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Hyporesponsiviness to Erythropoietin Therapy in End Stage Renal Disease Patients on Regular Haemodialysis

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Abstract: *Background:* Many factors can alter the response to erythropoietin treatment and approximately 5–10% of patients present an evident resistance in response to erythropoietin therapy. These include: iron deficiency, inflammation, infections, malignancy, dialysis, blood loss, hyperparathyroidism, aluminum toxicity and vitamin B12 or folate deficiencies. *Objective:* To evaluate and search for causative factors that predispose to Anemia resistance to erythropoietin therapy in End stage renal failure patients on regular hemodialysis. P*atients and methods:* This is descriptive prospective study enrolling 350 patients with End stage renal disease on regular hemodialysis, during January 2019 to January 2020 at Al-Emamain Al-Kadumian Medical City / Nephrology unit. 117 (44 female and 73 male) patients enrolled in this study whom met the inclusion criteria: Hgb level below 11 mg / dl despite adequate erythropoietin dose, regular adequate HD, Iron and folic acid supplementation. Amonthly bases measurement of CBC, CRP, S. Albumin, S. Ca, S. Phos, S. PTH, S. Ferritin and Transferrin Saturation were obtained. *Results:* 39% of patients have anemia resistance to erythropoietin. 48.7% of cases were taking Angiotensin converting enzyme inhibitors or angiotensin receptor blockers while 51.3% not. Hemoglobin level was significantly affected with ACEi or ARBs drugs use 8.20±1.17 mg/dl with drug use versus 8.95±0.82 mg/dl without ACEi or ARBs (p value <0.001). Hemoglobin level average was 7.85±1.01 mg/dl in female patients while 8.99±0.87 in male patients (p value<0.001). The mean WBC 7799 ± 2278 $\times 10^3/mm^3$ shows negative effect on Hgb level (p value < 0.001), The Hgb level was negatively corelated with serum ferritin level (mean S. ferritin 592.9577 ± 270.707ng/ml) (p value 0.031). CRP level negatively corelate with Hgb level (p value< 0.001) while Albumin Level Positively corelated (p value < 0.001). Regarding Parathyroid, S. Ca and S. Pho level impacts on Hgb level shows negatively correlate of Hgb with PTH (mean 691.7144±324.66 pg/ml)(p< 0.001) and S. Pho (mean 5.4637 ± 1.01585 mg/dl) (p value 0.024) and positive correlate with S. Ca (8.40744± 0.660188 mg/dl) (p value 0.023). *Conclusion:* The level of hemoglobin response to erythropoietin is significantly affected by Gender (female require higher dose), ACEi and ARBs treatment, WBC, CRP, Serum Albumin, Serum Calcium, Serum Ferritin, Serum Phosphorus and Serum Parathyroid hormone.

Keywords: End Stage Renal, Hemodialysis, Erythropoietin

1. Introduction

As kidney disease progresses, anemia increases in prevalence, affecting nearly all patients with stage 5 CKD. Anemia in CKD is associated with reduced quality of life and increased cardiovascular disease, hospitalizations, cognitive impairment, and mortality. Anemia in CKD is typically normocytic, normochromic, and hypo proliferative. some other conditions may cause microcytic or macrocytic anemia.

Although relative Erythropoietin deficiency may contribute to the anemia of CKD, it is not the sole cause. Indeed, anemia of CKD is resistant to ESAs in approximately 5%–10% of patients anemia of CKD is a multifactorial process due to relative EPO deficiency, uremic-induced inhibitors of erythropoiesis, shortened erythrocyte survival, and disordered iron homeostasis. [1]

Diagnose anemia in adults and children more than 15 years with CKD when the Hb concentration is less than 13.0 g/dl (130 g/l) in males and 12.0 g/dl (120 g/l) in females. [2]

The introduction of recombinant human erythropoietin

(rHuEPO) into clinical practice in the 1980 s was a major breakthrough in the treatment of the anemia of patients with CKD. The development of erythropoietin was aimed at replacing the insufficient endogenous erythropoietin (EPO) production related to CKD progression. [2]

