Hemoglobin Fluctuation Effect on Morbidity, Mortality, and Hospitalization in Hemodialysis Patients

Essam Khedr[1], Mona Hosny[1], Amr Mohab[1] and Osama Shalaby[2]

[1] Internal Medicine Department, Faculty of Medicine, Ain Shams University, Egypt.
[2] Ministry of Health, Cairo, Egypt
abdulsalammh999990@yahoo.com

Abstract: Background: Nephrologists and other practitioners face a significant dilemma with regard to the management of anemia in patients undergoing long – term hemodialysis. Fluctuations in Hemoglobn levels (Hemoglobin cycling), may have a negative effect on patient survival and can frustrate the clinician who is trying to maintain a stable Hemoglobin value. **Patients & Methods:** 500 patients on prevalent hemodialysis were enrolled in the study. They were divided into 6 groups according to stable Hemoglobin levels and Hb variability range throughout the six months of the study: we found 12.6 % of patients in Low Hb Group 1 (stable Hb levels below 11 g / dl); 5.8 % in Target range Hb Group 2 (stable Hb levels in the range of 11 – 12 g / dl); 3 % in High Hb Group 3 (stable Hb levels above 13 g / dl); 41.6 % in LAL fluctuation Group 4 (low amplitude fluctuation between low and target range levels); 13.4 % in LAH fluctuation Group 5 (low amplitude fluctuation between target range and high levels); 23.6 % in HA fluctuation Group 6 (high amplitude fluctuation between low and high levels). **Results:** We had no mortality cases among our patients. Hospitalization rate was 40 % in High Hb Group 3; 28.6 % in Low Hb Group 1; 24.6 % in HA fluctuation Group 6; 22.4 % in LAH fluctuation Group 5; 13 % in LAL fluctuation Group 4; and 10.3 % in Target range Hb Group 2. High Hb Group 3 had a significantly higher risk for hospitalization than Target range Hb Group 2 (OR = 5.77, CI = 1.19 – 28.04, $P = 0.05$). Age and female gender were two risk factors for hospitalization in some groups of the study ($P < 0.05$).within different groups, most cases having hospitalization events showed a drop in their mean Hemoglobin levels with no specific pattern and a minority of hospitalized cases showed an increase in their Hb levels. **Conclusion:** High and low Hb levels were both associated with high hospitalization rates while fluctuating Hb level moderately exposed patients to hospitalization risk**.**

[Essam Khedr, Mona Hosny, Amr Mohab and Osama Shalaby. **Hemoglobin Fluctuation Effect on Morbidity, Mortality, and Hospitalization In Hemodialysis Patients.** *Life Sci J* 2014;11(10):1326-1340]. (ISSN:1097-8135). http://www.lifesciencesite.com. 195. doi:10.7537/marslsj111014.195.

Key Words: Hemoglobin - Morbidity – Mortality – Hospitalization – Hemodialysis.

1. Introduction

Anemia is a common complication of chronic kidney disease (CKD). The prevalence of anemia varies with the degree of renal impairment in predialysis patients with CKD, but once end – stage kidney failure occurs, all patients are eventually affected, Hemodialysis Australia and New Zealand Regisytry Annual Report, Obrador *et al.,* Hsu *et al.,* Anemia reduces physical capacity, well being, neurocognitive function, and energy level. It worsens quality of life both in predialysis and dialysis patients, Man, Anemia also induces adaptive cardiovascular mechanisms to maintain tissue oxygen supply.This leads to left ventricular hypertrophy, left ventricular dilatation, and myocardial ischemia, which are risk factors for cardiovascular disease and death, Locatelli *et al.,* a; Rao and Pereira, Hemoglobin levels in individuals with CKD fluctuate frequently above or below the recommended target levels within short periods of time. Both pharmacologic features and dosing of erythropoeisis – stimulating agents may lead to cyclic pattern of hemoglobin levels within the recommended range, Kalantar – Zadeh *et al.,* Szeto *et al.,* found that substantial variability in Hemoglobin values in pre – dialysis Chinese CKD who were not treated with rHuEPO.

Management of anemia in hemodialysis patients is complex because of the delayed and prolonged effect of ESAs on erythrocyte production, the effect of hemodialysis and hemodialysis adequacy and inflammation effect on erythrocyte survival and ESA responsiveness, hemodialysis - related blood loss, and other factors (De Meester *et al.,* McCarthy *et al.,* Several longitudinal studies revealed the complexity of maintaining stable hemoglobin levels over time. As a consequence, patients may have increased risk of hospitalization and mortality, because both low and high hemoglobin levels are associated with increased cardiovascular events and death, Kausz *et al.,* Szeto *et al.,* The duration of time that hemoglobin remains higher or lower than the target thresholds may be important to adverse outcomes. It isn`t clear whether adverse effects of hemoglobin variability are because of the therapy with erythropoiesis – stimulating agents and iron or despite such a therapy, Ebben *et al.,* Kalantar – Zadeh and Aronoff, Szeto *et al.*

Patients and Methods

This study was conducted on 500 hemodialysis patientsrandomly chosen, who were on prevalent hemodialysis and who survived the first 6 months of 2009. All patients included in the study were using High – Flux dialysers and bicarbonate based dialysate, having regular thrice weekly dialysis sessions for four hours each. Hemoglobin levels were obtained from the monthly routine laboratory tests present in the patients files, which were done according to standard methods. We have also taken out of their records: age, gender, comorbidities, and hospitalization history.

