Chapter 7: Changes in Haemoglobin over Time

This chapter examines the changes in haemoglobin which occur over time in individuals and the variations with time in achievement of the Renal Association Standard by Centres.

Data selection

At the end of each quarter of the calendar year the Registry collects the most recent haemoglobin data for each patient.

For the analysis relating to the start of dialysis, data used are, for each new patient in 1998, the haemoglobin recorded during the quarter in which renal replacement therapy by dialysis started. The measurement was thus made within 1 to 90 days of starting dialysis.

For al other data points there had been no change of treatment modality in the previous 3 months and there had been no transfer between centres in the previous 3 months. Data from centres are shown if there was more than 50% completeness, though centres were only included in the statistical analysis if there was greater than 75% completeness.

Haemoglobin at start of dialysis

Centre	% data return	Median Hb g/dl	Quartile range	% Hb > 10g/dl	95% CI for %Hb > 10
A	66	10.6	9.2-11.6	61	49-72
B	93	10.1	9.2-11.1	56	49-63
C	95	9.3	8.2-10.4	39	45-66
D	100	9.7	8.9-10.9	45	40-70
E	76	9.0	8.4-10.0	28	47-63
F	90	9.4	8.9-10.6	30	37-57
G	94	9.1	8.1-9.8	24	36-54
H	94	9.9	8.7-11.0	47	30-48
I	100	10.1	9.0-11.4	55	23-53
J	91	10.2	9.3-11.0	56	25-49
K	92	9.4	8.4-10.5	34	24-46
M	93	10.1	9.0-11.2	55	17-44
O	96	9.7	7.2-9.3	37	17-41
P	93	9.1	9.1-10.6	28	20-36
Q	99	9.6	8.0-10.1	36	17-32
R	87	9.5	8.7-10.7	41	8-21
E&W	**89**	**10.6**	**8.6-10.8**	**61**	**38-43**

Table 7.1 Haemoglobin at start of dialysis

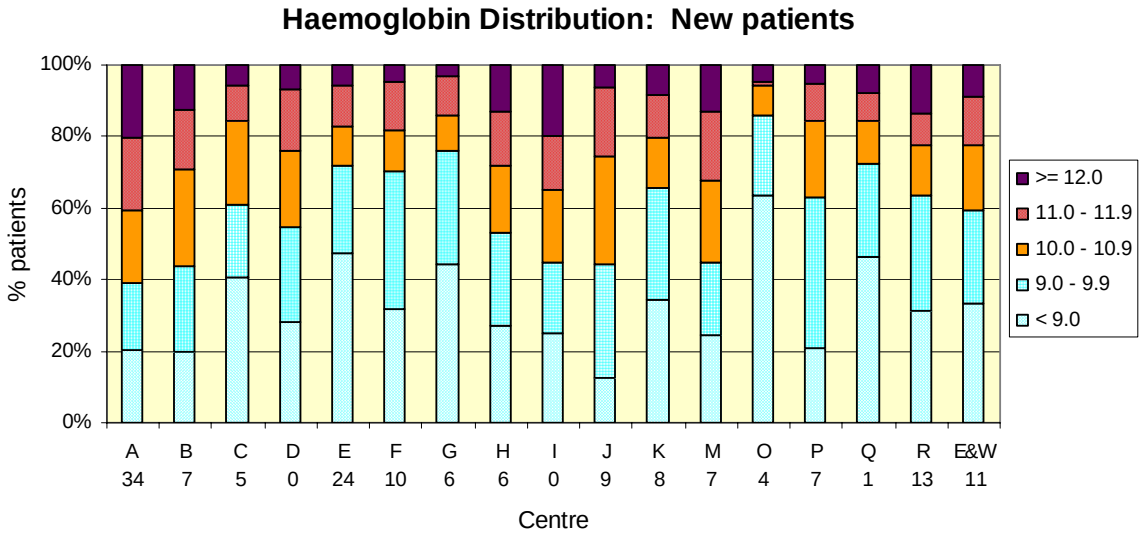

Figure 7.1 Haemoglobin distribution at start of dialysis

At the start of dialysis there was a wide range of median haemoglobin between centres from 8-9.8 g/dl. The percentage haemoglobin greater than 10.0g/dl varied from 15-43% in the centres with greater than 75% completeness. For the new patients the median haemoglobin and achievement of the Standard were both lower than for contemporaneous prevalent haemodialysis patients in the 1st quarter of 1998 (figure 7.2).

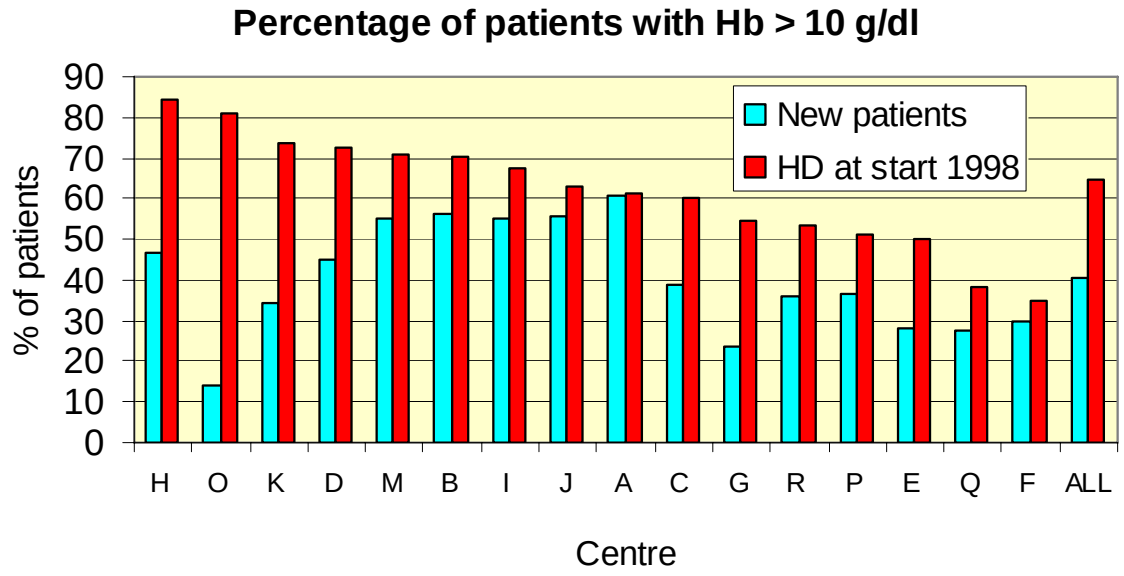

Figure 7.2 % with haemoglobin>10 g/dl: new and all prevalent patients

Changes in haemoglobin of individuals in the first year of dialysis

For the cohort of patients recorded by the Registry as starting renal replacement therapy in 1997 changes in haemoglobin during the first year on dialysis were monitored. These are shown in figure 7.3, which includes both haemodialysis and peritoneal dialysis patients. The Renal Association Standard includes patients after 3 months of treatment but this data indicates that haemoglobins do not plateau until after a year. Although the effect may be exaggerated by the fact that median haemoglobin of all prevalent patients on the Registry is increasing year on year, the cross-sectional analysis presented in chapter 6 also confirms that patients in the first few months of renal replacement therapy by dialysis have lower haemoglobin than those established on treatment for one year or more.