In initiating and maintaining Erythrocyte stimulation agents (ESA) therapy, recommend balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, hypertension). So hemoglobin target should be ≤11.5 g/dL and not to exceed 13 g/dL in male and 12 g/dl in female. [2]

Epoetin alfa should be initiated at a dose of 50–100 IU/kg subcutaneously, one to three times a week. The initial goal of treatment is to achieve a rate of weekly increase in hemoglobin levels of 0.3 g/dL. [3]

Although there is no consensus about the definition for erythropoietin resistance, the evaluation of resistance is recommended if there is an increase ≥25% in erythropoietin dose or <1 mg/dL gain in hemoglobin levels after 2–4 weeks of treatment. [3]

According to the most recent guidelines, hypo responsiveness to ESA therapy is identified when the Hb concentration does not increase from baseline after the first month of ESA treatment on appropriate weight- based dosages or if after treatment with stable doses, patients require two increases in ESA doses up to 50% beyond the dose at which their condition had previously been stable. Patients who are hyporesponsive have a worse prognosis than those who do respond. [4]

Many factors can alter the response to erythropoietin treatment and approximately 5–10% of patients present an evident resistance to erythropoietin therapy. Several conditions are commonly associated with erythropoietin resistance, including iron deficiency, inflammation, infections, malignancy, dialysis, blood loss, hyperparathyroidism, aluminum toxicity and vitamin B12 or folate deficiencies. [5]

Age and gender have great impact on responsiveness to EPO. with advanced age there is increase burden of inflammation, malnutrition and blood loss. greater need of EPO in adult females may be due to androgenic stimulation of erythropoiesis in males. Similarly, women with preserved capacity for menstrual cycles, despite the hypo gonadotrophic effect of CKD, often require greater amounts of EPO. [6]

Iron deficiency or impairment of iron availability is the most frequent cause of erythropoietin treatment resistance in patients under dialysis. [7] In these patients, the deficiency or reduction of total iron stores can occur due to an increase in demand of this nutrient during the production of red blood cells in the bone marrow. This absolute iron deficiency may also be related to the dialysis procedure, which promotes premature destruction of red blood cells (hemolysis), but also due to gastrointestinal bleeding, or frequent laboratory blood tests and surgeries, which patients can be submitted to. [8] In functional iron deficiency, suitable stores of this nutrient can be observed, but the mobilization of iron to the blood- stream is insufficient to reach the demand of the erythroid marrow. This condition is common in inflammatory states due to the cytokines that block the release of iron from deposits. [3]

It is known that the release of cytokines such as interferon-gamma (IFN-δ), tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1) and interleukin 6 (IL-6) can induce erythropoietin erythroid progenitor cell resistance or impair the release of stored iron in the reticuloendothelial system for the production of hemoglobin. Infectious diseases may also be related to anemia resulting in chronic inflammation. [3] Recent study shows that parvovirus B19 and cytomegalovirus (CMV) infections are potential causes of anemia in dialyzed patients, hyporesponsive to erythropoietin through elevated inflammatory mediators or through development of pure red cell aplasia with B19 infection. [5]

Regarding Cofactor deficiency and malnutrition in Hemodialysis patient, the main causes of protein energy malnutrition include low intake of nutrients; muscle loss due to increased protein catabolism and decrease in their synthesis; insulin resistance; loss of nutrients by dialysis and oxidative stress, Laboratory tests show low percentages of transferrin saturation index, low serum albumin concentrations and body mass index (BMI) [3]. Deficiencies of folic acid and vitamin B12 may be associated with anemia and resistance to treatment with erythropoietin. Thus, when macrocytosis is detected, the levels of these nutrients should be evaluated. [3]

