

CHAPTER 7: ANAEMIA MANAGEMENT

Summary

Target Haemoglobin

- The mean and median haemoglobin for HD and CAPD patients range from 9.3 to 10g/dl.
- There is trend towards continued improvement in the level of haemoglobin achieved in all centres.
- Less than 50% of patients on haemodialysis or peritoneal dialysis has haemoglobin of >10g/dl.
- The haemoglobin level achieved in haemodialysis patients is similar to peritoneal dialysis

Factors Influencing Haemoglobin; Ferritin, Erythropoietin dosing.

- The majority of patients that were on erythropoietin have adequate iron stores as measured by the serum ferritin. The mean serum ferritin was 400 to 500 mcg/l.
- Most patients had transferrin saturation greater than 20% .
- Parenteral iron was rarely used in most dialysis units.
- The use of erythropoietin was steadily increasing over the years for both haemodialysis and CAPD patients, but the doses were lower.
- The majority of patients (>80%) were on 4000 units or less per week of erythropoietin.

Haemoglobin and Mortality

- In HD, the mortality was least in patients with haemoglobin of 10-12 gm/dl and highest with haemoglobin less than 8 gm/dl.
- In CAPD, there was no significant difference in mortality between the various haemoglobin groups, except in the less than 8g/dl group, where mortality was the highest.
- There was no survival advantage for dialysis patients with haemoglobin > 12 gm/dl.
- The risk of death was greater in HD patients compared to CAPD patients with a haemoglobin of less than 8 gm/dl.
- For all dialysis patients (HD & CAPD combined), significant difference was found in mortality between patients with haemoglobin < 10 g/dl compared to those with haemoglobin 10 to <11g/dl. There was however no difference in mortality in patients with haemoglobin 11 to <12g/dl or above

7.1 Target Haemoglobin

Introduction

A pivotal area in the management of renal patients on dialysis is the management of anaemia. Anaemia if uncorrected results in tiredness, lethargy, sleep disturbances, decreased exercise capacity, sexual dysfunction, poorer quality of life, left ventricular hypertrophy, disturbed brain function and other consequences including increased morbidity and mortality.

Recombinant human erythropoietin (RHuEpo) has been available since 1985 and used in Malaysia since 1989. This has increased haemoglobin concentration. There is however, more scope for improvement.

The target haemoglobin level as recommended by various authorities are;

European Best practice guidelines recommends that the target haemoglobin is that >85% of the patient population should have a haemoglobin concentration of >11g/dl. [1]

The K/DOQI guidelines states the target range for haemoglobin should be 11 – 12 g/dl. [2]

The UK Renal Association recommends that the target haemoglobin is 10g/dl and 85% of the dialysis population should reach this target after 6 months on dialysis. [3]

The Malaysian Dialysis consensus states that patients with chronic renal failure should achieve a target haemoglobin of 10g/dl within 6 months of being seen by a nephrologist, unless there is a specific reason. [unpublished]

Results

Over the last 10 years from 1993 to 2002, the mean and median haemoglobin level achieved in haemodialysis (HD) and peritoneal dialysis (PD) patients have improved. The percentage of patients with haemoglobin less than 10g/dl has decreased with a corresponding increase in patient with haemoglobin concentration of 10 to 12 g/dl and haemoglobin greater than 12g/dl. This finding was noted both in patients with and without erythropoietin treatment. (Tables 7.1.1 to 7.1.4, Figures 7.1.1 to 7.1.4) The haemoglobin level achieved in haemodialysis patients was comparable with peritoneal dialysis patients.

This trend, though encouraging is still far short of the target of 85% with haemoglobin greater than 11 g/dl recommended by the UK Renal Association and European Best Practice guidelines and is even short of the local unpublished recommendations. In the European Survey of Anaemia Management haemoglobin reached target levels of 11g/dl. in only 53.6% of patients. In the UK Renal Registry, 81% of HD patients and 86% of PD patients achieved the haemoglobin target of 10g/dl. [4]

Table 7.1.1 Distribution of Haemoglobin Concentration without Erythropoietin, all HD patients, 1993 – 2002

