# HAEMATOLOGICAL PROFILE, SERUM IRON AND FERRITIN LEVEL IN ANAEMIA OF INFLAMMATION

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#### ABSTRACT

#### BACKGROUND

Anaemia of Chronic Disease (ACD) is the most common anaemia found in hospitalised patients and it is the second most prevalent after Iron-Deficiency Anaemia (IDA). ACD seen in patients with chronic infections, malignancy, autoimmune disorders. Condition also termed as "Anaemia of Inflammation".

#### AIM AND OBJECTIVE

Combined clinical history, haematological evaluation, serum iron and ferritin estimation to reach diagnosis of ACD.

#### MATERIAL AND METHODS

Patients of chronic infection, autoimmune disorder, or malignancy admitted to different Departments of M.K.C.G.M.C. and Hospital are included in the study during period of 2010-2012. Routine haematological profile, ESR, serum iron, serum ferritin estimation was done.

#### RESULTS

80% patients have decreased serum iron, 20% normal serum iron, and 50% patients have increased S. ferritin, 40% normal S. ferritin, 10% decreased S. ferritin.

#### CONCLUSION

Our study emphasises anaemia of chronic disease can be diagnosed and differentiated from iron-deficiency anaemia by estimating the serum iron and ferritin level with proper clinical correlation. This can decrease the morbidity in hospitalised patients and irrational iron therapy can be avoided.

#### **KEYWORDS**

Anaemia of Inflammation (AI), Anaemia of Chronic Disease (ACD), Iron-Deficiency Anaemia (IDA).

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**INTRODUCTION:** Anaemia is defined as a reduction of the total circulating red cell mass below normal limits.<sup>1</sup> Anaemia is derived from Greek word, which means lack of blood. Anaemia is a prevalent yet under recognised and undertreated condition that imposes substantial costs to payers<sup>2</sup> and negative consequences on the health and Quality of Life (QOL) of affected individuals. For improved patient care, clinicians need to be more cognizant of the symptoms of anaemia and more vigilant in its treatment to ensure better outcomes both clinically and financially.

Anaemia is a condition in which the number of circulating red blood cells, the concentration of haemoglobin

Financial or Other, Competing Interest: None. Submission 23-06-2016, Peer Review 03-07-2016, Acceptance 20-07-2016, Published 28-07-2016. Corresponding Author: Dr. Bichitrananda Roul, Assistant Professor, Department of Anatomy, Pt. JNM Medical College, Raipur. E-mail: bichi4u2000@yahoo.co.in DOI: 10.18410/jebmh/2016/706 (Hb gm%), or the percentage volume of packed red blood cells in a centrifuged blood specimen (haematocrit [HCT]) is lower than normal. The World Health Organization criteria for anaemia are Hb less than 12 g/dL in premenopausal women and less than 13 g/dL in men and postmenopausal women.<sup>3</sup> Anaemia can be an isolated condition, such as that caused by a nutritional deficiency (e.g. iron, folate, vitamin B12) or it may develop secondary to another disease or its treatment.<sup>2</sup>

The anaemia that is often observed in patients with infectious, inflammatory, or neoplastic disease that persist for more than one or two months is called Anaemia of Chronic Disease (ACD).<sup>4</sup> Anaemia of Chronic Disease (ACD) or Anaemia of Inflammation (AI) is the most prevalent anaemia in hospitalised patients.<sup>5,6,7</sup> According to the Centres for Disease Control and Prevention (CDC), 5.5 million annual ambulatory care visit have anaemia as their primary cause. Most often, the anaemia is due to a nutritional deficiency. A chronic disease is the second most

prevalent cause of anaemia, but the estimate of the particular disease responsible varies widely. Although, anaemia of chronic disease is common, it is under recognised and undertreated.

A med claim database study examined approximately 2.3 million Medicare and commercial health plan members with solid tumours, Chronic Kidney Disease (CKD), Human Immunodeficiency Virus (HIV) infection, Inflammatory Bowel Disease (IBD), Rheumatoid Arthritis (RA), or congestive heart failure.<sup>8</sup> Anaemia was diagnosed in 3.5% of the patients, and of those, only 15% received an identified treatment for it.<sup>8</sup>