The 500 hemodialysis patients enrolled in the study were classified into the following original groups:

1 – Low Hb Group 1:(consistently stable Hemoglobin levels below 11 g / dl all through the six months of the study).

2 – Target Range Hb Group 2: (consistently stable Hemoglobin levels within target range [11 to 12 g / dl] all through the six months of the study)

3 – HighHb Group 3: (consistently stable Hemoglobin levels above 13 g / dl all through the six months of the study).

4 – LAL fluctuation Group 4 [Low amplitude fluctuation with low Hemoglobin levels]: (Hemoglobin levels fluctuating between low and target – range levels all through the six months of the study).

5 – LAH fluctuation Group 5 [Low amplitude fluctuation with high Hemoglobin levels]: (Hemoglobin levels fluctuating between target – range and high levels all through the six months of the study).

6 – HA Fluctuation Group 6 [High amplitude fluctuation]: (Hemoglobin fluctuating between low and high levels all through the six months of the study).

Each of the original six groups will be further subdivided according to hospitalization history into subgroup A (with no events such as hospitalization, co – existent disease exacerbation, new co – morbidity, and death) and subgroup B (having events such as those previously mentioned).

A co – morbid condition will be considered to be present when one of the following condition will be evident: Evidence of coronary heart disease, congestive heart failure, dysrhythmia, other cardiac disease (including valvular disease), cerebrovascular accident/transient ischemic attacks, peripheral vascular disease, chronic obstructive pulmonary disease, cancer, gastrointestinal bleeding, and hepatic disease.

We excluded from the study all patients suffering from conditions or using drugs affecting hemoglobin levels, including hemolytic states, Patients having hemoglobinopathies, and increased red blood cells breakdown due to hypersplenism.

Statistical Analysis

Data was statistically analyzed using SPSS (statistically package for social science) program version 21. Data was shown as mean, range or value and 95 % confidence interval (95 %) and frequency and

-Chi – square test done for qualitative variable analysis. Chi – square test was used to test the association of a factor with an outcome.o

- Anova test was done to compare three variables or more, ONE qualitative variable and the other two are quatitative variables normally distributed to detect mean and standard deviation. Post hoc test was done to detect the relationship between variables within groups.

- Student t –test was used for comparison between two groups means.

- ODDs ratio and its 95 % confidence intervals were calculated for the studied risk factors

-Logistic regression analysis was carried out to identify the significant risk factors associated with hospitalization.

P values were considered as follows: $P < o.o5$ [significant], $P < 0.1$ [borderline significant], $P < 0.01$ [highly significant], and $P > 0.05$ [non-significant].

3. Results

The mean age of our 500 patients included in the study was 52.7±16.67 years. 455 patients out of 500 (91 %) were male patients and 45 patients out of 500 (9 %) were female patients. 486 patients out of 500 (97.2 %) had co – morbid conditions. 98 patients out of 500 (19.6 %) were hospitalized.We didn‘ t have in our study any mortality cases all through the six months of the study.

4. Discussion

Anemia is not a disease name but a condition in which the Hb level decreased. Hb transports oxygen to each body tissue, therefore, when anemia occurs, oxygen supply to tissues is reduced. (Tsubakihara *et al.,* The recognition and treatment of anemia in patients with end – stage renal disease (ESRD) has resulted in improved quality of life, physical performance, neurocognitive function, sexual function, and reduction in left ventricular hypertrophy (Mayer *et al.,* Eschbach *et al.,* Schaefer *et al.,* Canadian Erythropoietin Study Group, Grimm *et al.,* Macdougal *et al.,* Lundin *et al.,* Marsh *et al.,* Levin, McMahon and Dawborn, Painter and Moore, Temple *et al.,* Beusterien *et al.,* Massimetti *et al.,* Metry *et al.,* Jeren – Struji ‘ c *et al.,* Moreno *et al.,* Eckardt, Wu *et al.,* Fresenius Medical Care North America (FM – CAN) instituted a company- wide anemia management quality improvement program in 1997.

Table (1): Number of patients, gender distribution, age, and co – morbidity in each of the original six groups of our study.

characteristics	Hemoglobin level fluctuation classification					
	Low	Target	High	LAL	LAH	HA
% of total						
No	63	29	15	208	67	118
%	12.6	5.8	3	41.6	13.4	23.6
Gender						
Male						
No	60	20	15	190	61	109
%	95.2	69	100	91.3	91	92.4
Female						
No	3	9	0	18	6	9
%	4.8	31	0	8.7	9	7.6
Age						
mean	51.9	56.7	44.2	52.8	53.2	52.7
SD	±15.2	±10.1	±14.4	±17.5	±19.4	±16.6
Co-morbidity						
No	60	29	15	208	67	118
%	95.2	100	100	100	100	100

Table (2): Comparison of Gender distribution among the original six groups of the study.

characteristics							χ^2	*P*-value
	Low	Target	High	LAL	LAH	HA		
Gender								
Male								
No	60	20	15	190	61	109	20.3	S
%	95.2	69	100	91.3	91	92.4		
Female								<0.05
No	3	9	0	18	6	9		
%	4.8	31	0	8.7	9	7.6		

X^2 = Chi – Square test S = signjficant

Table (3): Mean Hemoglobin levels in each of the original six groups of the study within each of the six months of the study.