Year	No. of subjects	Mean	Std Dev	Median	LQ	UQ	% Patients <10 g/dL	% Patients ≥10 & ≤12 g/dL	% Patients >12 g/dL
1993	639	8.4	2	8.1	7.0	9.6	80	15	5
1994	784	8.6	1.9	8.4	7.1	9.7	79	15	6
1995	809	8.9	1.9	8.6	7.4	10.0	74	18	8
1996	812	9.1	1.9	8.9	7.7	10.3	71	21	8
1997	896	9.3	1.9	9	8.0	10.5	68	23	9
1998	1119	9.1	1.9	8.9	7.8	10.3	70	21	8
1999	1401	9.1	1.9	8.9	7.8	10.3	70	23	7
2000	1754	9.4	2.1	9.1	7.9	10.6	67	23	11
2001	1809	9.4	1.9	9.3	8.0	10.6	63	27	10
2002	1710	9.6	2.1	9.4	8.1	10.9	61	26	13

Table 7.1.2 Distribution of Haemoglobin Concentration on Erythropoietin, HD patients, 1993 – 2002

Year	No. of subjects	Mean	Std Dev	Median	LQ	UQ	% Patients <10 g/dL	% Patients ≥10 & ≤12 g/dL	% Patients >12 g/dL
1993	57	7.7	1.5	7.6	6.6	8.8	91	9	0
1994	149	7.8	1.4	7.6	6.8	8.8	93	7	0
1995	207	8.7	1.5	8.9	7.6	9.8	81	18	1
1996	400	8.7	1.6	8.5	7.5	9.6	81	17	3
1997	775	8.9	1.6	8.9	7.8	9.9	75	22	2
1998	972	9.1	1.6	9.1	7.9	10.2	71	27	2
1999	1504	9.1	1.5	9.1	8.1	10.2	71	27	3
2000	2336	9.4	1.7	9.4	8.3	10.5	64	30	5
2001	3051	9.4	1.6	9.4	8.3	10.5	64	31	5
2002	3617	9.5	1.7	9.5	8.4	10.6	62	31	7

Figure 7.1.1 Mean of haemoglobin Concentration without Erythropoietin (rHuEpo), HD patients, 1993-2002

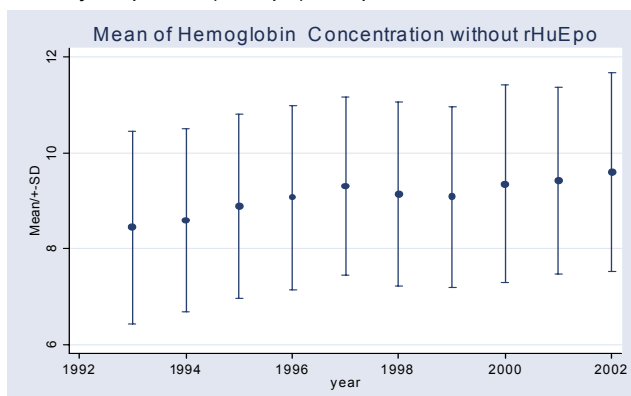


Figure 7.1.2 Mean of haemoglobin Concentration on Erythropoietin, HD patients, 1993-2002