ACD/AI was first described in 1930 and fully characterised by Cartwright and Wintrobe in 1950.9 Hallmark of ACD/AI is dysregulation of iron homeostasis with increased uptake and retention of iron within cells of reticuloendothelial system, limitation of availability of iron for erythroid progenitor cells. and iron-restricted erythropoiesis.7 ACD/AI characterised bv blunted erythropoietin response by erythroid precursor, decrease red cell survival, and defect in iron absorption and macrophage iron retention.<sup>10</sup> The anaemia is caused by the inhibitory effects of inflammatory cytokines on erythrocyte production. Among the cytokines, IL-6 has a central role acting by increased production of iron regulatory hormone hepcidin by hepatocytes. Hepcidin blocks the release of iron from macrophages and hepatocytes causing the characteristic hypoferraemia and limiting availability of iron to the developing erythrocytes.<sup>11</sup>

Anaemia in chronic disease varies in severity. Patients usually have mild-to-moderate anaemia,<sup>12</sup> erythrocyte usually normocytic normochromic, however, hypochromasia and microcytosis may be seen (20%-40%).<sup>13</sup> Characteristically, serum iron concentration low, Total Iron-Binding Capacity (TIBC) is reduced, transferrin saturation subnormal, but iron stores i.e. ferritin increases or normal.<sup>9</sup>

In view of all the above facts, combined haematological profile, ESR, serum iron and ferritin, TIBC estimation was done in patients with chronic disease and having anaemia.

**MATERIALS AND METHODS:** The present study entitled "Haematological profile, serum iron and ferritin level in anaemia of inflammation" was carried out in the Department of Pathology, M.K.C.G. Medical College, Berhampur, during period of October 2010 to August 2012. Patients admitted to various Departments in M.K.C.G. Medical College and Hospital with infections like tuberculosis, chronic abscess, sepsis, inflammatory conditions, malignancy were taken into study.

#### Inclusion Criteria:

- 1. Patients of either sex irrespective of age group.
- 2. Patients with chronic infectious, inflammatory, or malignant conditions.
- 3. Patients with informed consent.

#### **Exclusion Criteria:**

- 1. Patients refusing for consent.
- 2. Patients suffering from kidney disease or hepatic disease.
- 3. Patients received iron or blood transfusion.
- 4. Patients with bleeding, haemolytic disorder, haematological malignancy.

After obtaining a well-informed consent, all patients were subjected for thorough clinical examination and detailed clinical history. Blood sample drawn on routine basis and laboratory parameters for example haemoglobin, Erythrocyte Sedimentation Rate (ESR), CBC (Complete blood count), serum iron and ferritin estimation by automated haematology cell counter model ms4.

At the end of the study, data were analysed using Microsoft Excel and GraphPad Prism 5 trial version (GraphPad Software, San Diego, CA, USA). ANOVA; post ANOVA Tukey's multiple comparison 't' test p<0.05 was considered significant.

#### **OBSERVATIONS:**

Examination Done	No. of cases	
Total No. of cases	261	
Cases with anaemia	154	
Biochemical study done	70	
Table 1: Case Evaluation		

Total 261 cases with chronic diseases underwent screening for anaemia during the period of 2 years.

Among total 261 cases, anaemia was seen in 154 cases (59%).

Out of which, 70 cases underwent biochemical test (serum iron, ferritin, TIBC estimation), constituted the study population.



Figure 1: Case Evaluation

Clinical Diagnosis	No. of cases	Percentage	
Infectious disease	45	64%	
Non-infectious inflammatory disease	19	27%	
Malignancy	06	09%	
Total 70 100%			
Table 2: Distribution of Cases According to Clinical Diagnosis (n=70)			



Figure 2

Table 2 shows distribution of cases according to their clinical diagnosis. It shows maximum number (64%) cases of chronic disease were of infectious type, next common was of inflammatory disease.

## Distribution of Cases According to Serum Iron and Ferritin Levels:

Patients were divided into three categories on the basis of serum values:

- 1. IDA (Decreased serum ferritin and serum iron).
- 2. ACD (Decreased serum iron with normal or increased S. ferritin).
- 3. Non-ACD (normal serum iron with normal/high S. ferritin).

Groups	No. of Cases	S. Ferritin	S. Iron	Type of Anaemia
Group 1	23	Normal	Low	ACD
Group 2	27	High	Low	ACD
Group 3	09	Low	Low	IDA
Group 4	11	Normal/high	Normal	Non-ACD
Table 3: Categories of Anaemia				

Diagnosis	Total no. of Cases	Percentage	
ACD	50	71%	
IDA	09	13%	
Non-ACD	11	16%	
Table 4: Distribution of Cases According to Type of Anaemia (n=70)			

Table 3 show the categorisation of cases according to their biochemical parameters. Group 1 and group 2 belong to the category of ACD, Group 3 to the category of IDA, Group 4 the category of non-ACD.

Table No. 4 showing out of 70 patients of chronic disease and anaemia, maximum cases were of category ACD (n=50 or 71%), rest are IDA (n=9 or 12.85%), and non-ACD (n=11 or 15.75%).