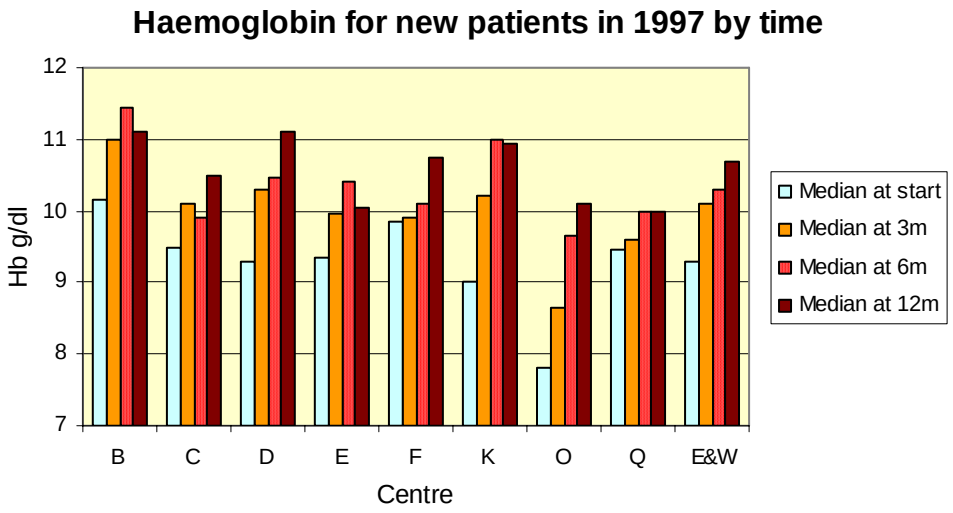

Figure 7.3 Change in haemoglobin for new patients.

Changes in haemoglobin of prevalent patients 1997-1998

This data relates to all patients alive on dialysis at selected time points. Data over 2 years is available from centres which sent returns to the Registry in 1997.
The data are summarised in table 7.2

	Mean	s.d.	Median	90% Range	Quartile Range
Haemodialysis					
Qtr 1 1997	10.2	1.6	10.2	7.6-13.0	9.1-11.2
Qtr 1 1998	10.6	1.7	10.5	7.7-13.5	9.3-11.7
Qtr 4 1998	10.8	1.7	10.8	8.0-13.7	9.7-11.9
Peritoneal dialysis					
Qtr 1 1997	10.8	1.7	10.7	8.2-13.7	9.7-11.8
Qtr 1 1998	10.8	1.7	10.7	8.1-13.6	9.7-11.9
Qtr 4 1998	10.9	1.7	10.9	8.2-13.6	10.0-12.0

Table 7.2 Change in Hb for all centres in 1st qtr. of 1997, 1998 and 4th qtr. of 1998.

In the following figures data presented for each centre are, in sequence, from the end of 1st quarter 1997, 1st quarter 1998 and the 4th quarter 1998.

Haemodialysis

Adequate data on haemodialysis patients was available from eight centres

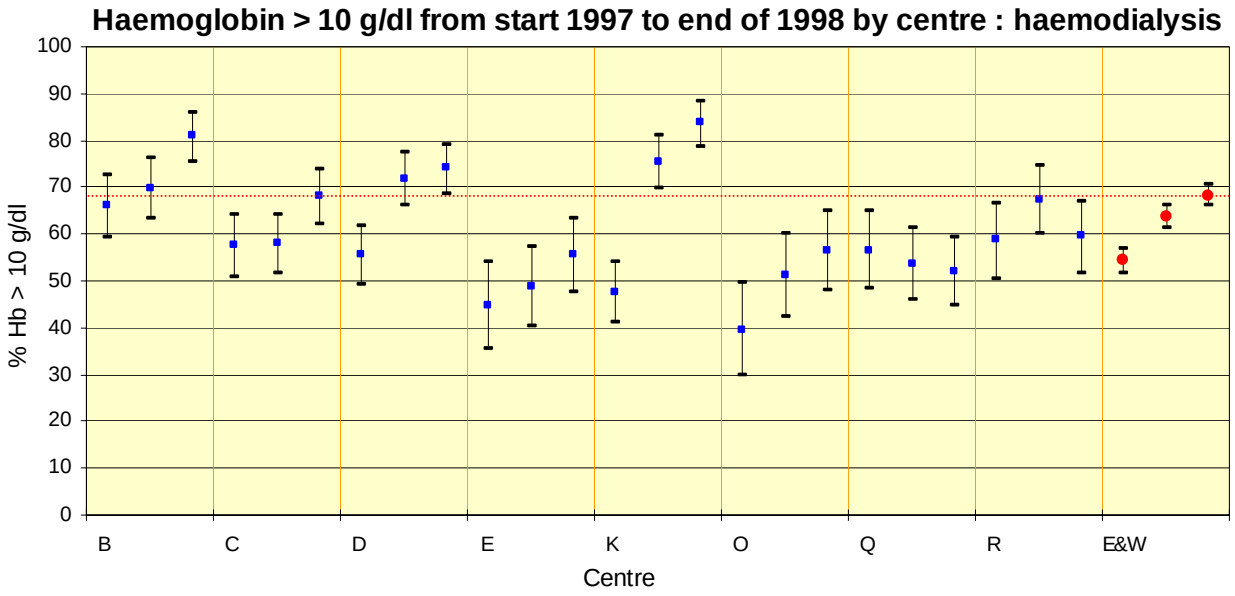

Figure 7.4 Hb > 10 g/dl from 1997 to end 1998, on haemodialysis
Data presented for each centre are, in sequence, from the end of 1st quarter 1997, 1st quarter 1998 and the 4th quarter 1998