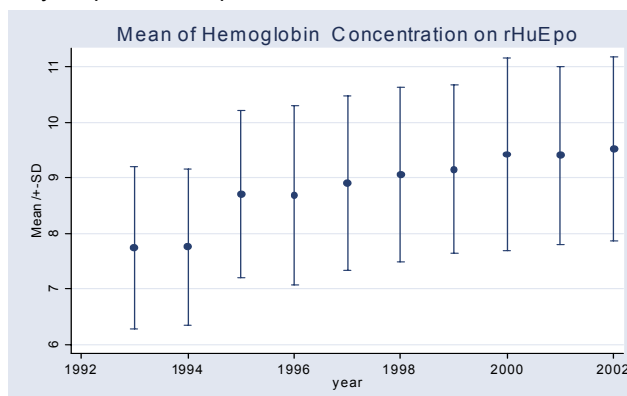
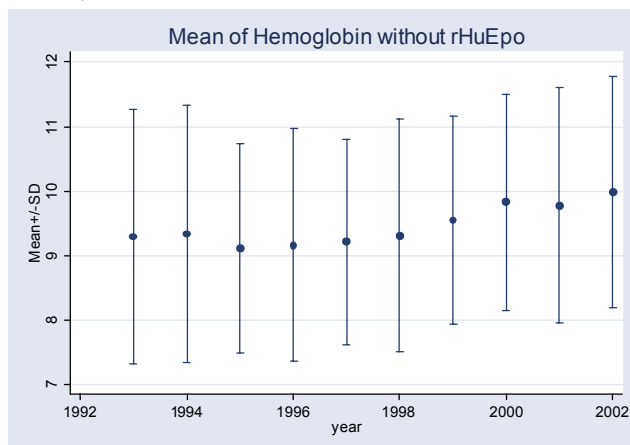
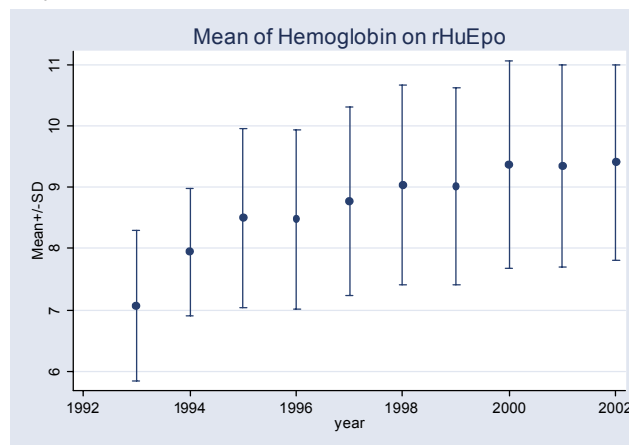


Table 7.1.3 Distribution of Haemoglobin concentration without Erythropoietin, CAPD patients, 1993 - 2002

Year	No of subjects	Mean	Std Dev	Median	LQ	UQ	% Patients <10 g/dL	% Patients ≥10 & ≤12 g/dL	% Patients >12 g/dL
1993	91	9.3	2.0	9.1	7.9	10.2	71	20	9
1994	99	9.3	2.0	9.1	7.8	10.3	69	21	10
1995	209	9.1	1.6	8.9	8	10.1	73	22	5
1996	274	9.2	1.8	9.1	7.8	10.2	72	22	6
1997	298	9.2	1.6	9.1	8.1	10.3	71	24	5
1998	301	9.3	1.8	9.2	8.1	10.3	68	26	6
1999	336	9.5	1.6	9.5	8.4	10.5	64	29	7
2000	342	9.8	1.7	9.7	8.7	10.9	57	34	8
2001	405	9.8	1.8	9.7	8.6	10.7	58	33	9
2002	433	10	1.8	9.9	8.8	11	53	36	10

Table 7.1.4 Distribution of Haemoglobin concentration on Erythropoietin, CAPD patients, 1993– 2002

Year	No of subjects	Mean	Std Dev	Median	LQ	UQ	% Patients <10 g/dL	% Patients ≥10 & ≤12 g/dL	% Patients >12 g/dL
1993	8	7.1	1.2	6.7	6.2	8.3	100	0	0
1994	20	7.9	1.0	8.0	7.0	9.0	100	0	0
1995	45	8.5	1.5	8.4	7.5	9.3	89	9	2
1996	92	8.5	1.5	8.5	7.3	9.4	86	13	1
1997	175	8.8	1.5	8.6	7.7	9.8	79	18	2
1998	238	9.0	1.6	8.8	8.0	10.1	74	21	5
1999	262	9.0	1.6	8.9	7.9	10.2	73	24	4
2000	299	9.4	1.7	9.2	8.1	10.6	65	29	6
2001	345	9.3	1.6	9.4	8.2	10.5	65	30	6
2002	431	9.4	1.6	9.3	8.4	10.4	67	27	6

Figure 7.1.3 Mean of haemoglobin Concentration without Erythropoietin, CAPD patients, 1993-2002**Figure 7.1.4** Mean of haemoglobin Concentration on Erythropoietin, CAPD patients, 1993-2002

7.2 Factors Influencing Haemoglobin – Iron Status and Erythropoietin Dosing

Introduction

Proper iron management is of paramount importance to ensure optimum response to erythropoietin. There are various markers/parameters employed to indicate the iron status in patients. These are serum iron, ferritin, total iron binding capacity (TIBC), transferrin saturation (TSAT) and percentage hypochromic red blood cells. The common parameters used locally are serum iron, ferritin and transferrin saturation.