The inadequacy of the dialysis dose is an important cause of anemia in patients under dialysis. In order to evaluate whether the dialysis procedure is removing enough uremic toxins, the patient's blood is sampled at the start and at the end of dialysis. The levels of urea in the two blood samples are then comparedThe Kt/V value, the dialyzer urea clearance (K) is multiplied by dialysis time (t), and the product divided by the patient's urea distribution volume (V) were calculated and was on target (≥1.3). [2, 9]

Hyperparathyroidism contribute to anemia unresponsiveness in HD patient, there is a higher prevalence of anemia and greater EPO requirement among HD subjects who are in the upper 50th percentile of intact parathyroid hormone. As a proof of causal relationship, surgical parathyroidectomy led to an improved control of anemia and a lower need for ESA. [6] According to the NKF/KDOQI, PTH levels between 150 and 300 pg/mL are desirable in patients undergoing dialysis. [3]

Angiotensin-converting enzyme inhibitors (ACEi) are commonly prescribed to chronic kidney disease (CKD) patients due to their beneficial effect on the cardiovascular system. The renin-angiotensin system regulates blood pressure controlling vascular resistance and plasma volume. The importance of renin- angiotensin system in erythropoiesis was thoroughly investigated in recent past. Angiotensin- converting enzyme (ACE) stimulates the mitosis of stem cell and the differentiation of erythroid progenitors. Angiotensin II (AT II) acts as a growth factor, stimulating erythroid progenitor cells, and thereby enhances

secretion of erythropoietin (EPO). ACE inhibitor (ACEi) treatment decreases the serum AT II level, which consequently results in decline of serum erythropoietin concentration. Also ACEi decrease renal perfusion through dilatation of efferent and afferent arteriole and decreasing erythropoietin production. [10]

ACE inhibitors treatment negatively correlates with anemia parameters in HD patients. Treating HD patients receiving ESA with ACE inhibitors should be conducted carefully. It is necessary to determine an adequate dosage of ACE inhibitors to provide satisfactory cardio protection but not to Affect erythropoiesis. Decreases in hemoglobin levels occur in adults with CKD after therapy with ACE inhibitors and/or ARBs. [11]

Although treatment with Erythropoietin is well tolerated by most patients, a small number produce antibodies that can neutralize either endogenous EPO and recombinant proteins. Most cases of antibody production have been associated with the formulation of epoetin alfa when administered subcutaneously. [12]

In some cases, the anti-erythropoietin (anti-EPO) antibody production can lead to development of serious PRCA (pure red cell aplasia) and transfusion-dependent anemia. Recent studies have shown that anti-EPO antibody-mediated PRCA is a rare but important adverse effect in patients with CKD who take rHuEPO. [13]

Some genetic polymorphisms may result in individual response variations to rHuEPO. [14]

2. Patients and Method

2.1. Study Settings and Design

Prospective study held At Al-Emamain Al-Kadumain medical City at Dialysis units which treat 350 Patient on regular hemodialysis under supervisions of Nephrologist.

Time frame: For the period from January 2019 to January 2020.

2.2. Patients Assessments

All patients (350) on regular hemodialysis for one year and above with three sessions per week and 4 hours duration of each session using GAMBRO Dialysis system were evaluated in this study.

2.3. Inclusion Criteria

Patients with hemoglobin level below 11gm/dl despite treatment with erythropoietin were confined for further evaluation and serial measurements of attributable factors for such unresponsiveness in scheduled time. [2]

117 (44 female and 73 male) patients were involved in our study who met the above criteria.

Each patient subjected to hemodialysis for 3 to 4 hours per session with 3 sessions per weak and receiving erythropoietin (Eprex® Janssen) according to body weight (4000-2000 UI) with each session along with intravenous infusion of venofer® iron supplementation.

2.4. Exclusion Criteria

Involves 233 patients whom hemoglobin level above 11.5 g/dl, patient not on optimum hemodialysis dose and those whom not compliance with their treatment.

Patients with hemoglobinopathy, history of blood loss, active bleeding, active hemolysis, history of blood transfusion, history of kidney transplant, polycystic kidney disease and patients with history of malignancy were also excluded.

