.

Regarding the mean of $LVID_D$ it is found that mean $LVID_D$ is 4.93 ± 0.73 this results correspond to the results of study done by dr.C.R.Jothi at Rajah Muthiah Medical College Hospital , Annamalai University, Chidambaram in 2015 in which the mean of $LVID_D$ is 4.84 ± 0.66 . both study shown that $LVID_d$ have normal diameter .

Regarding the the mean of $LVID_s$ in this study 3.37 ± 0.5 for female 3.73 ± 0.21 for male which is a proximate to study done by In-Jeong Cho etal in which mean of $LVID_s$ is 3.15 ± 0.37. both study shown that there is increase in $LVID_s$ as a consequence of hyperdynamic circulatory state. Anemia is known to cause vascular and cardiac changes mainly increased preload and decreased afterload. These factors increase systolic wall stress. Over time this stress weakens the LV and leads to LV systolic dysfunction [18].

Regarding the mean of PWT_D, it is found that mean of PWT_D $0.95 \pm 0.1$for male and 0.89 ± 0.2 for female which corresponded to the results of Hakkı Simsek etal in which the mean of PWT_D 0.9 ± 0.12. both study shown that PWT_D have normal thickness but with upper limit .

Regarding the mean of SWT_D, it is found that the mean of SWT_D is 1 ± 0.22 for female this results correspond to the results of Hakkı Simsek etal study in which the mean of SWT_D 0.93 ± 0.13,. this difference is due to fact that measurement of echo is operator dependent .

Regarding the EF level , it ranged between (52-79) with only one patient have EF below 55 (mildly reduced). the EF mean 65.88 ± 3.44 The result of this study is proximate to the study done by dr.C.R.Jothi in which the mean 61.26 ± 12.61 .both study show no cardiac dysfunction except one patient with severe anemia show mild systolic dysfunction (EF=52%) ,this result correspond to fact that myocardial contractility would decrease when hemoglobin was below 7 g/dL and subsequent lead to decrease Ef [8].

In term of severity of anemia :

It is found that $LVID_D$ is remained normal unlike $LVID_s$ which found to be elevated in all group of anemia in compare to Qiao Zhou etal study which is shown that only sever anemic patent have increase in $LVID_s$,this difference is due to fact that measurement of echo is operator dependent.

in compare to Qiao Zhou etal study ;Both study show that SWT_D are elevated in severe and moderate group while PWT_D are elevated in severe group only, this related to fact that as consequence to structural remodeling in hyperdynamic circulatory , increasing in septal wall thickness preceded posterior wall thickness.

Both study shows that LV mass is elevated in all group of severity ,This results were consistent with a previous report that a low Hb level can cause heart enlargement and the LV mass increases in patients with IDA . This is mainly related to a persistently hyperdynamic circulatory state in patients with IDA, which is associated with remodeling of the myocytes and vasculature [19].

Regarding EF of this study and Qiao Zhou etal study , both study shoes that sever anemia have lowest EF value (62 vs 58). As Sever anemia cause state of hypoxia that cause vasodilatation and decrease preload and decrease cardiac muscle contractility both lead to decrease Ef [7].

Both study shows increasing LV Mass in all severity of anemia as a consequence to structural remodeling in hyperdynamic circulatory.

(6) Conclusion

- Low hemoglobin level was associated with change in cardiac chambers ($LVID_S$), increase septal and posterior wall thickness and increased LV mass in the subjects without cardiovascular risk factors or overt cardiovascular disease.
- Echocardiographic feature of anemia may preceded changes in EF.
- severe anemia is more correlated with SWT_D.

(7)Recommendation

- Preforming a study on the incidence of iron deficiency anemia on wider population.
- Assessing echo changes after corrected anemia to check reversibility.
- Use more echo parameter and Doppler study for evaluation of patient.

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