	Low	Target	High	LAL	LAH	HA
First month						
Mean	9.38	11.78	13.22	10.75	12.22	11.8
±SD	1.51	0.55	0.94	1.48	0.9	2.17
Second month						
Mean	9.21	11.4	13.5	10.49	12.82	11.25
±SD	1.37	0.79	0.48	1.31	1.11	1.92
Third month						
Mean	9.1	12.01	13.22	10.4	12.74	11.17
±SD	1.35	0.56	0.89	1.28	1.05	1.70
Fourth month						
Mean	8.90	12.23	13.14	10.7	11.7	11.39
±SD	1.40	0.81	0.27	1.31	2.48	1.80
Fifth months						
Mean	8.54	11.97	13.58	10.61	12.37	11.8
±SD	1.7	0.53	0.98	1.17	0.67	1.69
Sixth month						
Mean	9.19	11.96	13.5	10.76	12.46	11.07
±SD	1.26	0.64	0.9	1.08	0.69	2.41

Table (4): Comparison of Gender distribution, age, and co – morbidity percentage in Non – Hospitalized Low Hb subgroup 1 A and Hospitalized Low Hb subgroup 1 B.

	subgroup 1 A	subgroup 1 B	test	*P*-value
% of total No %	45 71.4	18 28.6		
Gender Male No % Female No %	42 93.3 3 6.7	18 100 0 0	χ^2=1.26	>0.5
Age mean ±SD	46.6 15.3	60 18	T=7.9	<0.05
Co-morbidity No %	39 65	18 100	χ^2=7.8	<0.05

X^2 = Chi – Square test, T = student t – test

Table (5): Comparison of Non – hospitalized Low Hbsubroup 1 A and hospitalized Low Hbsubroup 1 B as regards mean Hemoglobin levels within the 6 months of the study.

	subgroup 1 A	subgroup 1 B	T	*P*-value
First month Mean ±SD	9.22 1.60	9.76 1.20	1.6	>0.05
Second month Mean ±SD	9.15 1.32	9.38 1.51	0.35	>0.05
Third month Mean ±SD	9.24 1.15	8.73 1.75	1.8	>0.05
Fourth month Mean ±SD	8.96 1.48	8.76 1.21	0.4	>0.05
Fifth months Mean ±SD	8.87 1.75	7.73 1.28	6.2	<0.05
Sixth month Mean ±SD	9.46 1.02	8.5 1.5	8.3	<0.05

T = Student t test

Table (6): Comparison of gender distribution, age, and co – morbidity percentage in Non – Hospitalized Target Range Hb subgroup 2 A and Hospitalized Target Range Hb subgroup 2 B.

	subgroup 2 A	subgroup 2 B	test	*P*-value
% of total No %	26 89.7	3 10.3		
Gender Male No % Female No %	 20 76.9 6 23.1	 0 0 3 100	χ^2 = 7.4	<0.05
Age mean ±SD	56 10.5	62 -	T= 0.8	>0.05
Co-morbidity No %	26 100	3 100	χ^2	–

X^2 = Chi – Square test, T = Student t – test

Table (7): Comparison of the mean hemoglobin levels between Non – Hospitalized Target Range Hb subgroup 2 A and Hospitalized Target Range Hb subgroup 2 B within the six months of the study.

	subgroups		T	*P*-value
	2 A	2 B		
First month Mean ±SD	11.85 0.54	11.2 0	4.2	<0.05
Second month Mean ±SD	11.52 0.82	11.1 0	0.75	>0.05
Third month Mean ±SD	12.09 0.53	11.3 0	6.4	<0.05
Fourth month Mean ±SD	12.38 0.7	10.9 0	12	<0.05
Fifth months Mean ±SD	12.01 0.5	11.6 0	1.64	>0.05
Sixth month Mean ±SD	11.9 0.65	12.5 0	2.4	>0.05

T = Student t - test

Table (8): Comparison of gender distribution, age, and co – morbidity percentage in Non – Hospitalized High Hb subgroup 3 A and Hospitalized High Hb subgroup 3 B.

	subgroup 3 A	subgroup 3 B	test	*P*-value
% of total No %	9 60	6 40		
Gender Male No % Female No %	 9 100 0 0	 6 100 0 0	-	
Age mean ±SD	39 17.1	51 3.8	T= 2.8	>0.05
Co-morbidity No %	9 100	6 100	-	

Table (9): Comparison between Non – Hospitalized High Hb subgroup 3 A and Hospitalized High Hb subgroup 3 B as regards mean hemoglobin levels in the six months of the study.

	Subgroup 3A	subgroup 3 B	T	*P*-value
First month Mean ±SD	13.16 1.23	13.3 0.21	0.067	>0.05
Second month Mean ±SD	13.56 0.35	13.4 0.65	0.41	>0.05
Third month Mean ±SD	13 0.48	12 0.60	26	<0.000
Fourth month Mean ±SD	13 0.18	13 0.32	4.1	>0.05
Fifth months Mean ±SD	13.76 1.24	13.3 0.32	0.78	>0.05
Sixth month Mean ±SD	13.23 0.78	13.9 0.98	2.1	>0.05

T = Student t – test

Table (10): Comparison of gender distribution, age, and co – morbidity percentage in Non – Hospitalized LAL fluctuation subgroup 4 A and Hospitalized LAL fluctuation subgroup 4B.

			test	*P*-value
	subgroup 4 A	subgroup 4 B		
% of total No %	181 87	27 13		
Gender Male No % Female No %	 166 91.7 15 8.3	 24 88.9 3 11.1	χ^2=0.23	>0.05
Age mean ±SD	52.1 18.2	57.2 10.5	T=1.9	>0.05
Co-morbidity No %	175 96.6	27 100	χ^2=0.92	>0.05

X^2 = Chi – Square test, T = Student t – test.