2.5. Baseline Assessment

Including history, clinical examination, drugs history and compliance with treatment were confirmed.

Each patient was evaluated on monthly basis with laboratory investigations including: complete blood count, CRP, Iron study, Serum Albumin, PTH, Ca and phosphorus. The mean value of each measure was calculated at end of study for further analysis.

With strict monitoring of patient's compliance with: erythropoietin injections, dialysis sessions, iron and folic acids supplementation.

2.6. Data Collection

Data were obtained used a Data sheet which contain questionnaire plus data field arranged according to months from May 2019 till October 2019. Blood samples were taken at dialysis units and investigated in Al- Emamain Alkathomain medical city / laboratory department.

2.7. Statistical Method

Mean value of variable parameters were calculated and entered using Microsoft Excel 2019.

Statistical analysis was done using SPSS (statistical package for social science) Version 24 for windows.

2.8. Ethical Issues

Approved by Iraq board internal medicine committee.

3. Results

Total cases involved in study 117 patients (44 females, 73 males) with mean age of 49.38 ±12.93 year ranging from 21 to 75 years old. mean HD duration was 3.14±1.84 year with rang from 1 to 8 years.

The main cause of renal failure was Diabetic Nephropathy 40.1%, HTN and Diabetic Nephropathy 18.8%, Hypertensive nephropathy 17.9%, Obstructive nephropathy 11.1%, Vasculitis 3.4%, Congenital disease 3.4%, Nephrotic Syndrome 2.6% and Amyloidosis 2.6%.

60.7% of the cases were Virology negative status, while 36.8%, 2.6% were HCV positive, HBV positive respectively.

48.7% of cases were taking ACEi or ARBs. And 55.6% were on A/V fistula while 44.4% on double lumen Access for HD. Table 1 shows the main demographic features.

Table 1. *Basic Demographic features.*

Variable		value
Age Mean ± SD year Range (Min-Max) year		49.38±12.93 54 (21-75)
Duration of hemodialysis (years)		3.14±1.84 7 (1-8)
Sex	Female	44 (40.1%)
	Male	73 (62.4%)
Causes	Diabetic nephropathy	47 (31.6%)
	HTN + DN	22 (18.8%)
	Hypertensive nephropathy	21 (17.9%)
	Obstructive nephropathy	13 (11.1%)
	Vasculitis	4 (3.4%)
	Congenital	4 (3.4%)
	Nephrotic syndrome	3 (2.6%)
	Amyloidosis	3 (2.6%)
Virology	Negative	71 (60.7%)
	HBV	3 (2.6%)
	HCV	43 (36.8%)
ACEi or ARBs	Yes	57 (48.7%)
	No	60 (51.3%)
Venous Access	A/V fistula	65 (55.6%)
	Double lumen	52 (44.4%)

Hemoglobin level mean was 7.85±1.01 g/dl in female patients while 8.99±0.87 g/dl in male patients (p value <0.001).

Also, Hemoglobin level was significantly affected with ACEi drugs use 8.20±1.17 g/dl with drug use versus 8.95±0.82 g/dl without ACEi (p value <0.001) as shown in table 2.

Table 2. *Effects of Gender, ACEi and Venous Access on Hemoglobin level.*

Parameters	Variable	Hgb level g/dl	p value
Gender	Male	8.99±0.87	<0.001**
	Female	7.85±1.01	
ACEi or ARBs	yes	8.20±1.17	<0.001**
	no	8.95±0.82	
Venous Access	Double lumen	8.55±1.01	0.91
	A/V fistula	8.57±1.14	

Venous Access type compared to hemoglobin level also shown in table 2.

Figure 1 shows the correlation between Hgb level and duration on HD (p value 0.081).