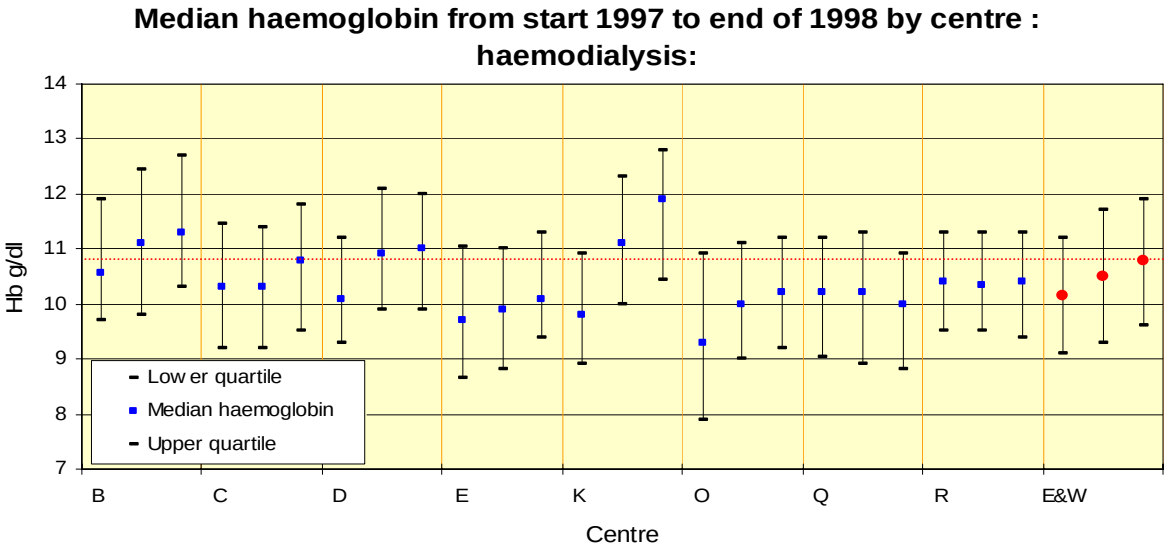

Figure 7.5 Median haemoglobin 1997-1998 on haemodialysis
Data presented for each centre are, in sequence, from the end of 1st quarter 1997, 1st quarter 1998 and the 4th quarter 1998

Comparing the 1st quarter of 1997 with the 4th quarter of 1998 showed that 7 out of the 8 centres recorded an increase in achievement of the Renal Association Standard for haemodialysis patients. Only centre Q, which has no funding for erythropoietin and makes frequent use of blood transfusion to maintain haemoglobin, showed a decline. Centre K has made the largest improvement. Overall in these units there was a

significant increase from 53% to 68% in the percentage of patients reaching the Renal Association Standard.

Peritoneal dialysis

Adequate data for peritoneal dialysis were available from 9 centres

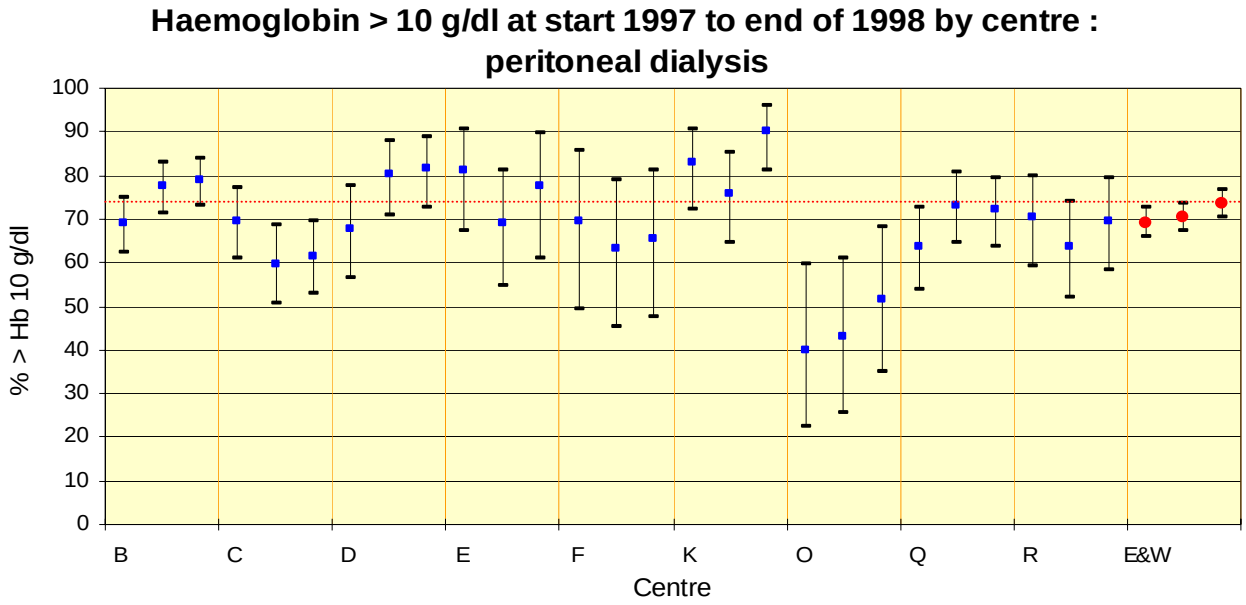

Figure 7.6 Percentage with Hb ≥ 10g/dl 1997 to end 1998, on Peritoneal dialysis
Data presented for each centre are, in sequence, from the end of 1st quarter 1997, 1st quarter 1998 and the 4th quarter 1998