Table (11): Comparison of Non – Hospitalized LAL fluctuation subgroup 4A and Hospitalized LAL fluctuation subgroup 4B as regards mean hemoglobin levels in the six months of the study.

			T	*P*-value
	subgroup 4A	subgroup 4B		
First month Mean ±SD	10.66 1.45	10.34 1.61	5.01	>0.05
Second month Mean ±SD	10.48 1.29	10.55 1.45	0.06	>0.05
Third month Mean ±SD	10.51 1.24	9.91 1.47	5.2	<0.05
Fourth month Mean ±SD	10.79 1.22	10.07 1.68	7.2	<0.05
Fifth months Mean ±SD	10.73 1.11	9.82 1.27	15.1	<0.00
Sixth month Mean ±SD	10.79 1.09	10.6 0.98	0.73	>0.05

T = Student t – test.

Table (12): Comparison of Non – Hospitalized LAH fluctuation subgroup 5 A and Hospitalized LAH fluctuation subgroup 5 B as regards gender distribution, age, and co – morbidity percentage.

			test	*P*-value
	Subgroup 5 A	Subgroup 5 B		
% of total No %	72 77.6	15 22.4		
Gender Male No % Female No %	 52 100 0 0	 9 60 6 40	χ^2=22.8	<0.05
Age mean ±SD	53.01 10.08	50.4 16.56	T=0.5	>0.05
Co-morbidity No %	50 96.2	15 100	χ^2=0.5	>0.05

X^2 = Chi – Square test, T = Student t – test.

Table (13): Comparison of Non – Hospitalized LAH fluctuation subgroup 5A and Hospitalized LAH fluctuation subgroup 5B as regards mean hemoglobin levels in the six months of the study.

	subgroup 5 A	subgroup 5 B	T	*P*-value
First month Mean ±SD	12.35 0.76	13.2	13.2	<0.001
Second month Mean ±SD	12.82 0.67	12.84 2.04	0.002	>0.05
Third month Mean ±SD	12.7 1.001	12.9 1.26	0.41	>0.05
Fourth month Mean ±SD	12.3 1.06	9.5 1.28	19	<0.001
Fifth months Mean ±SD	12.3 0.66	12.66 0.66	2.6	>0.05
Sixth month Mean ±SD	12.42 0.67	12.6 0.73	0.74	>0.05

T = Student t – test.

Table (14): Comparison of Non – Hospitalized HA fluctuation subgroup 6A and Hospitalized HA fluctuation subgroup 6B as regards gender distribution, age, and co – morbidity percentage.

	Subgroup 6 A	Subgroup 6 B	test	*P*-value
% of total No %	89 75.4	29 24.6		
Gender Male No % Female No %	 83 93.25% 6 6.75%	 23 79% 6 21%	χ^2= 9.31	<0.05
Age mean ±SD	54.8 19.6	48.2 18.26	T= 2.5	>0.05
Co-morbidity No %	86 96.6	29 100	χ^2= 1.003	>0.05

X^2 = Chi – Square test, T = Student t – test.

Table (15): Comparison of mean hemoglobin levels between Non – Hospitalized HA fluctuation subgroup 6A and Hospitalized HA fluctuation subgroup 6B in the 6 months of the study.

	subgroup 6 A	subgroup 6 B	T	*P*-value
First month Mean ±SD	11.7 2.3	12.1 1.74	0.8	>0.05
Second month Mean ±SD	11.09 2.03	11.73 1.45	2.4	>0.05
Third month Mean ±SD	11.05 1.84	11.55 1.09	1.93	>0.05
Fourth month Mean ±SD	11.45 1.91	11.19 1.4	1.46	>0.05
Fifth months Mean ±SD	11.92 1.58	11.44 1.99	1.77	>0.05
Sixth month Mean ±SD	10.94 2.57	11.47 1.82	1.06	>0.05

T= Student t – test.

Table (16): Risk assessment (Odds Ratio) for

			total	χ^2	OR (95% CI)	*P*-value
	Group 1	Group2				
-ve	45	26	71			>0.05
+ve	18	3	21	3.745	0.28	
Total	63	29	92		(0.078-1.07	

Hospitalization between Low Hb Group 1 and Target Range Hb Group 2.

Table (17): Risk assessment (Odds Ratio) for Hospitalization between Target Range Hb Group 2 and High Hb Group 3.

			total	χ^2	OR (95% CI)	*P*-value
	Group 2	Group 3				
-ve	26	9	35	5.3	5.77	<0.05
+ve	3	6	9		(1.19-28.04	
Total	29	15	44			

Table (18) Risk assessment (Odds Ratio) for Hospitalization between Target Range Hb Group 2 and LAL fluctuation Group 4.

			total	χ^2	OR (95% CI)	-value
	Group 2	Group 4				
-ve	26	181	207	0.16	1.293	>0.05
+ve	3	27	30		(0.366-4.565	
Total	29	208	237			

Table (19): Risk assessment (Odds Ratio) for Hospitalization between Target Range Hb Group 2 and LAH fluctuation Group 5.

			total	χ^2	OR (95% CI)	*P*-value
	Group 2	Group 5				
-ve	26	52	78	1.927	2.5	>0.05
+ve	3	15	18		(0.664-9.415	
Total	29	67	96			

Table (20): Risk assement (Odds Ratio) for hospitalization between Target range Hb Group 2 and HA fluctuation Group 6.