The European Best Practice Guidelines (EBPG) recommends the following:

“serum ferritin > 100 mcg/l, TSAT > 20%, percentage of hypochromic cells < 10%. The optimum levels are ferritin 200-500 mcg/l, percentage of hypochromic cells < 2-5% and TSAT 30-40%”. [1]

The K/DOQI guideline also recommends that target serum ferritin should be > 100 mcg/l. [2]

The UK Renal Association Standard recommend a serum ferritin > 100 mcg/l and <10% hypochromic red cells (transferrin saturation > 20%) ; serum ferritin should not consistently exceed 800 mcg/l. [3]

Findings from the European Survey of Anemia Management (ESAM) were as follows;

- The mean erythropoietin dose administered was 107.8 units/kg/week.
- Intravenous erythropoietin was used more often than subcutaneous erythropoietin for HD patients
- Two thirds of patients on intravenous erythropoietin had 3 injections per week compared to one quarter subcutaneous erythropoietin once per week and another third on twice weekly injections. [4]

For effective use and benefit of erythropoietin, guidelines on its use should be adhered to. Certain patient characteristics however determine erythropoietin dose requirements. [5] Children and young adults, black race, lower residual renal function, poor nutritional status, longer duration on HD, diabetes, failed kidney transplants, pregnancy and haemoglobinopathy require higher erythropoietin dose. On the other hand, the elderly, white race, higher residual renal function, good nutritional status, recently started on HD, non-diabetics, no history of previous transplant, polycystic kidney disease and hepatitis have been associated with lower erythropoietin requirement.

Results

Over the last 10 years, the percentage of patients having serum ferritin more than 100 mcg/l has been between 80 -90 %. The mean serum ferritin for all patients on dialysis both with and without erythropoietin therapy has been rising and has mostly been greater than 400 µg/L. (Table 7.2.3, 7.2.4, 7.2.7, 7.2.8). The majority of patients (> 90%) were on oral iron supplements. Only 2 to 7% of patients were exposed to parenteral iron. However of late there has been an increased use of parenteral iron most noticeable in the government haemodialysis centers. Erythropoietin use increased from 8% in 1993 to 67% in 2002 in HD patients compared to a smaller increase of 8 to 49% in CAPD patients over the corresponding period to achieve similar haemoglobin levels. (Tables 7.2.1 & 7.2.5). The median dose of erythropoietin for both HD and CAPD patients was 2000-4000 units of erythropoietin per week.

The percentage of patients on higher doses of erythropoietin has been steadily decreasing over the years with a corresponding increase in the percentage of patients on lower doses of erythropoietin– of less than 4000 units /week. The dose of erythropoietin required for patients on CAPD and the trend in erythropoietin dosage over the years were similar to patients on HD. (Tables 7.2.2 and 7.2.6)

Table 7.2.1 Treatment for Anemia, HD patients

Year	Number	% on Erythropoietin	% received blood transfusion	% on oral Iron	% received parenteral Iron
1993	718	8	20	0	0
1994	963	16	10	94	1
1995	1034	20	9	95	1
1996	1256	33	8	92	3
1997	1697	46	8	92	4
1998	2142	46	13	92	4
1999	2998	51	15	90	5
2000	4395	56	15	88	5
2001	5196	62	13	88	5
2002	5674	67	11	86	7

Table 7.2.2 Distribution of Erythropoietin dose per week, HD patients 1994-2002

Year	1994	1995	1996	1997
No. of patients	147	202	396	751
% - 2000 u/week	13	9	9	21
% 2-4000 u/week	56	67	67	61
% 4-6000 u/week	9	6	6	5
% 6-8000 u/week	19	16	16	11
% 8-12000 u/week	3	1	2	2
% >12000 u/week	1	0	0	0

Year	1998	1999	2000	2001	2002
No. of Patients	920	1474	2365	3134	3686
% - 2000 u/week	27	33	35	34	33
% 2-4000 u/week	54	52	51	50	51
% 4-6000 u/week	6	5	6	7	8
% 6-8000 u/week	10	9	6	6	6
% 8-12000 u/week	2	1	2	2	2
% >12000 u/week	0	0	0	0	0

In spite of good mean and median serum ferritin and transferrin saturation, and the greater use of erythropoietin in both the CAPD and HD patients, less than 50% of dialysis patients achieved the recommended target haemoglobin of 10g/dl. This could be due to various factors. The change of erythropoietin dosage over the years probably reflected the clinicians' confidence and experience

in using erythropoietin. Perhaps in the early years only patients with persistently severe anaemia (haemoglobin <6g/dl) were started on erythropoietin. It is interesting to note that with the decreasing dose of erythropoietin being used albeit in larger proportion of patients, the level of haemoglobin has steadily increased over the years as noted earlier.