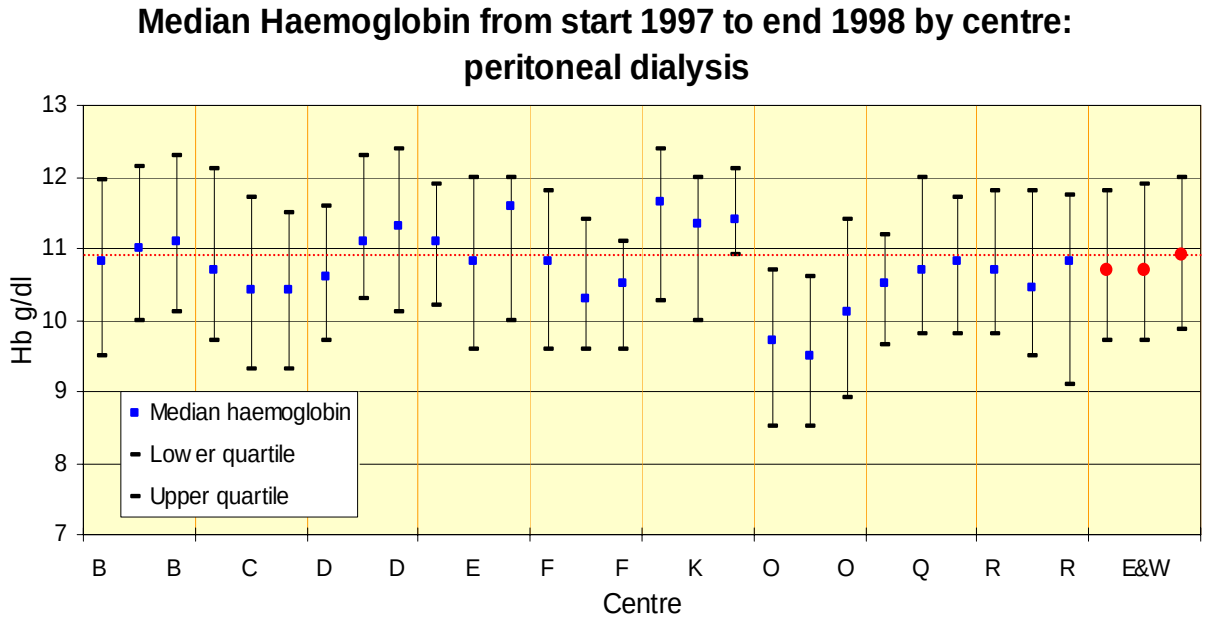

Figure 7.7 Median haemoglobin 1997- 1998 on peritoneal dialysis
Data presented for each centre are, in sequence, from the end of 1st quarter 1997, 1st quarter 1998 and the 4th quarter 1998

Patients on peritoneal dialysis started with higher haemoglobins than haemodialysis patients, and changes through 1997-1998 were smaller and more variable. Overall in these units there was a trend upward from 70% to 74% of patients with haemoglobin above the Standard.

Comment

The difference between haemodialysis patients and peritoneal dialysis patients narrowed in this time. At the start the achievement of the haemoglobin Standard was 56% for haemodialysis compared with 70% for peritoneal dialysis, and at the end 68% compared with 74%

In most centres there is no evidence of a reduction in spread of data to suggest an improvement in targeting over the two year time period. Centre K for patients on haemodialysis, has an asymmetric quartile range with a smaller upper quartile. This may indicate a more selective management of patients with higher haemoglobins and requires further investigation.

Change in haemoglobin achieved through 1998

This data relates to all patients alive on dialysis at selected time points. Sixteen centres returned sufficient haemoglobin data in both the first and fourth quarters of 1998 for analysis of both haemodialysis and peritoneal dialysis patients. (figures 7.8-11).

The data are summarised in table 7.3.

	Mean	s.d.	Median	90% Range	Quartile Range
Haemodialysis					
Qtr 1 1998	10.6	1.7	10.5	7.7-13.5	9.4-11.7
Qtr 4 1998	10.8	1.7	10.8	8.0-13.7	9.7-11.9
Peritoneal dialysis					
Qtr 1 1998	10.9	1.7	10.8	8.1-13.8	9.8-12.0
Qtr 4 1998	11.0	1.6	11.1	8.4-13.7	10.0-12.0

Table 7.3 Change in Hb for all centres returning data in 1st and 4th quarter of 1998.

The median haemoglobin in the centres over the time period is shown below (figures 7.9, 11). A reduction in the spread of data shown by reduction in the inter-quartile range may indicate success in targeting a particular haemoglobin concentration. There is a suggestion of narrowing of the range in peritoneal dialysis patients in centres I and K (figure 7.11) The spread of data for patients in all centres is shown in table 7.3.

Haemodialysis

During 1998 14 of 16 centres recorded an increase in the percentage of haemodialysis patients with haemoglobin of 10g/dl between the 1st and 4th quarters
In peritoneal dialysis patients 13 of 16 centres recorded an increase in the percentage of patients reaching the Standard haemoglobin between the 1st and 4th quarters of 1998.

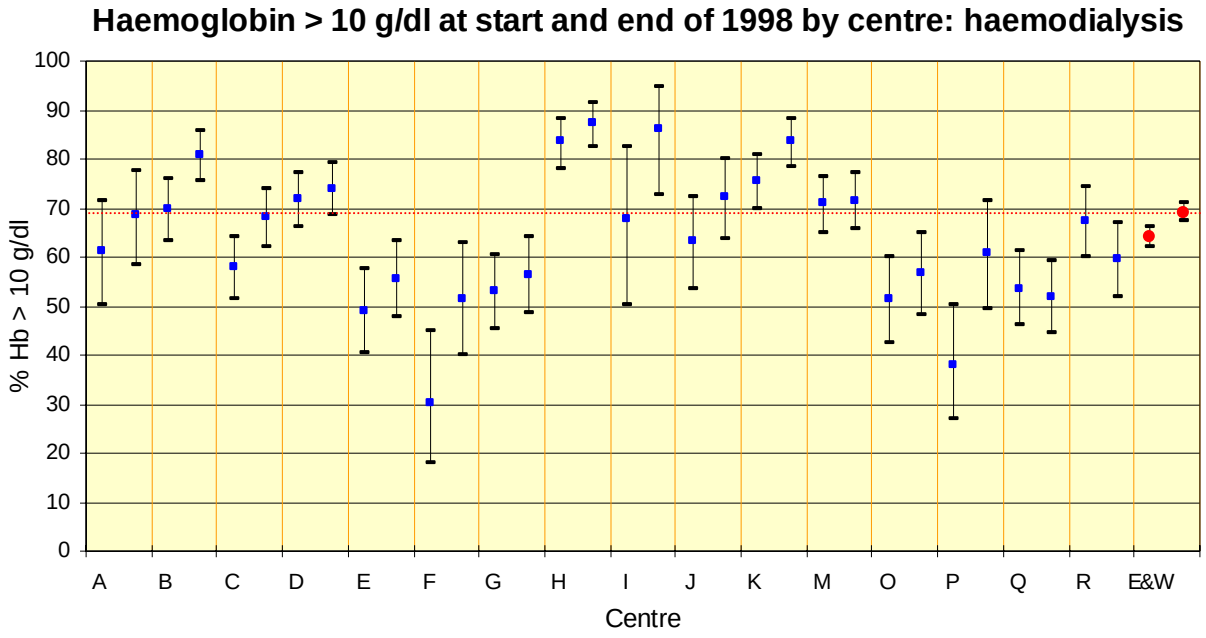

Figure 7.8 Hb > 10g/dl at start and end of 1998, on Haemodialysis
Data from each centre are from the end of the first and fourth quarters of 1988