Figure 3

	Mean Valu	Mean Values of Iron Parameters			
Categories of anaemia	S. Iron (n=60-160 µgm/dL)	. Iron TIBC :60-160 (n=200-400 μgm/dL)			
ACD/AI	37.20	236.4	390.78		
IDA	18.33	804.33	16.6		
Non-ACD	119.1	347.0	374.27		
Table 5: Distribution of Iron Parameters According to Type of Anaemia					

Table 5 showing mean values of iron parameters in different categories of anaemia. ACD/AI showing decreased S. iron, but increase in S. ferritin value. TIBC was normal in ACD. In IDA, there was both decreased S. iron and ferritin level with increased TIBC level. Non-ACD cases mean S. iron and TIBC levels were in normal range, but increase in mean ferritin value was noted.





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Diagnosis	Male	Female	M:F ratio	
ACD/AI (n=50)	24	26	1:1.08	
IDA (n=09)	3	6	1:2	
Non-ACD (n=11)	4	7	1:1.75	
Table 6: Sex Distribution in				
Different Types of Anaemia				

The table 6 shows almost equal sex ratio in ACD, in IDA females are two times more prevalent than males, and in non-ACD incidence in female is more than males.





Age Group (In yrs.)	Females	Males	Number of Cases
0-10	00	02	02(04%)
11-20	03	01	04(08%)
21-30	02	03	07(14%)
31-40	05	03	08(16%)
41-50	04	07	11(22%)
51-60	06	03	09(18%)
>60	06	05	11(22%)
Total	26	24	50(100%)
<i>Table 7: Age and Sex Distribution Cases in ACD (n=50)</i>			

Table 7 shows age and sex distribution of cases in ACD (n=50). There is increase in no. of cases as the age increases. 62% of cases presented after fourth decade. Age ranges from 7 yrs. to 72 yrs. with mean age = 44.37 yrs. Sex ratio (F:M=1.1:1); almost equal.

Mean age in IDA patients were 37.62.



Figure 6

Haematological Parameters	Mean value±sd	Values	No. of cases	%
Llaamaglahin		<7	26	
(am%)	8.62±2.32		34	
(91170)			20	40
		<77	13	26
MCV(FL)	80.27±12.6	78-96	37	74
	>96	00	00	
	27 84+6 24	<27	21	42
MCH(PO)	27.07±0.27	≥27	29	58
	30 84 + 5 55	<30%	16	32
	50.04±5.55	>30%	34	68
Table 8: Values of Different Haematological				
Parameters in ACD (n=50)				

Table 8 shows mean and SD of different haematological parameters and number of cases below or within normal reference range.

Mean value of Hb was =  $8.62\pm2.32$  gm%, mild degree of anaemia (>10 gm%) was observed in 40% cases, moderate degree (7-10 gm%) in 34% cases, severe anaemia (<7 gm%) in 26% case.

Mean value of MCV was  $80.27\pm12.6$  fL, microcytic red cells (MCV <77 fL) seen in 26% cases, others (74%) were within normal range.

Mean value of MCH was 27.8 $\pm$ 6.24 pg, 42% had MCH less than the normal value.



Figure 7

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Figure 8

Peripheral Blood Picture	No. of Cases	Percentage
Normochromic normocytic	23	46
Normocytic hypochromic	06	12
Dimorphic	08	16
Microcytic hypochromic	13	26
Total	50	100
Table 9: Distribution of Cases Depending on RBCMorphology in ACD (n=50)		

Table 9 shows the distribution of cases depending on the red cell morphology. Most common type of morphological picture in ACD was normochromic normocytic (46% cases) followed by microcytic hypochromic in 26% cases. Normocytic hypochromic red cells were seen in 12% cases and dimorphic picture was present in 16% cases.



Figure 9

Haemoglobin (gm %)	No. of Cases	Mean ESR (mm in 1 <sup>st</sup> Hr)	
<7	13	102.38±19.9	
7-10	17	91.24±34.58	
>10	20	70±14.02	
Table 10: Correlation of Severity of Anaemia with     Disease Activity (ESR) among ACD Cases (n=50)			

Table 10 showing the haemoglobin ranges and their respective mean ESR values. Cases with low Hb value have high ESR. On statistical analysis, correlation co-efficient, r = -0.51, which means negative (INVERSE) correlation between haemoglobin level and ESR.