	Groups		total	χ^2	OR (95% CI)	*P*-value
	Group 2	Group 6				
-ve	26	89	115	2.769	2.824	>0.05
+ve	3	29	32		(0.796-10.020)	
Total	29	118	147			

Table(21):Logistic regression of the risk factors causing hospitalization

Variables	B	SE	Wald	*P* - value
Group1				
Sex	21.23	23205.4	0.000	>0.05
Age	0.065	0.027	5.79	<0.05
HB	0.004	0.402	0.000	>0.05
Co-morbidity	-21.56	23205.43	0.000	>0.05
Group2				
Sex	-0.753	6925.2	0.000	>0.05
Age	5.53	282.8	0.000	>0.05
HB	-172.9	22616.8	0.000	>0.05
Group3				
Age	0.074	0.045	2.711	>0.05
HB	-2.201	2.017	1.19	>0.05
Group4				
Sex	0.382	0.682	0.313	>0.05
Age	0.014	0.013	1.185	>0.05
HB	-0.555	0.29	3.66	>0.05
Co-morbidity	19.069	16389.8	0.000	>0.05
Group5				
Sex	22.94	15483.7	0.000	>0.05
Age	-0.038	0.042	0.805	>0.05
HB	-1.588	0.862	3.396	>0.05
Co-morbidity	20.356	28420.7	0.000	>0.05
Group 6				
Sex	1.918	0.836	5.260	<0.05
Age	-0.011	0.013	0.734	>0.05
HB	0.438	0.283	2.389	>0.05
Co-morbidity	19.5	23205	0.000	>0.05

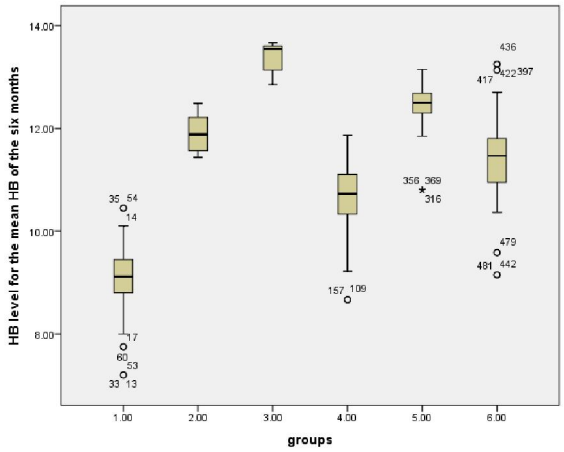

Figure (1): shows mean Hemoglobin level within each of the six groups of the study throughout the six months of the months.

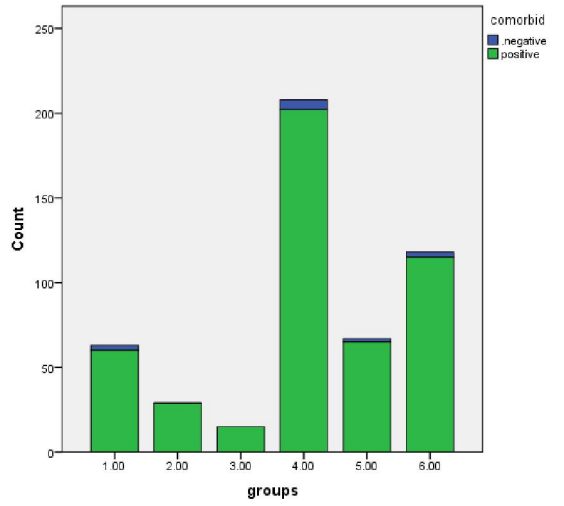

Figure (2): Shows the ratio of presence and absence of co-morbidity within each of the six groups of the study.

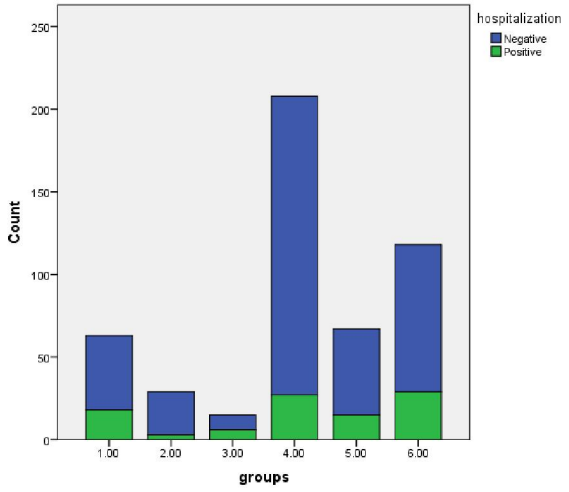

Figure (3): Shows the ratio of presence or absence of hospitalization within each of the six groups of the study.