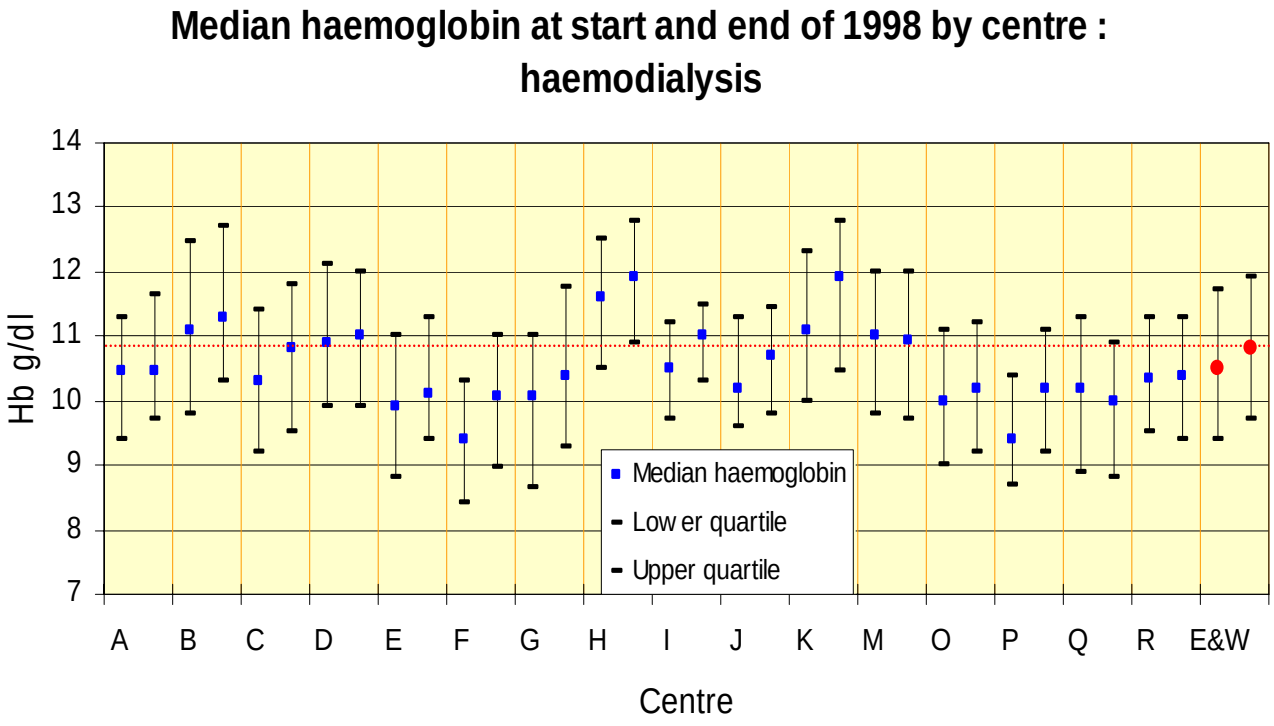

Figure 7.9 Median Haemoglobin, Haemodialysis, start and end of 1998
Data from each centre are from the end of the first and fourth quarters of 1988

Peritoneal dialysis

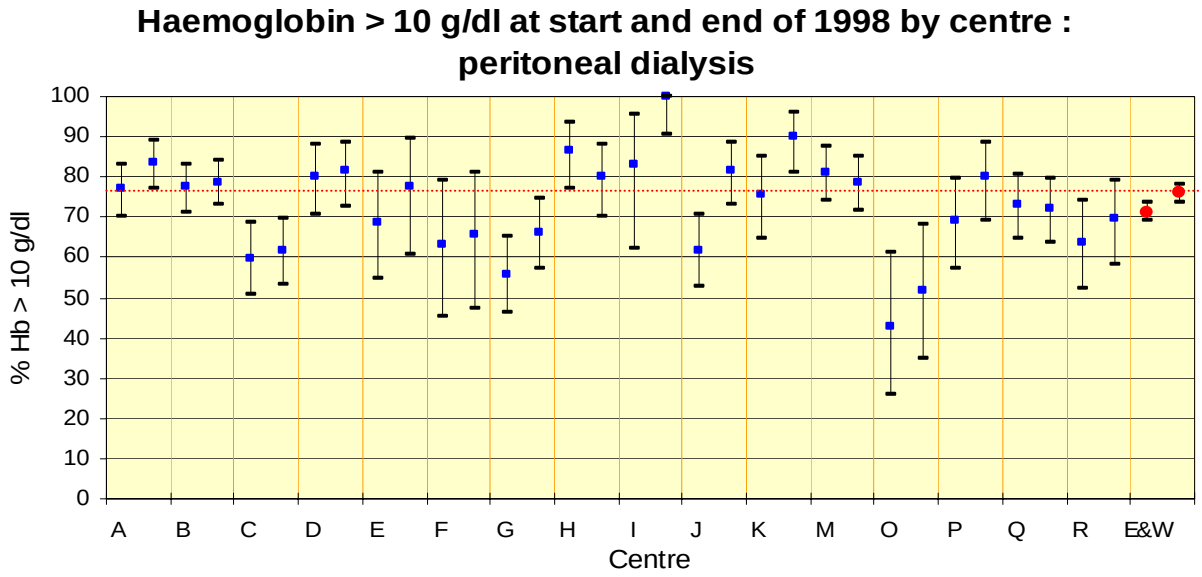

Figure 7.10 Hb > 10g/dl at start and end of 1998, on Peritoneal Dialysis
Data from each centre are from the end of the first and fourth quarters of 1988