Table 7.2.3 Distribution of Serum Ferritin without Erythropoietin, HD patients, 1994 –2002

Year	No of subjects	Mean	Std Dev	Median	LQ	UQ	% Patients ≥ 100 ug/L
1994	15	256.4	279.2	189	36.5	274	67
1995	42	293.3	249.5	199.5	135	401	79
1996	63	310.3	286.8	218	82	492	71
1997	280	493.1	349.3	435.5	162.5	850.5	86
1998	224	430.8	383.2	297.5	128.4	636.5	80
1999	337	517.9	424.3	402.8	162.8	809.5	86
2000	571	487.5	416.8	363.2	152.5	741	83
2001	758	537.6	453.9	383.5	172	828	87
2002	755	518.9	441.1	376	170	781	85

Table 7.2.4 Distribution of Serum Ferritin on Erythropoietin, HD patients, 1994 – 2002

Year	No of subjects	Mean	Std Dev	Median	LQ	UQ	% Patients ≥ 100 ug/L
1994	9	286.6	288.3	210	148.5	295.5	78
1995	97	526.4	321.3	500	243	816	94
1996	156	494.9	348.7	397.5	173.5	856.3	89
1997	472	543.3	346.7	496.3	219	966.8	90
1998	329	549.8	381.8	477	249.5	803	91
1999	587	561.2	418.6	453	225	830	93
2000	1177	588.5	456.4	476	219	863	91
2001	1639	598.1	444.3	491.3	236	899	91
2002	2071	601	461	475.3	236	891	92

Figure 7.2.3 Mean of Serum Ferritin without Erythropoietin, HD patients, 1993-2002

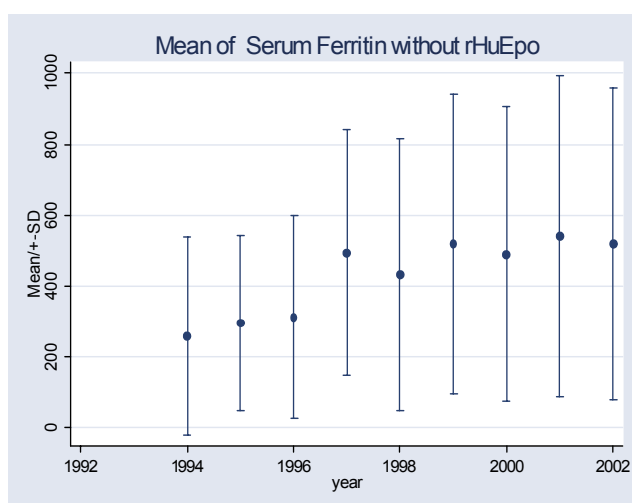


Figure 7.2.4 Mean of Serum Ferritin on Erythropoietin, HD patients, 1993-2002

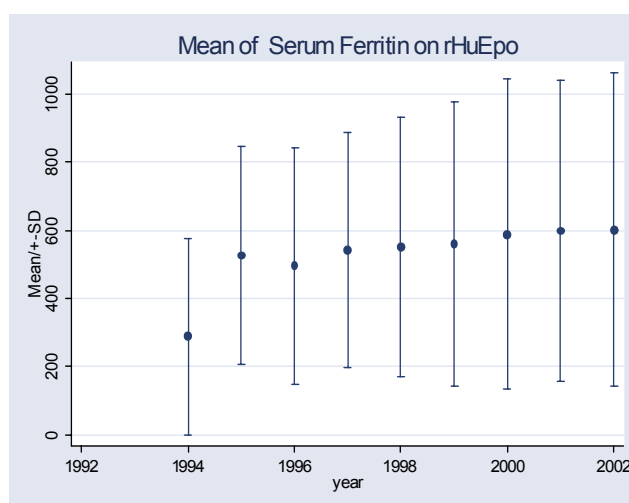


Table 7.2.5 Treatment for Anaemia, CAPD patients

Year	Number	% on Erythropoietin	% received blood transfusion	% on oral Iron	% received parenteral Iron
1993	102	8	13	0	0
1994	122	17	7	97	1
1995	256	18	9	98	1
1996	371	25	8	97	1
1997	477	37	12	96	3
1998	541	44	16	96	3
1999	610	44	14	94	0
2000	662	46	11	92	4
2001	781	45	11	91	2
2002	889	49	11	93	2

