How do Patients who are Known to the Renal Units Start Chronic Haemodialysis?

Renal Ünitelerce Bilinen Hastalar Kronik Hemodiyalize Nasıl Başlar?

ABSTRACT

INTRODUCTION: A significant number of known ESRD patients start dialysis as an emergency. Key factors that determine emergency dialysis initiation have not been well identified.

MATERIAL and METHODS: Ninety out of 159 patients studied were known for> 6 months and divided into Emergency dialysis (EmG n=46) and Elective dialysis (EG n=44) groups.

RESULTS: Most diabetic patients started dialysis as an emergency (75% vs. 25% p=0.008). At the start, EmG had higher median urea (3.5 vs. 3.8 g/dl p=0.05), a lower bicarbonate (19 vs. 21.5 mEq/L, p=0.04) and haemoglobin (9.4 vs10.5 g/dl p=0.005).

Three months pre-dialysis, EmG had a lower serum albumin (3.2 vs. 3.6 g/L, p=0.001) and haemoglobin (10.4 vs. 11, p=0.06), a higher CRP (21 vs. 5, p=0.08) and better preserved eGFR (11 vs. 9, p=0.001).

In multivariate analysis, only a diagnosis of diabetes and a CRP >30 were independent risk factors for starting dialysis as an emergency. Having an albumin >3.5 was associated with a reduced risk of having an emergency start to dialysis.

CONCLUSION: Apart from having diabetes, it seems difficult to predict emergency start of dialysis in known ESRD patients. Randomised controlled studies can further identify importance of high CRP and low serum albumin in relation to emergency initiation of dialysis.

KEY WORDS: Albumin, C Reactive protein, Emergency dialysis, Diabetes

ÖZ

GİRİŞ: SDBY bulunduğu bilinen hastaların önemli bir kısmı diyalize acil şartlarda başlar. Diyalize acil şartlarda başlamayı belirleyen ana faktörler henüz tanımlanmamıştır.

GEREÇ ve YÖNTEMLER: Çalışılan 159 hastanın 90'ı > 6 aydır bilinmekteydi ve Acil diyaliz (EmG n=46) ve Elektif diyaliz (EG n=44) gruplarına bölündü.

BULGULAR: Çoğu diyabetik hasta diyalize acil şartlarda başladı (%75 ve %25, p=0,008). Başlangıçta EmG grubunda medyan üre (3,5 ve 3,8 g/dl, p=0,05) daha yüksekti, bikarbonat (19 ve 21,5 mEq/L, p=0,04) ve hemoglobin (9,4 ve 10,5 g/dl, p=0,005) ise daha düşüktü.

Diyalizden 3 ay önce EmG grubunda serum albumin (3,2 ve 3,6 g/L, p=0,001) ve hemoglobin (10,4 ve 11, p=0,06) daha düşüktü, CRP (21 ve 5, p=0,08) daha yüksekti ve eGFR (11 ve 9, p=0,001) daha iyi korunmuştu.

Multivaryant analizde sadece diyabet tanısı ve CRP >30 diyalize acil şartlarda başlamak açısından bağımsız risk faktörleriydi. Albumin düzeyinin >3,5 g/L olması diyalize acil şartlarda başlanması riskinde bir azalmayla ilişkiliydi.

SONUÇ: Bilinen SDBY hastalarında diyabetli olmak dışında diyalize acil şartlarda başlanmasını öngörmek zor görünmektedir. Randomize kontrollü çalışmalar diyalize acil şartlarda başlanması açısından yüksek CRP ve düşük serum albumini bulunmasının önemini daha iyi tanımlayabilir.

ANAHTAR SÖZCÜKLER: Albumin, C Reaktif protein, Acil diyaliz, Diyabet

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INTRODUCTION

The initiation of dialysis for most patients with chronic kidney disease (CKD) should be in a planned way as an outpatient. Emergency dialysis (the unplanned start of dialysis) may arise either due to late referral of the patient to the renal services or because of an acute deterioration in renal function in a patient with previously stable CKD.