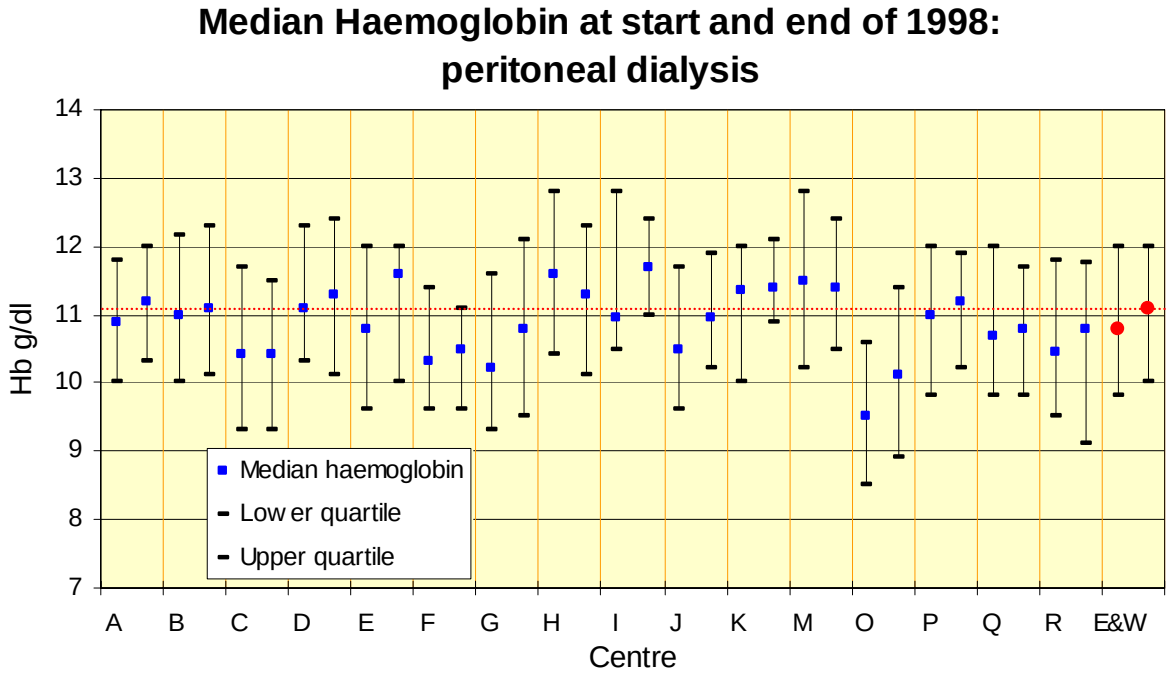

Figure 7.11 Peritoneal Dialysis results at start and end of 1998
Data from each centre are from the end of the first and fourth quarters of 1988

Analysis of changes in haemoglobin of individuals during 1998

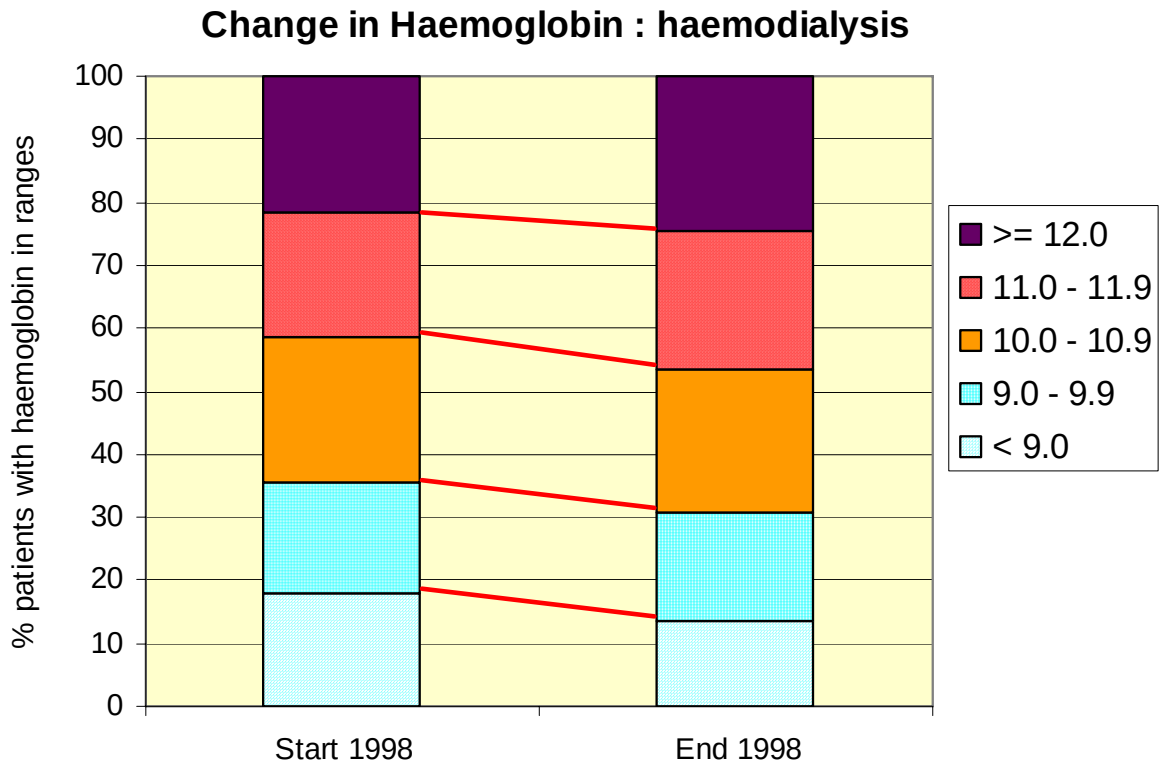

Figure 7.12 Change in haemoglobin distribution through 1998
All patients on the Registry at end of first and last quarters of 1998

Analysis of the haemoglobin distributions in populations at different time points masks significant volatility in the haemoglobin of individuals. Thus considering figure 7.12, the proportion of Registry patients in each haemoglobin band at the beginning and end of 1998 is similar and there appears to be little movement taking place. This is very misleading as the two populations of patients are different: some have died or been transplanted and new patients have started dialysis. By tracking the sequential haemoglobin changes of individual patients it becomes clear that the populations in each haemoglobin band at the two time points is quite different. This is illustrated in figure 7.13.