Table 7.2.6 Distribution of Erythropoietin dose per week, CAPD patients 1994-2002

Year	1994	1995	1996	1997
No of patients	20	45	86	170
% - 2000 u/week	30	31	28	19
% 2-4000 u/week	65	62	63	66
% 4-6000 u/week	0	0	0	2
% 6-8000 u/week	5	4	7	11
% 8-12000 u/week	0	2	2	1
% >12000 u/week	0	0	0	0

Year	1998	1999	2000	2001	2002
No of patients	225	259	287	336	427
% - 2000 u/week	25	35	31	32	30
% 2-4000 u/week	56	50	53	51	52
% 4-6000 u/week	6	3	5	7	6
% 6-8000 u/week	12	9	9	7	10
% 8-12000 u/week	1	2	3	2	3
% >12000 u/week	0	0	0	0	0

Table 7.2.7 Distribution of Serum Ferritin without Erythropoietin, CAPD patients, 1994 – 2002

Year	No of subjects	Mean	Std Dev	Median	LQ	UQ	% Patients ≥ 100 ug/L
1994	1	164.5	0	164.5	164.5	164.5	100
1995	4	532.3	405.9	548.5	181.5	883	100
1996	40	403.6	302.3	288.5	188.5	622.5	88
1997	133	469	333.5	392	198	718	88
1998	92	492.4	368.3	405	208.2	687.5	87
1999	124	553.7	400.1	499.3	255.3	686.8	94
2000	144	505.9	433.8	420	152.3	675.5	88
2001	223	543.8	417.5	440	216.9	754	91
2002	235	635	492.2	510	225	938	93

Table 7.2.8 Distribution of Serum Ferritin on Erythropoietin, CAPD patients, 1994 – 2002

Year	No of subjects	Mean	Std Dev	Median	LQ	UQ	% Patients ≥ 100 ug/L
1994	8	333.1	319.3	252.5	113.3	549	75
1995	11	497.2	349.2	349	175	999	100
1996	49	646.6	311.4	679	438	999	98
1997	129	550.8	323.7	496	256	862	93
1998	135	611.2	438.3	524.7	257	839.5	93
1999	136	604.8	436.3	540.6	264.6	870.1	93
2000	180	608.2	416.7	560	295.2	846.3	92
2001	261	645.9	449.2	557.5	275.7	885.4	93
2002	344	666.4	463	536	284	999.8	94

Figure 7.2.7 Mean of Serum Ferritin without Erythropoietin, CAPD patients, 1993-2002

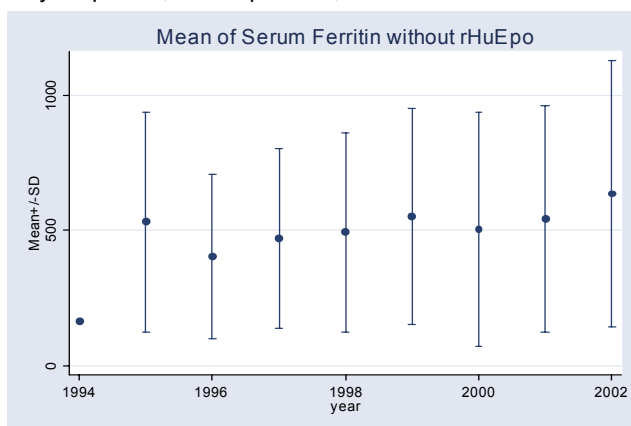
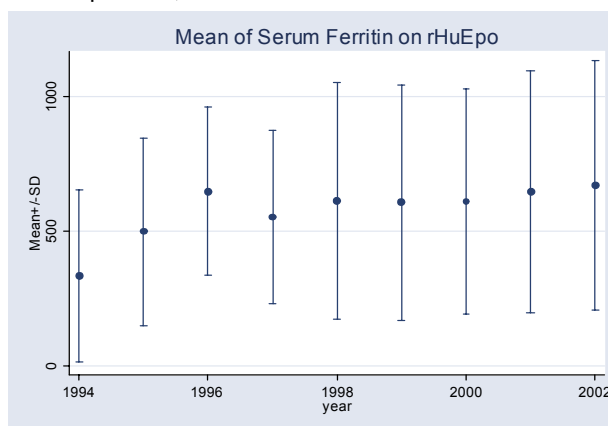