Numerous studies have shown the adverse effect of late referral including an increase in morbidity and mortality. Emergency dialysis may also be psychologically traumatic and carries an increased burden with extra costs for the renal services (1, 2, 3 and 4). Emergency hospital admissions are also associated with an increased risk of hospital acquired infections such as Clostridium Difficile and Methicillin Resistant Staphylococcus Aureus (MRSA).

However, it has been observed that a significant number of patients start dialysis in emergency conditions despite being well known to the renal services. Relatively little is known about the proportion of such patients or their characteristics.

We therefore performed a retrospective observational study to determine the frequency of the emergency initiation of dialysis in patients known to a large regional renal unit for at least six months in advance of first renal replacement therapy (RRT). We were interested to find key factors responsible for and their predicting value in advance to prevent unplanned start of RRT.

MATERIAL and METHODS

The Richard Bright Renal Unit is a large regional renal unit providing all forms of renal replacement therapy to a dialysis population of 1.5 million and renal transplant population of 2.25 million. There are currently 542 prevalent dialysis patients and 715 prevalent transplant patients. The annual rate for starting dialysis at the time was 120 patients/million population. Approximately 100 renal transplants are performed each year of which, in the last year, about 33% were living donor transplants and about 10% were performed pre-emptively before the start of dialysis.

For this study, all the patients starting haemodialysis in our unit over the preceding twelve month were identified in January 2006. Ethics approval was granted by the central office for research and ethics committee (COREC). Patients were categorised according to their duration of follow up by the renal unit prior to the initiation of haemodialysis (> or < six months). Patients known for more than 6 months were further subdivided into emergency and elective dialysis groups according to whether their first RRT was as a hospital admission (Emergency group) or as an outpatient (Elective group).

Patient demographics, clinical details and biochemical values were obtained from electronic records and hospital notes at specific time points that included 90 days before starting dialysis, the most recent clinic assessment before starting dialysis and at the start of dialysis itself.

The patient's age, gender, weight and BMI at start of RRT were recorded. The clinical details obtained included: length of time the patient was known to the renal unit before the start of RRT, cause of chronic kidney disease, presence or absence of diabetes mellitus, associated co-morbidities, the number of outpatient clinic appointments in the 6 months before starting haemodialysis, the occurrence of a clinic appointment in the two weeks before commencing treatment, haemodialysis vascular access history, whether the dialysis education team had reviewed the patient, the reason(s) for admission (when relevant) and the reason(s) for initiating RRT. We also recorded information regarding treatment of anaemia with erythropoietin stimulating agents (ESA) and treatment of hyperparathyroidism with 1,25 dihydroxy vitamin D3 (alfacalcidol or calcitriol). The status of patients at 12 months (alive or dead) and cause of death was also obtained.

The biochemical values recorded included urea, creatinine, eGFR (calculated using the 4 variable MDRD formula), potassium, bicarbonate, haemoglobin, ferritin, calcium, phosphate, parathyroid hormone (PTH), albumin and C-reactive protein (CRP). When values for PTH, ferritin, and CRP were not available at the defined time points, values recorded within 14 days of the relevant time point were used. To examine the rate of change in renal function in the preceding 6 months before starting dialysis, at least 3 readings for serum Cr and eGFR were recorded for each patient. Slopes were then obtained for each group by plotting renal functions against time.

The diagnosis of chronic kidney disease and cause of death were reported according to the ERA-EDTA codes and co-morbidity data as defined by the UK Renal Registry (6) were used. The distance from each patient's home address to the hospital was calculated using Google maps internet software. Patients were divided into two groups depending on whether or not they lived within 10 miles radius of the hospital.

Statistical Analysis

The emergency (EMG) and elective (EG) groups were compared with each other on demographic characteristics and several other biological markers.

Continuous parametric variables were compared between groups by a 2 sided Student t-test and non-parametric variables by the Mann-Whitney test. Binary and categorical variables such as gender, presence of diabetes and other continuous variables that had been formerly categorised were tested between the groups by the Chi-square test, provided that enough values were expected under the assumption of independence for each combination of factors.