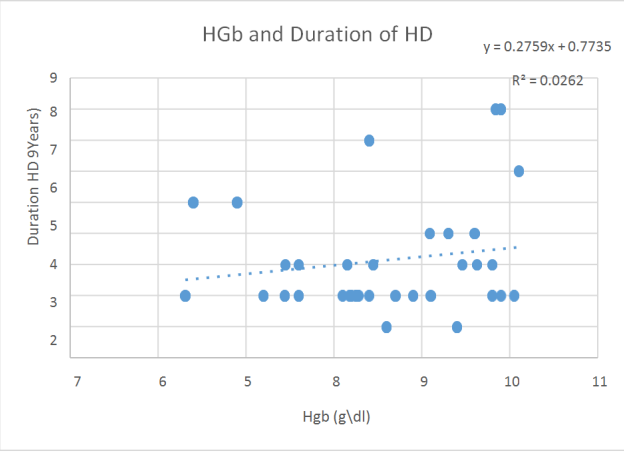

Figure 1. *Correlation between Hgb level with Duration on HD.*

Also, the correlation between Hgb level and Age of patient was shown in figure 2 with (p value 0.09).

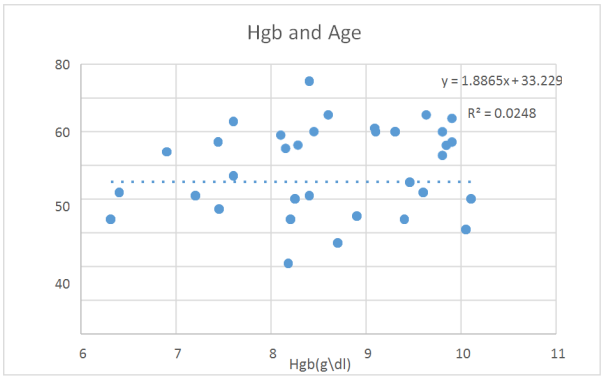

Figure 2. *Correlation between Hgb level and Age of patient.*

Complete blood count was also compared to level of Hgb as shown in table 3 with mean WBC 7799 ± 2278×10^3/mm^3 (p value < 0.001), PLT 237 ± 47 ×10^3/mm^3 (p value 0.595) and MCV 77.2 ± 6.513(fl) (p value 0.493).

Table 3. *Correlation of Hgb level to other CBC parameters.*

Parameter	Mean HGB (g/dl)	SD±	P value
WBC×10^3/mm^3	7799.974	2278.6049	< 0.001
PLT×10^3/mm^3	237.4952	47.86711	0.595
MCV (fl)	77.2814	6.51309	0.493

The Hgb level was negatively corelated with serum ferritin level in figure 3 with mean S. ferritin 592.9577 ± 270.707 ng/ml (p value 0.031).

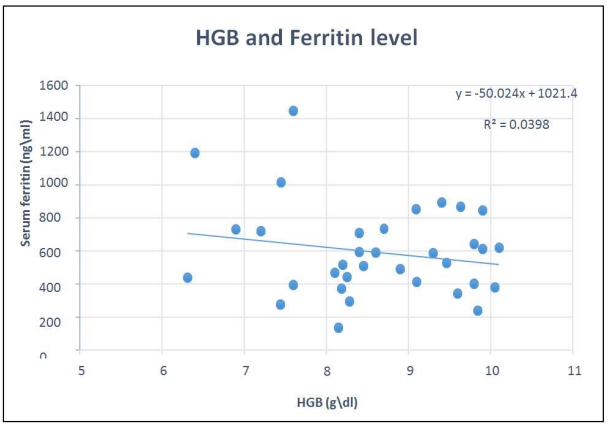

Figure 3. *Correlation of Hgb level to Serum Ferritin.*

The mean transferrin saturation level was 29.965 ± 8.68% SD (p value 0.139) as shown in table 4.

Table 4. *Effects of Iron status on Hemoglobin.*

Parameter	Mean	SD±	P value
S. ferritin (ng/ml)	592.9577	270.70781	0.031
Transferrin saturation	29.96543	8.680894	0.139

The CRP level negatively corelate with Hgb level (p value< 0.001) as shown in figure 4 while Albumin Level Positively corelated (p value < 0.001) as shown in figure 5.