It has since been observed that patients show fluctuations in Hemoglobin levels above and below the target range when followed up over time (Lacson *et al.,* Frequent changes of guidelines [Afssaps, European Medicines Agency (EMEA, Public statement; Locatelli *et al.,* together with multitude of reference data and the lack of harmony between different guidelines, create confusion and hinder clinical adherence (Chan *et al.,* The National Kidney Foundation - Kidney Outcomes Quality Initiative (K / DOQI) Clinical Practice Guidelines recommend a target Hemoglobin level range of 11 to 12 g / dl (Hct 33 % to 36 %), for patients with ESRD (National Kidney Foundation, National Kidney Foundation, Lacson *et al.,* Tsubakihara *et al.,* The revised European Best Practice Guidelines (EBPGs), May 2004), reported that maintaining Hemoglobinemia higher than 14 g / dl is undesirable (Locatelli *et al.,* b; De Meester *et al.,* According to Lacson *et al.,* three main factors have contributed to Hemoglobin level variability: (1) Variability in Hb / Hct target(s) and action threshold (s) (2) Variability in anemia management penetration and effectiveness (intra-individual variability), and (3) variability in individual patient responses to erythropoietin (EPO) and intravenous Iron (either biological or co –morbidity related), also being approved by Owen and Lowrie, Besarab *et al.,* Tonelli *et al.,* InterindividualHb values variability is due to multiple factors, including genetics (level of fetal Hemoglobin or potential racial differences), environmental (climate or altitude), assay or sampling differences (method or timing of measurement), and other related physiological determinants (lung function / diffusion capacity). Other contributors to this variability include seasonal variation, sampling methods, comorbid conditions such as nutritional status and other co-existing diseases, concomitant medication, clinical status (eg. Gastrointestinal bleeding, marrow fibrosis, hyperparathyroidism and inflammation), reimbursement policies and quality assurance policies (Maes and De Meyer, National Kidney Foundation, Tonelli *et al.,* Vasquez and Vinella, Berns *et al.,* Fishbane and Berns, Fishbane and Berns, De Meester *et al.,* Other causes of renal anemia include uremic toxin or endotoxin, aberrant red cell kinetics, shorter life span of red blood cells, and residual blood in the hemodialysis circuit of HD patients (Tsubakihara *et al.,* Szeto *et al.,* Also Hb levels in HD patients vary depending on hemoconcentration due to fluid removal caused by HD (Berns, K / DOQI, Tsubakihara *et al.,* Race may affect the relationship between Epoetin dose and Hb concentration and mortality and hospitalization (Robinson *et al.,* Collins *et al.,* Lacson *et al.,* Servilla et al., Tsubakihara *et al.,* in their study on Japanese hemodialysis patients, have reported that

the level for diagnosing anemia has been set at <13.5 g / dl in males and < 11.5 g / dl in females.

With growing life expectancy and better quality of the treatment, the dialysis population becomes older and has more comorbidities, resulting in a high hospitalization rate. There is evidence that good adherence to the treatment can reduce hospitalization risk in HD patients (Saran *et al.,* Vaiciuniiene *et al.,* Optimizing the management of anemia in CKD patients at high risk of cardiovascular events, may have the potential to substantially reduce morbidity due to cardiovascular disease (Levin *et al.,* Chan *et al.,* in their study showed that the use of ESA reduced hospitalization significantly.

In our study, the group having the greatest number of patients was LAL fluctuation Group 4, comprising 41.6 % of the study population, followed by HA fluctuation Group 6 comprising 23.6 % of the patients, then LAH fluctuation Group 5 comprising 13.4 % of the patients, with these three fluctuating groups constituting altogether (78.6 %) of the study population, which is the majority of patients enrolled in our study.

Fishbane and Berns, reported that Hemoglobin cycling has occurred in 90 % of patients of their study, Lacson *et al.,* reported important fluctuations in 95 % of studied patients over a period of 6 months, Van der Putten *et al.,* reported Hb cycling in 100 % of studied patients over one – year period.This was also confirmed by Bellizzi *et al.,* Berns *et al.,* Kalantar – Zadeh *et al.,* Patel *et al.,* Kainz *et al.,* The remaining three groups having more stable Hemoglobin levels constituted the least proportion of participants in our study (21.4 %), with Low Hb Group 1 constituting 12.6 % of the study population, Target Hb Group 2 5.8 %, and High Hb Group 3 3 %.

The results of the statistical surveys by the Japanese Society for Dialysis Therapy, at the end of 2005 and 2006, revealed that approximately 40 % of HD patients still had Hb levels less than 10 g / dl (Statistical Survey Committee of the Japanese Society for Dialysis Therapy, Statistical Survey Committee of the Japanese Society for Dialysis Therapy, Tsubakihara *et al.,* and the Dialysis Outcomes and Practice Patterns Study (DOPPS) reported that in 2012 nearly 20 % of long – term hemodialysis patients had Hemoglobin levels less than 10 g / dl (Ann Arbor Research Collaborative for Health, Brunelli *et al.,* McCarthy *et al.,* Male gender constituted 100 % of High Hb Group 3 and more than 90 % of each of Low Hb Group1, LAL fluctuation Group 4, LAH fluctuation Group 5, and HA fluctuation Group 6. Male gender constituted only 69 % of patients participating in Target HbGroup 2, which had the highest percent of female patients (31 %) among the six studied groups. This discrepancy in gender distribution has led to a significant difference ($P < 0.05$) mainly between Target Hb Group 2 and to a lesser extent between High Hb Group 3 and each of the other 4 groups. This may imply that there may be a connection between male gender and Hb level fluctuation in patients on Hemodialysis and that the more the contribution of female gender the more we are directed towards stable Hemoglobin levels within the studied Hemodialysis group.