A logistic regression model was also fitted to include possible predictors of an emergency start of dialysis with

emergency/elective as the outcome variable. The inclusion of multiple factors in the model was mostly limited by the number of observations and the relative high number of missing values on a few variables that might have been related to the outcome. We thus fitted two independent logistic regression models that would investigate our primary objectives. The models included among the predictors: sex, diabetes and alternatively albumin or CRP as categorical variables and the goodness of fit for each model was tested by the Hosmer-Lemeshow formula. Age was excluded because its contribution to the increase of the likelihood of the model was not significant.

Patient survival was analysed by the Kaplan-Meier method and differences between the two groups compared by the log-rank test.

RESULTS

A total of 159 patients started RRT in our unit over the 12 months period; HD was the first line treatment modality in 137 patients. Ninety out of those patients were known to the renal unit for more than 6 months and were included for further analysis, 46 (51%) patients were in the emergency dialysis group (EmG) and 44 (49%) in the elective dialysis groups (EG) as shown in flow chart in Figure 1.

Baseline patient characteristics and primary renal diagnoses were well matched in both groups except for more patients with primary renal diagnosis of diabetes mellitus in the EmG (Table I). Numbers of co-morbidities recorded for either group were also similar as shown in Table II. At the time of first referral to the renal services, there was no difference for baseline renal function between the two groups (p=0.34), however patients in the EmG were followed up by the renal unit for a longer period of time (p=0.02).

Prior to start of first RRT; compared with the EG, subjects in the EmG were less likely to have been reviewed by the pre-dialysis education team (82% vs. 98%, p=0.016). Although not significant but smaller number of patients in the EmG were receiving treatment for hyperparathyroidism (45% vs. 63%, p=0.08). There was no difference for erythrocyte stimulating

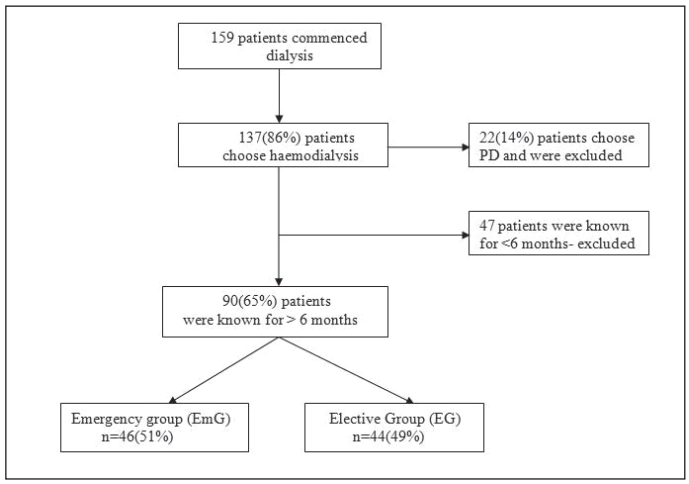

Figure 1: *Flowchart outlining patients' pathway in the study.*

Table I: Baseline characteristics of patients.

	EmG	EG	p value
Number of patients	n=46	n=44	
Age (years)	64 (25-87)	68 (20-90)	0.2
Male (%)	25 (54%)	30 (65%)	0.2
BMI	27 (18-54)	28 (21-41)	0.2
Primary renal diagnosis			
Diabetes	20 (43%)	7 (16%)	0.008
Renovascular	6 (13%)	6 (14%)	ns
Glomerulonephritis	4 (9%)	8 (18%)	ns
Pyelonephritis	2 (4%)	3 (7%)	ns
Polycystic kidney disease	2 (4%)	3 (7%)	ns
Other	5 (11%)	7 (16%)	ns
Uncertain	7 (15%)	10 (23%)	ns

Table II: Co-morbidities.

	n	EmG	n	EG	p
Coronary artery disease	46	20%	44	23%	0.7
Cerebrovascular disease	46	6%	44	4.5%	0.6
PVD	46	4%	44	7%	0.6
Angina	38	16%	33	21%	0.5
Previous MI in last 3 months	38	3%	33	6%	0.4
Previous MI in > last 3 months	38	10%	33	9%	0.8
CABG	38	10%	33	12%	0.8
Heart failure	37	22%	33	15%	0.4
DM not as a primary diagnosis	41	7%	35	23%	0.05
COPD	33	8%	33	3%	0.3
Liver	38	3%	33	3%	0.9
Malignancy	38	10%	33	18%	0.3
Smoking	38	10%	33	15%	0.5