Figure 7.2.8 Mean of Serum Ferritin on Erythropoietin, CAPD patients, 1993-2002



7.3 Haemoglobin and Mortality

Introduction

It is well established that level of haemoglobin is an independent marker of mortality in dialysis patients. However the optimum haemoglobin affecting survival outcome is still debatable. Most registry data – USRDS, UK Renal Registry and Australian and New Zealand data advocate a haemoglobin of greater 11 g/dl. There has been no demonstrable survival benefit with achievement of higher haemoglobin level

Results

The adjusted 5-year survival (adjusted for age, gender, primary diagnosis and time on renal replacement therapy(RRT) in relation to haemoglobin for both the HD and CAPD patients were the best for patients with haemoglobin between of 10-12 gm/dl. It is the worst for those with haemoglobin less than 8 gm/dl. Haemodialysis patients with haemoglobin of 10-12g/dl have significantly better survival compared with all those with haemoglobin less than 10g/dl [p=0.000]. In CAPD patients however, those with haemoglobin 10 -12 g/dl have a significantly better survival only when compared to patients with haemoglobin less than 8g/dl and not the other groups with different levels of haemoglobin probably of the smaller

Number of subjects in CAPD. There appears to be no survival benefits in both HD & CAPD patients with haemoglobin greater than 12 gm/dl. For those with haemoglobin less than 8 g/dl, the risk of death was greater in HD compared to CAPD patients. (Table 7.3.1, 7.3.2).

However, once the HD and CAPD patients were combined together for the same analysis, significant difference in risk for mortality were noted between all the groups of patients with haemoglobin less than 10 g/dl compared to the group with haemoglobin of 10 to < 11g/dl, hence justifying the added expenditure on erythropoietin. There was a non-significant difference in risk of mortality between patients with haemoglobin of 10 to < 11 g/dl and those with haemoglobin 11 g/dl or higher. (Table and Figure 7.3.3). This may possibly be due to the small number of patients with haemoglobin more than 11 g/dl. This somewhat conforms to the European Best Practice Guidelines [1] and K/DOQI Guidelines [2] that advocate haemoglobin concentration of greater than 11 gm/dl and meets local standards. It would be interesting to know whether continued improvements in haemoglobin level over the years which had translated to improved patient survival up to 10 g/dl would continue to show improvement in patient survival once more patients achieve haemoglobin greater than 11 g/dl.

Table 7.3.1 Adjusted five-year patient survival in relation to Haemoglobin (Hb), HD patients 1997-2002 (Adjusted for age, gender, primary diagnosis and time on RRT)

Hb (g/dl)	N	Hazard Ratio	95% CI	P value
Hb <8	1374	3.26	(2.71,3.93)	0.000
Hb 8-<9	1493	1.62	(1.34,1.97)	0.000
Hb 9-<10	1486	1.42	(1.17,1.73)	0.000
Hb 10-<12*	1282	1.00		
Hb >12	184	1.16	(0.78,1.73)	0.466

* Reference group

Table 7.3.2 Adjusted five-year patient survival in relation to Haemoglobin (Hb), CAPD patients 1997-2002 (Adjusted for age, gender, primary diagnosis and time on RRT)

Hb (g/dl)	N	Hazard Ratio	95% CI	P value
Hb <8	164	1.60	(1.07,2.40)	0.022
Hb 8-<9	285	1.26	(0.91, 1.75)	0.172
Hb 9-<10	345	1.19	(0.89,1.59)	0.234
Hb 10-<12*	376	1.00		
Hb >12	59	1.06	(0.59,1.90)	0.847