In Non – hospitalized Target range Hb subgroup 2 A, male gender constituted 76.9 % and female gender constituted 23.1 %, while in Hospitalized Target range subgroup 2 B, female constituted 100 % of the hospitalized patients ($P <0.05$), which strongly relates hospitalization to female gender inspite of having Target range Hb and also inspite that the majority of patients within this group were of male gender. This remark was repeated again. Non – hospitalized LAH fluctuation subgroup 5 A was formed entirely of male patients (100 %), while Hospitalized LAH fluctuation subgroup 5 B was formed of male patients (60 %) and female patients (40 %), given that male gender constituted more than 90 % of the original LAH fluctuation Group 5. Nearly the same situation was repeated on comparing HA fluctuation subgroup 6A and HA fluctuation subgroup 6B, having 21% of hospitalized patients females, although more than 90 % of patients of the original HA fluctuation Group 6 were of male gender. Logistic regression has showed that in HA fluctuation Group 6, gender was an effective risk factor in predisposing this group of patients to hospitalization ($P < 0.05$).

Vaciuniene *et al.,* in their study showed in a Univariate analysis and Cox Regression analysis an association between increased hospitalization risk and female gender.

In all other subgroups, there was no significant difference as regards gender between Hospitalized and Non – hospitalized subgroups of patients, as male gender predominated all these groups.

At beginning of patients enrollment in our study, age was the highest in Target Hb Group 2 and the least in High Hb Group 3, having non – significant differences ($P > 0.05$) as compared together and to the remaining groups. Logistic regression analysis showed that in Low Hb Group 1, age was the effective risk factor in predisposing this group of patients to Hospitalization ($P < 0.05$), and this confirms our findings. This means that Hemodialysis patients having stable low Hemoglobin level associated with mean age above the fifth decade were more prone to Hospitalization than other patients‘ groups with different Hemogllobin levels, inspite that some of the Hospitalized subgroups had this same range of age. Age was significantly higher in Hospitalized Low Hb

subgroup 1 B as compared to Non – hospitalized Low Hbsubgroup 1 A ($P < 0.05$).

Tsubakihara *et al.,* in their study on Japanese hemodialysis patients, have stated that in both men and women, hemoglobin levels decreased along with an increase in age.

Vaciuniene *et al.,* reported an association between older patients' age and increased hospitalization risk, in hemodialysis patients.

Comorbidities existed in 95.2 % of Low Hb Group 1, while it was present in 100 % of all the other five groups. This may imply that stable low Hemoglobin level in HD patients seemed to protect this group of patients from the risk of co- morbidities, but in a statistically non – significant way ($P > 0.05$).

Hospitalized Low Hb subgroup 1B had a significantly higher co-morbidity percent than Non – hospitalized Low Hb subgroup 1A ($P < 0.05$). Non – hospitalized Low Hb subgroup 1A had the least percent of co – morbidity among all subgroups (65 %), while in all other groups co – morbidity existed in more than 90 % of their patients.

Vaciuniene *et al.,* in their study found an increased risk of hospitalization in patients with worse disability and higher co – morbid conditions.

Hyporesponsiveness to epoetin administration may reflect co – existing comorbidity. (Fishbane and Berns, Ebben *et al.,* Adamson, Servilla *et al.,* Lopez – Gamez *et al.,* reported greater co – morbidity in patients with severe anemia.

The highest hospitalization percent was present in High Hb Group 3 (40%), followed by Low Hb Group 1 (28.6%) [inspite of showing a slightly less co – morbidity percent than the other five groups], both of them being considered having a relatively stable Hemoglobin levels throughout the study. The least hospitalization percent existed in LAL fluctuation Group 4 (13%) as well as in Target range Hb Group 2 (10.3%), which means that having target range Hb or a fluctuating Hblevel between low and target range seemed to protect HD patients from hospitalization risk. Intermediate hospitalization percent was found in both HA fluctuation Group 6 (24.6%) and LAH fluctuation Group 5 (22.4%), which means that having Hemoglobin level fluctuation doesn 't necessary mean being at increased risk of hospitalization. Also High Hb Group 3 having the highest Hospitalization percent, had a statistically significant higher risk for Hospitalization (5.7 times) than Target range Hb Group 2 (OR=5.77, CI=1.19–28.05, P=0.05). When comparing each of the remaining four patient's groups (Low Hb Group 1 patients, LAL fluctuation Group 4 patients, LAH fluctuation Group 5 patients, and HA fluctuation Group 6 patients) to Target range Hb Group 2 patients, no statistically significant difference in predisposition to hospitalization risk was found ($P>0.05$).

Hospitalized subgroups (including Hospitalized Target range Hemoglobin group), showed Hospitalization was linked to a more or less statistically significant drop in Hemoglobin levels Hospitalized subgroups as compared to Non – hospitalized groups mean Hemoglobin levels, to their own mean levels all through the study, and to mean Hemoglobin levels of their original groups. This was apparent in different months of the study according to each group. An exception to this idea existed in HAfluctuation subgroup 6Bpatients, where we found a significant increase or decrease in Hb levels away from their own mean Hemoglobiin levels, from Non – hospitalized patients' Hemoglobin mean levels, or from the mean Hemoglobin levels of their originalgroup throughout the study.There was no specific patterns as regards Hemoglobin level decrease or increase in the different Hospitalized subgroups of the study.