Figure 10

ESR	Number of Patients MCV <77 fL (n=13)	Percentage	
≥100	09	69%	
<100	04	31%	
Table 11: Relation Between ESR with Microcytic Blood Picture (n=13)			

Table 11 shows out of 13 case with microcytic anaemia 09 patients (69%) have very high ESR (>100 mm/hr) and 04 patients (31%) have ESR <100 mm/hr.



Figure 11

	Duration	Mean ± SEM Values Of Red Cell Indices			
Group No.	in Months	Haemoglobin (gm %)	MCV (fL)	MCH (pg)	MCHC (%)
1(n=17)	0-2	9.49±0.35	85.45±1.8	28.37±0.98	32.63±0.94
2(n=11)	3-5	9.36±0.82	83.3±3.6	28.59±1.73	31.97±1.74
3(n=22)	>5	7.6*±0.52	74.86*±3.03	24.3*±1.22	28.61±1.33
F 4.35 4.27 3.94 3.02					3.02
Р		<0.05	<0.05	< 0.05	>0.05
Table 12: Red Cell Indices in Relation to Duration of Disease					

\*signifies  $\rightarrow p < 0.05$ .

ANOVA, post ANOVA Tukey's multiple comparison 't' test p<0.05 was considered as significant.

The above data of table 12 represents the mean  $\pm$  SEM value of different haematological parameters (Hb, MCV, MCH, and MCHC) according to duration of disease. Post ANOVA 't' test revealed the Hb%, MCV, MCH of group-3 (>5

months) decreased significantly (p <0.05) in comparison to group 1(0-2 months). There was no significant difference of Hb%, MCV and MCH levels among Gr.1 and Gr.2.

There is no significant difference (p>0.05) in MCHC% among the three groups with respect to duration of disease.



Figure 12

Group No.	Duration In	Mean±Sem of Different Iron Parameters				
	Months	S. Iron (µgm/dL)	S. Ferritin (ngm/dL)	S. TIBC (%)		
1(n=17)	0-2	44.06±1.47	280.4±27.94	223.2±16.75		
2(n=11)	3-5	37.8±4.31	392.2±91.07	265±15.19		
3(n=22)	>5	31.64**±2.92	475.4*±54.5	233.6±15.01		
F		5.501	3.6	1.29		
Р		<0.01	<0.05	NS		
Table 13: Iron Parameters in Relation to Duration of Disease in ACD (n=50)						

\*signifies  $\rightarrow p < 0.05$ 

\*\*signifies  $\rightarrow$  p<0.01 NS $\rightarrow$  Not Significant.

The above data of table no. 13 showing the serum iron parameters with respect to duration of disease.

Post ANOVA 't' test revealed that the S. iron of group 3 (>5 months) decreased significantly (p<0.01) in comparison to group 1 (0-2 months). There was no significant difference in iron levels among groups 1 and 2 (3-5 months).

S. ferritin of group 3 increased significantly in comparison to group 1 (p<0.05). There was no significant difference in ferritin levels among groups 1 and 2.

No significant difference in TIBC (p=NS) values among the three groups with respect to duration of disease.



Figure 13

	ESR(mm/hr)	S. IRON(µgm/dL)	Correlation Co-Efficient: r			
Mean Value	85.12	37.2	-0.64			
SD	27.01	12.65				
Table 14: Correlation of Serum Iron and Ferritin with ESR in ACD (n=50)						

	ESR(mm/hr)	S. FERRITIN (ngm/dL)	Correlation Co-Efficient: r			
Mean Value	85.12	382.58	0.596			
SD	27.01	232.38				
Table 15						

Table 14 showing the correlation between ESR and S. iron. On comparing ESR with S. iron, the correlation coefficient (r) came to be -0.64, which means a NEGATIVE OR INVERSE correlation between disease activity (ESR) and S. iron.

Table 15 showing the correlation between ESR and S. ferritin. On comparing ESR with S. ferritin, the correlation co-efficient (r) came to be 0.596, which means a positive correlation between disease activity (ESR) and S. ferritin.

By correlating serum iron with S. ferritin, the correlation co-efficient (r) was = -0.552; which means a NEGATIVE correlation between S. iron and S. ferritin.





**DISCUSSION:** Anaemia of Chronic Disease (ACD) or Anaemia of Inflammation (AI) is the most prevalent anaemia in hospitalised patients and overall it is the second most prevalent one after anaemia caused by iron deficiency. Although, anaemia of chronic disease is common, it is under diagnosed and undertreated. ACD patients usually have mild-to-moderate anaemia, erythrocyte usually normocytic normochromic, however, hypochromasia, and microcytosis may be seen (20%-40%). Characteristically, as the serum iron concentration declines, it is misdiagnosed as irondeficiency anaemia. Though, serum iron is low, they (ACD) have adequate iron stores. Combination of serum iron, TIBC, ferritin distinguishes ACD from IDA.