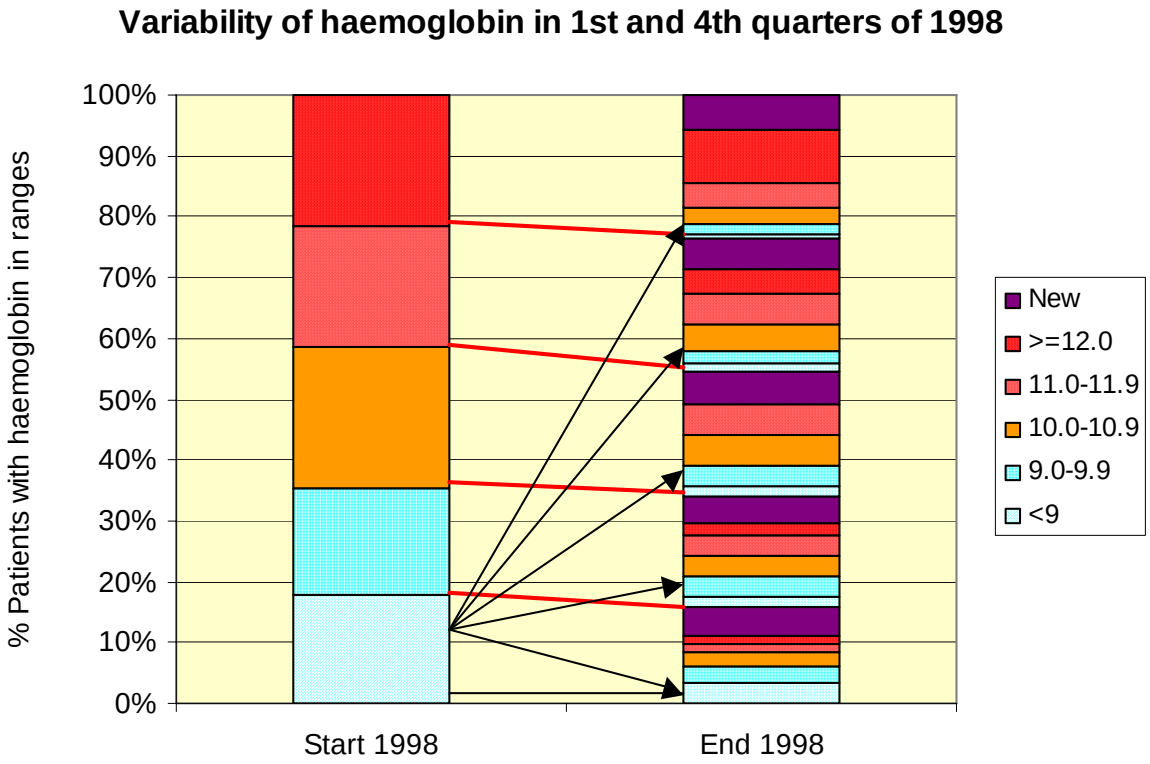

Figure 7.13 Change of haemoglobin in individuals from 1st to 4th quarters of 1998

Figure 7.13 is complex. The left column represents the proportion of patients in each haemoglobin band in the first quarter of 1998. The heavy lines linking this column to the right column define the same haemoglobin bands in the right column, which shows the situation at the end of 1998. The individual patients retain their shading code from the first quarter. It can be seen for example, that patients who are severely anaemic with haemoglobin less than 9 g/dl at the beginning of the year appear in all bands at the end of the year (illustrated by light linking lines). Likewise patients with the higher haemoglobins at the start of the year are distributed throughout the range by the end of the year.

From further study of figure 7.13 it is clear that a minority of patients in any haemoglobin band at the end of the year were in that category at the beginning of the year. New patients (those starting RRT or returning to dialysis after a failed transplant or transferring in to the centre) also comprise a large proportion of patients in each category at the end of the year.

Significant proportions of patients did start and end the year with low haemoglobin. If there is to be an improvement in the percentage of patients with acceptable haemoglobin, it is important to understand more of the characteristics of these patients and reasons for their failure to improve. However it is equally important to understand more about those patients who become anaemic from an initially satisfactory position, and to develop protocols for early recognition and prevention of this.

Determinants of haemoglobin variability

To investigate factors influencing haemoglobin change, individuals were divided into four groups described below.

Group A (remains anaemic) = Hb < 10g/dl in 1st and 4th quarter of 1998
Group B (Hb improves) = Hb < 10g/dl in 1st quarter and ≥ 10g/dl in 4th quarter
Group C (Hb falls) = Hb ≥ 10g/dl in 1st quarter and < 10g/dl in 4th quarter
Group D (Hb in Standard) = Hb ≥ 10g/dl in 1st and 4th quarter

1850 patients were on **haemodialysis** in both the first and fourth quarters of 1998 and 1705 had haemoglobin data available at both time points (table 7.4).

Group	No. of patients	% of patients
A	231	13.5
B	326	19.1
C	207	12.1
D	941	55.2

Table 7.4 Haemodialysis patients

966 patients were on **peritoneal dialysis** in the first and fourth quarters of 1998 and 857 had haemoglobin data at both time points (table 7.5).

Group	No. of patients	% of patients
A	103	12.0
B	136	15.9
C	113	13.2
D	505	58.9

Table 7.5 Peritoneal dialysis patients

The data suggest similar levels of volatility between patients on haemodialysis and peritoneal dialysis. In both modalities 12-15% of patients remained anaemic throughout the year, and 12-13% of patients developed anaemia during the year

Haemoglobin variability and age

Analysis of variance was used to compare the mean ages in each group and the data are shown in Table 7.6.

Group	No of patients	Mean age	Standard deviation
A	359	55.1	15.9
B	484	57.0	15.6
C	349	57.3	16.1
D	1481	58.1	15.6

Table 7.6 Haemoglobin variability and age

There was no significant variation in the mean age of patients in the four groups after adjusting for treatment centre (F=2.1, p=0.096).

Haemoglobin variability and ferritin

This analysis used the most recent ferritin in a 6-month period and the corresponding haemoglobin for that period. Analysis of variance was used to compare the log ferritin in the 4 groups adjusting for treatment centre. Centres G, H and J were excluded due to less than 75% data completeness. The results are shown in table 7.7

Group	No of patients	Log ferritin	S.D. log ferritin	Geometric mean ferritin
A	283	2.53	0.42	343
B	363	2.41	0.38	257
C	275	2.52	0.40	334
D	1104	2.33	0.41	215

Table 7.7 Haemoglobin variability and serum ferritin

A statistically significant variation was found between the four groups ($F = 32.1$ $p<0.0001$).