Despite receiving greater Epoetin doses for attaining similar hemoglobin levels, African – Americans have better health outcomes, lower mortality, and hospitalization rates and survive longer on hemodialysis therapy, as compared to White patients, inspite of having lower Hemoglobin levels (Robinson *et al.,* Collins *et al.,* Lacson *et al.,* and Servilla *et al.,* Understanding the physiologic characteristics of hematopoiesis should cause one to appreciate the time required for the body to react to changing EPO stimulus, and the reaction time varies widely among patients with ESRD, ranging from a few weeks to a few months (Lacson *et al.,* National Kidney Foundation, Vaciuniene *et al.,* in their study reported a highly significant inverse association of Hemoglobin level with hospitalization risk in a Cox – Regression analysis ($P< 0.0001$).Thijssen *et al.,* found in a Logistic Regression analysis an inverse highly significant relationship between Hemoglobin level and mortality ($P<0.001$, OR=0.818, CI = 0.724 – 0.924).

Servilla *et al.,* reported that the hazard for all cause and cardiovascular mortality and for hospitalization increased for hemoglobin concentration less than the referent Hemoglobin level of 11 to 11.9 g / dl. A similar trend was observed for non – cardiovascular mortality, except that the hazard increase was statistically significant for only Hemoglobin level less than 10 g // dl as was stated also by Kainz *et al.,* It has also been reported that with Hb variability (Hemoglobin cycling), particularly when Hb levels abruptly decrease, cardiovascular complications occur most frequently. This was confirmed in the CHOIR study conducted on Non – Dialysis patients with chronic kidney disease and in the FDA review, which revealed that abrupt decrease

in Hb levels was more serious than abrupt increase and that Hb cycling (variability) is identified as a large problem (Division of Medical Imaging and Hematology Products and Office of Surveillance and Epidemiology (OSE) of the FDA, Fishbane and Berns, Tsubakihara *et al.,* Also, greater Hemoglobin variability (high amplitude swings), has been suggested to be associated with comorbidity, intercurrent illness and a higher mortality in dialysis patients (Ebben *et al.,* Boudville *et al.,* Gilberston *et al.,* Kainz *et al.,* Szeto *et al.,* Rottembourg *et al.,* Brunelli *et al.,* found that Hemoglobin variability was not associated with all – cause mortality in incident Hemodialysis patients.

In the NHCT study in HD patients with concomitant cardiovascular diseases, it was reported that the risk of new onset of concomitant cardiovascular disease remains unchanged, if the increase in Hb levels does not exceed 0.55 g / dl / week (Division of Medical Imaging and Hematology Products and Office of Surveillance and Epidemiology (OSE) of the FDA, Tsubakihara *et al.,* Yang *et al.,* and Kainz *et al.,* reported that Hb variability was associated with an increased mortality if it is > 1 g / dl

The Normal Hematocrit Study, a randomized controlled trial, showed that complete correction of anemia in Hemodialysis patients with cardiac disease was not beneficial (Lacson *et al.,* Besarab *et al.,* Servilla *et al.,* In the CHOIR study, the guidelines established an upper limit of 12 g / dl for patients with serious cardiovascular disease, diabetic patients, or patients for whom the attending physician determines high Hemoglobin levels would not be appropriate (Locatelli *et al.,* b; K/DOQI, Singh and Fishbane, Tsubakihara *et al.,* De Meester *et al.,* Food and Drug Administration, Phrommintikul *et al.,* have reported increased risk for shunt occlusion believed to be associated with normalization of Hb levels.

The 2001 Annual Report of the Center for Medicare and Medicaid Services ESRD Clinical Performance Measures (CMS CPM) Project, showed that there was a progressive increase in the number of patients in Hemoglobin levels greater than 12 g / dl and that this was a consistent finding from 1997 through 2000.(Health care Financing Administration: 2001 Annual Report; Lacson *et al.,* Observational studies have suggested that mortality may be decreased in patients with higher Hemoglobin concentration (Regidor *et al.,* Lacson *et al.,* Ofsthun *et al.,* Li and Collins, Zhang *et al.,* Rao and Pereira, Robinson *et al.,* Servilla *et al.,* Collins *et al.,* and Lacson *et al.,* have reported that a Hemoglobin level greater than 11 g / dl or Hematocrit greater than 33 % was associated with 7 % to 22 % lower risk for hospitalization.

The Correction of Hemoglobin and Outcomes in Renal Insufficiency
(CHOIR) trial and the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial, conducted in patients with stages 3 and 4 chronic kidney disease, showed worse outcome when targeting greater Hemoglobin concentration (Drueke *et al.,* Singh *et al.,* Servilla *et al.,* In the CHOIR study, almost one third one – third of participants (having high hemoglobin level), had a history of myocardial infarction, stroke, undergoing of coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI) or limb amputation (Singh *et al.,* Tsubakihara *et al.,* These observations were confirmed in the Intention to Treat (ITT) analysis conducted on hemodialysis patients with Hb target of 13.5 g / dl (Dreuke *et al.,* Tsubakihara *et al.).*

Conclusion

Extremes of Hemoglobin levels as well as large Hemoglobin level swings are associated with increased hospitalization rates.

Acknowledgement

We would like to thank doctor Mohamed Sherif Hamady (Consultant Internal Medicine, King Fahd Hospital, Al Madina Al Monawara, KSA) for his precious effort in this work.

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10/21/2014