* Reference group

Figure 7.3.1 Patient Survival in Relation to Haemoglobin, HD patients 1997-2002 (Adjusted for age ,gender, primary diagnosis, time on RRT)

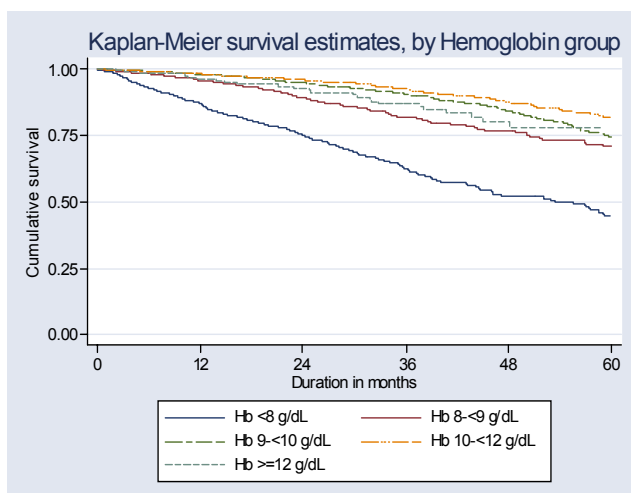


Figure 7.3.2 Adjusted Patient Survival in Relation to Haemoglobin, CAPD patients 1997-2002 (Adjusted for age ,gender, diagnosis, time on RRT)

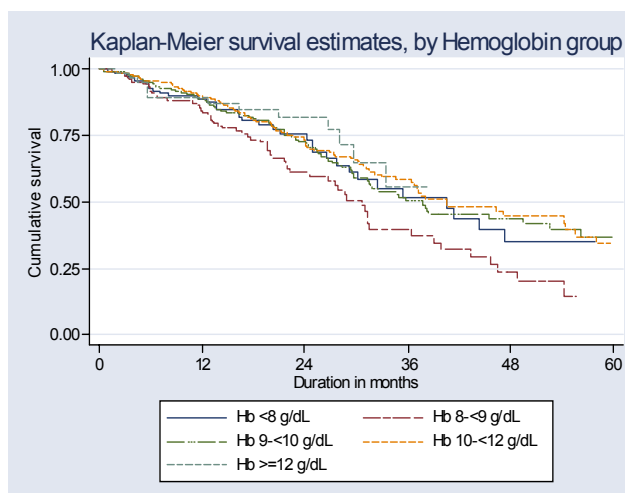
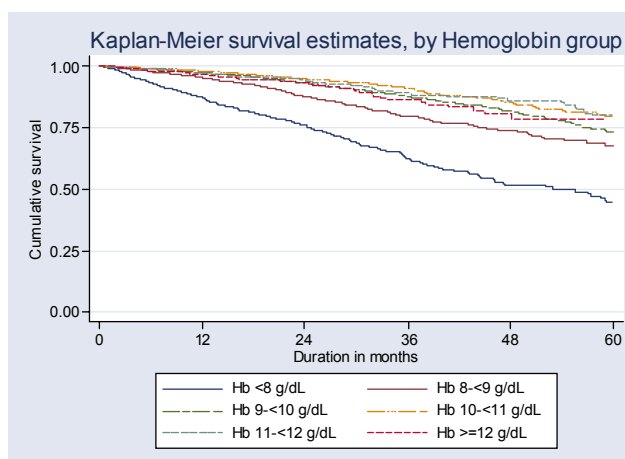


Table 7.3.3 Adjusted five-year patient survival in relation to Haemoglobin (Hb), All dialysis patients 1997-2002 (Adjusted for age, gender, modality, primary diagnosis and time on RRT)

Hb (g/dl)	N	Hazard Ratio	95% CI	P value
Hb <8	1538	2.99	(2.50,3.57)	0.000
Hb 8-<9	1778	1.56	(1.30,1.87)	0.000
Hb 9-<10	1831	1.40	(1.17,1.68)	0.000
Hb 10-<11*	1143	1.00		
Hb 11-<12	515	1.15	(0.89,1.49)	0.286
Hb >12	243	1.17	(0.83,1.64)	0.372

* Reference group

Figure 7.3.3 Patient Survival in Relation to Haemoglobin, All dialysis patients 1997-2002 (Adjusted for age ,gender, modality, primary diagnosis, time on RRT)



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