Differences in the geometric means of the groups are shown below after adjusting for treatment centre (table 7.8). The Bonferroni correction has been applied to p-values and 95% confidence intervals. This correction is used when performing multiple tests to take into account the increased probability of a result being significant by chance. The disadvantage of this test is that it is too conservative. It is possible to have a statistically significant F test value from ANOVA, but to have no individual means that differ significantly after applying the Bonferroni correction. Nevertheless there are highly significant differences between the groups.

Comparison	Ratio of Geometric means	95% confidence interval for ratio	p-value
A with B	1.37	1.14-1.65	<0.0001
A with C	1.00	0.83-1.22	1.0000
A with D	1.57	1.35-1.84	<0.0001
B with C	0.73	0.61-0.88	<0.0001
B with D	1.15	1.00-1.32	0.0564
C with D	1.57	1.34-1.83	<0.0001

Table 7.8 Comparison of groups by ferritin concentration

The data shows that those with persistently low or falling haemoglobin have higher serum ferritin than those with stable high or rising haemoglobin. Factors possibly explaining this include inability to utilise iron stores in those with low or falling haemoglobin, to repeated iron infusion in patients with other factors inhibiting haemoglobin response, or a raised ferritin associated with an illness that causes a fall in haemoglobin.

Haemoglobin variability and gender

The Mantel-Haenszel General Association statistic was used to test for an association with gender adjusting for treatment centre (table 7.9).

Group	% (N) Male	% (N) Female
A	56% (202)	44% (157)
B	58% (282)	42% (202)
C	59% (207)	41% (142)
D	64% (946)	36% (533)

Table 7.9 Haemoglobin variability and gender

A statistically significant association was found with gender (Q_{GMH} = 10.4, d.f = 3, p=0.015.) A logistic regression analysis was used to obtain odds ratios comparing each of the three groups with group D for males compared with females as shown below (table 7.10).

Comparison	Odds ratio [95% CI]	p-value
A with D	0.73 [0.57-0.93]	0.0101
B with D	0.77 [0.62-0.96]	0.0177
C with D	0.82 [0.64-1.04]	0.1077

Table 7.10 Comparison of groups with group D for gender

The data would suggest that females form a higher proportion of those with persistently low haemoglobin than they do of those with stable high haemoglobin. Taken with data presented in the previous chapter this again suggests that reaching the Standard haemoglobin in females may be more difficult than for males.

Haemoglobin variability and parathyroid hormone

The analysis used the most recent iPTH value over a 9-month period. The distribution of iPTH is skewed so the log iPTH was used in analysis of variance. Data from centres H, J, K, M, P and Q were excluded since there was less than 75% data completeness. Results are shown in table 7.11.

Group	No . of patients	Mean log iPTH	S.D. log iPTH	Geometric mean iPTH
A	183	1.28	0.59	18.8
B	269	1.16	0.65	14.4
C	185	1.18	0.64	15.0
D	656	1.16	0.62	14.5

Table 7.11 Haemoglobin variability and parathyroid hormone

There was no statistically significant variation in log iPTH between the 4 groups (F=1.2, p=0.3099).

Haemoglobin variability and time on treatment

Analysis of variance was used to compare length of time on dialysis in the 4 groups adjusting for treatment centre. Length of time on dialysis follows a skewed distribution

and the data was therefore log transformed. Length of time on treatment in days on 31st December 1998 was used. Results are shown in table 7.12.

Group	No of patients	Mean log days on treatment	S.D. Log days	Geometric mean years
A	355	3.14	0.38	3.87
B	472	3.14	0.37	3.89
C	345	3.15	0.33	3.95
D	1444	3.14	0.34	3.87

Table 7.12 Haemoglobin variability and time on treatment

No statistically significant difference was found in log time on treatment between the groups (F=0.05, p=0.9863).

Haemoglobin variability and urea reduction ratio

Only in-centre haemodialysis patients on thrice weekly dialysis were included in the analysis. Data from centres C, D, G, H, J and M were excluded from the analysis due to less than 75% completeness. Analysis of variance was used to compare the 4 groups adjusting for treatment centre. Results are in table 7.12.

Group	No of patients	Mean URR	Standard Deviation
A	101	65.2	10.8
B	132	66.4	9.0
C	84	62.9	10.1
D	365	65.0	8.6

Table 7.13 Haemoglobin variability and urea reduction ratio

A statistically significant association was found between the groups and urea reduction ratio (F = 2.7, p=0.0437). The differences between the groups are shown in table 7.14, together with p-values following application of the Bonferroni correction.

Comparison	Difference in Mean URR	95% confidence interval	p-value
A with B	-2.1	-5.3 - +1.0	0.4206
A with C	+1.1	-2.4 - +4.5	1.0000
A with D	-1.2	-3.9 - +1.5	1.0000
B with C	+3.2	-0.1 - +6.5	0.0563
B with D	+0.9	-1.5 - +3.3	1.0000
C with D	-2.3	-5.2 - +0.5	0.1907

Table 7.14 Comparison of groups for urea reduction ratio

Most of the difference is accounted for by lower URR in those with a falling haemoglobin (group C) than those with a rising haemoglobin (group B), but this does not reach statistical significance. Because of applying the Bonferroni correction, the individual means do not appear to be significant but this may be an over conservative interpretation.

Conclusion

There is wide variation between centres in the haemoglobin concentration of patients on starting dialysis. Factors influencing this may include differences in prescription of erythropoietin to predialysis patients, and differences in time of referral before dialysis. It currently takes up to 12 months after starting dialysis for many patients to reach the desired haemoglobin concentration. Most centres are seeing increasing achievement of the Renal Association Standard for haemodialysis patients. Even for Centres not participating in the Registry in 1997, there was probably an increased awareness of comparative audit and the Standards achieved from the published report. The picture is more mixed for peritoneal dialysis patients.

The headline figure for the percentage achieving the target haemoglobin within a unit disguises volatility haemoglobin concentrations of individuals. Significant proportions of dialysis patients (12-13%) did start and end the year with low haemoglobin. If there is to be an improvement in the percentage of patients with acceptable haemoglobin, it is important to understand more of the characteristics of these patients and reasons for their failure to improve. However it is equally important to understand more about those patients who become anaemic from an initially satisfactory position, and to also develop protocols for early recognition and prevention of this. The data presented here offer some help to better understanding of these changes.