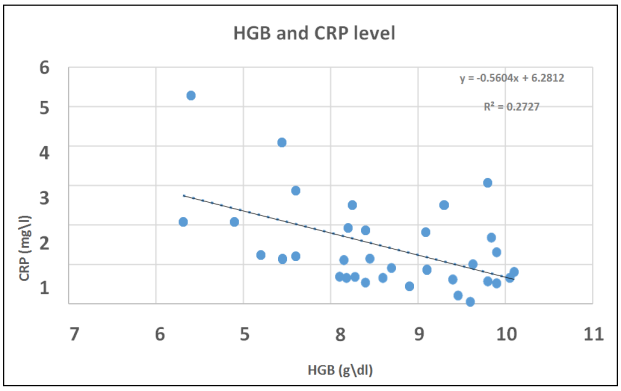

Figure 4. *Correlation of Hgb level with CRP.*

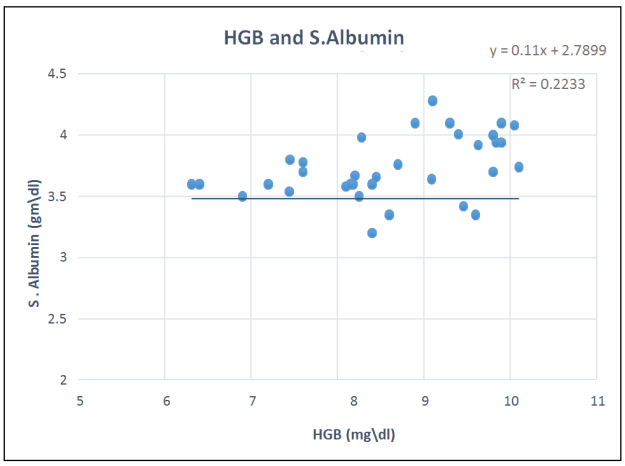

Figure 5. *Correlation of Hgb level with S. Albumin.*

Regarding Parathyroid, S. Ca and S. Pho level impacts on Hgb level were illustrated in table 5 shows negatively correlate of Hgb with PTH (mean 691.7144± 324.66) pg/ml (p< 0.001) and S. Pho (mean 5.4637 ± 1.01585) mg/dl (p value 0.024) and positive correlate with S. Ca (8.40744± 0.660188) mg/dl (p value 0.023).

Table 5. *The effect of PTH, S. Ca and S. Ph on Hemoglobin.*

Parameter	Mean Hgb (g/dl)	SD±	P value
PTH (pg/ml)	691.7144	324.66864	< 0.001
Phos (mg/dl)	5.4637	1.01585	0.024
Ca (mg/dl)	8.40744	.660188	0.023

Table 6 shows all laboratory parameters enrolled in this thesis. (PTHparathyroid hormone, Ca=calcium, phs=phophorus).

Table 6. *Laboratory parameters description.*

	Minimum	Maximum	Mean	Std. Deviation
HGB g/dl	6.31	10.10	8.5640	1.07898
MCV fl	65.00	90.00	77.2814	6.51309
WBC $\times 10^3/mm^3$	3877.0	13000.0	7799.974	2278.6049
PLT $\times 10^3/mm^3$	128.00	320.00	237.4952	47.86711
CRP mg/l	.050	5.290	1.48156	1.158009
Sferritin ng/ml	134.50	1446.00	592.9577	270.70781
TransferinSAT %	18.900	66.000	29.96543	8.680894
Albumin g/l	3.20	4.28	3.7321	.25119
PTHp g/ml	197.20	1697.00	691.7144	324.66864
Phos mg/dl	3.40	7.40	5.4637	1.01585
Ca mg/dl	7.180	10.000	8.40744	.660188