In the present study, prevalence of anaemia (table: 1) in chronic disease patients was 59%. Byomakesh et al (2009) reported anaemia prevalence of 65.5%. Wolfe et al<sup>14</sup> (2006) reported prevalence of 51%, Peeters et al<sup>15</sup> (1996) reported in 64% cases. Our finding was almost similar to their findings.

By categorisation of anaemia according to their serum iron and ferritin value (table no. 4); majority of cases (71%) were of category ACD followed by non-ACD 16% and IDA 13%. These findings were almost similar to Peeters et al, Byomakesh et al (2009) reported ACD in 50.8% cases and IDA in 49.2% cases. Opasich et al reported ACD prevalence of 57%, Cash and Sears et al<sup>16</sup> (1989) reported ACD prevalence of 60%. However, Gaetano et al (2005) differs from our study who reported 69% cases due to IDA and only 16.2% cases due to ACD.

In our study, sex distribution (table: 6) in ACD was almost equal in IDA and non-ACD, there was a female preponderance. However, Ray Yip et al observed a male preponderance in ACD and female preponderance in IDA. Byomakesh et al observed a male predominance both in ACD and IDA.

In ACD, a wide spectrum of age groups present ranging from 7 to 72 years (table no. 7) with mean age of 44.37 yrs. Significantly, 62% of cases were present after fourth decade. It corroborates with the study of Ismail et al<sup>17</sup> and Ray Yip et al.<sup>18</sup>

On analysing different haematological parameters (table: 8) in ACD, we observed mean and SD of Hb, HCT, MCV, and MCH were  $8.6\pm2.3$  gm/dL,  $27.8\pm6.2\%$ ,  $80.27\pm12.6$  fL,  $26.7\pm5.4$  pg respectively. The findings were almost similar to J Haska et al<sup>19</sup> except MCV was comparatively low in our study (their study, MCV was  $84.6\pm3.7$  fL). In our study, severe anaemia observed in 26% cases and MCV<77 fL in 26% cases. These findings corroborate with Cash and Sears et al. Jaffery et al reported MCV<77 fL in 10% cases. In our study, normal value of MCH observed in 58% cases. Jeffery et al reported normal MCH in 23% of cases.

Our study, the severity of anaemia was well correlated with the disease activity (table:10), and the correlation coefficient was r = -0.51, P<0.05. This finding was also observed by Jeffery et al<sup>20</sup> (p<0.05), Ray Yip et al(p<0.01), Ismail et al (p<0.005), and Byomakesh et al(p<0.001).

We analysed the red cell indices with respect to the duration of disease (table: 12). Post ANOVA 't' test revealed the Hb%, MCV, MCH of group-3 (>5 months) decreased significantly (p<0.05) in comparison to group 1 (0-2 months). There was no significant difference of Hb%, MCV, MCH levels among Gr.1 and Gr.2. Also, we found MCHC uninfluenced (p>0.05) by duration of disease. However,

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Jaffery et al reported in their study that Hb, MCH, MCV, MCHC were uninfluenced by duration of disease.

The parameters of serum iron profile were correlated with ESR (table no. 14 and 15). We found an inverse or negative correlation (r=-0.64) between S. iron and ESR. Positive correlation was seen between ESR and S. ferritin (r=0.596). Coenen et al<sup>21</sup> obtained highly significant correlation between ESR and ferritin (r=0.38, p<0.001). Ray Yip et al also observed in their study as ESR value rise mean serum iron value declines (p<0.01). Byomakesh et al in their study found S. iron was not significantly correlated with disease activity, but S. ferritin levels were significantly correlated (p<0.05). Ismail et al observed patients with active disease had a low S. iron and higher S. ferritin (p<0.005).

On analysing correlation between serum iron and ferritin, the correlation coefficient came to be r=-0.55, which means a negative correlation between S. iron and ferritin. Our finding corroborates with findings of Ismail et al (r=-0.57, p<0.02).

**CONCLUSION:** ACD/AI is an important cause of anaemia in chronic diseases. Diagnosis of ACD depends on proper clinical history, laboratory investigations (ESR, haematological profile, serum iron profile). Anaemia in chronic diseases is usually mild-to-moderate, but more pronounced in the presence of active disease. Characteristically, as the serum iron concentration low, it is misdiagnosed as iron-deficiency anaemia. Though, serum iron is low, they (ACD) have adequate iron stores. Iron therapy is not recommended in ACD. Combination of serum iron, TIBC, ferritin distinguishes ACD from IDA.

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