4. Discussion

Resistance to EPO has been observed in a large proportion of patients with chronic kidney disease (CKD) and it is associated with adverse outcomes, such as increased cardiovascular morbidity, faster progression to end-stage renal disease (ESRD) and all-cause mortality. [15]

39% of patients have anemia (Hb < 11 g/dl) with comparison to H. Farahat *et al.* a study was carried out on 97 ESRD patients maintained on regular hemodialysis attending Menoufia University Hospital. [16]

There was significant impact of gender on level of Hgb (p value <0.001) and its similar to which is attributed to the effect of androgens and estrogens on erythropoiesis. This was proved that women require higher dose of EPO to maintain Hgb level conducted in Coronado Daza *et al* study. [17]

Inhibition of renin angiotensin system inhibits erythropoiesis by decreasing angiotensin II availability, which is a growth factor for erythrocytes. Moreover, RAAS blockers can lead to an elevated level of negative regulator of erythropoiesis of acetyl-seryl-aspartyl-lysyl-proline (AcSDKP), The use of ACEi and ARBs drugs have negative correlaion on level of Hgb (p value <0.001) which was the similar to H. Farahat *et al.* study results which shows anemia more common in patient who take ACEi compare to non (78.3 vs. 26.8%, $P < 0.000$). [16]

There was no impact of Age of patients, Duration On HD, Type of venous Access on Hgb responsiveness which match the H. Farahat *et al* results. [16]

The level of Hgb was significantly correlated negatively with White Cell Count, (p value < 0.001) as shown in table 2, and mostly related to infection and inflammation affect erythropoiesis. This was confirmed with negative association of Hgb level and CRP level in figure 4 p value < 0.001. this result was similar to study A. Karaboyas, H. Morgenstren *et al* study which included 12389 patients conducted in 10 countries over 10 years duration that shows The associations were particularly strong among patients for whom the CRP level increase was sustained over the subsequent 3 months, further supporting a causal relation between inflammation and ESA hypo responsiveness. [18]

The MCV and Platelet value have no strong correlation with Hgb level as anemia may be micro, macro and normocytic in CKD patient and patient with bleeding disorder was excluded from our study.

The serum albumin level has positive correlation with Hgb level in our study that summarized in figure 5 (p value < 0.001). The result was similar to Samavat et al study which shows lower BMI and serum albumin as risk factors of hypo responsiveness. This points to malnutrition and chronic inflammation effect on erythropoiesis. [19]

Despite elevated level of serum ferritin, it was negatively correlate with Hgb level (p value < 0.001) in contrast the transferrin saturation shows no relation with Hgb level (p value 0.139) and its explained by the fact that the Patient compliance with treatment are the only included in study and patient with occult bleeding was excluded making this results applicable. While elevated in S. ferritin should increase

response to EPO as shown in Yokoyama *et al* study which is opposite in our results might be due to reactive elevation against infectious process which make the bone marrow hyporesponsive to EPO and shows paradoxical fall of Hgb in response to high S. Ferritin [18-20].

The Hgb level positively increased with serum calcium (p value 0.023) and negatively with Serum Phosphorus (p value 0.024) and PTH level (p value < 0.001) which is not shown in Samavat et al study (multicenter cross-sectional study, 1224 patients from 22 dialysis centers in Tehran, Iran, were enrolled) that reviled Serum PTH level was not significantly different between the study groups that are responsive and not responsive (P > 0.05). Since bone marrow fibrosis due to hyperparathyroidism is known as the cause of ESA resistance, the elevated level of PTH and phosphorus. Correlate negatively with Hgb level and Erythropoietin responsiveness. [19]

5. Conclusion

1) The level of hemoglobin response to erythropoietin is significantly affected by Gender of patient which is high in male compared to female.
2) Patients treated with ACEi and ARBs have lower response to EPO compared with patients whose didn't take these Drugs.
3) Inflammatory markers such as WBC and CRP have negative correlation on level EPO responsiveness.
4) Serum Serum Ferritin, Serum Phosphorus and Serum Parathyroid hormone level have negative impact.

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