Table III: Other characteristics and observations made at the time of first dialysis.

	n	EmG	n	EG	p
		Median (range)		Median (range)	
Cr at first assessment	34	3.5 (0.15-9.3)	31	3.8 (0.54-16.2)	0.3
eGFR at first assessment	34	35 (5-158)	31	29 (2-128)	0.3
Time from first assessment to start of dialysis (days)	43	1577(772-2990)	34	1054 (185-1560)	0.02
Patients on alfacalcidol	46	21 (45%)	44	28 (63%)	0.08
Frequency of assessment in 6 months before start of dialysis	38	4.8 (2-16)	35	4 (1.5-10)	0.6
Clinic appointment in last 2 weeks	44	21 (46%)	44	27 (61%)	0.1
Dialysis education team review	46	38 (82%)	44	43 (98%)	0.01

Note: Serum creatinine in mg/dl may be converted to μmol/L by multiplying by 88.4; urea in mg/dl to mmol/L by multiplying by 0.357

agents prescription between the two groups (p=0.85). Similarly, there was no significant difference between the two groups in the proportion of patients seen in clinic within 2 weeks of starting dialysis (p=0.66) or in the overall frequency of clinic follow up in the preceding six months (p=0.16), Table III.

Majority of the EmG patients started dialysis with temporary vascular access (34 [74%] vs. 10 [23%], p=0.01) and had more attempts at establishing both temporary and permanent vascular access {10(67%) in EmG had 3 or more attempts vs. 5(33%) in the EG, p=0.012}. The majority of admissions in the EmG were due to uraemic symptoms, fluid overload and due to an acute deterioration in renal functions Figure 2.

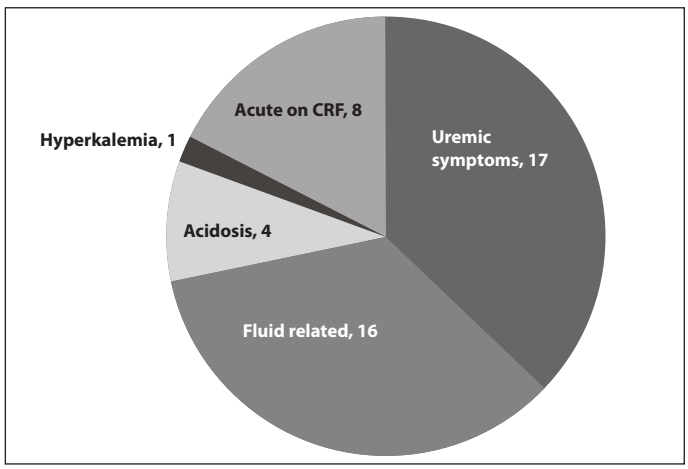

Figure 2: *Reasons for requiring admission to commence RRT*

- *Uremic symptoms: general malaise in the absence of another cause, loss of appetite, nausea and vomiting*
- *Fluid overload: 12 patients due to peripheral oedema and 4 due to pulmonary oedema.*
- *Acidosis: serum bicarbonate less than 10 mmol/L*
- *Hyperkalemia: serum potassium above 7 mmol/L*

At the time of the first RRT, patients in EmG had higher median urea (mg/dl: 99.4 vs. 86.8, p=0.05), lower serum bicarbonate concentration (mmol/L: 19 vs. 21.5, p=0.04) and a lower median haemoglobin (g/dl: 9.4 vs. 10.5, p=0.005) Table IV.

At the last routine clinic appointment (median 5 weeks before the start of dialysis, subjects in EmG had higher median CRP (p=0.03) and lower serum albumin (p=0.0005) levels. They also had better preserved renal function with higher median eGFR (p=0.003) as shown in Table V.

Table IV: Laboratory variables at the start of dialysis.

	EmG(n=46)	EG(n=44)	p
	Median(range)	Median(range)	
Urea (mg/dl)	99 (56-190)	87 (45-168)	0.05
Bicarbonate (mEq/L)	19 (5-32)	21.5 (11-35)	0.04
Haemoglobin (g/dl)	9.5(5.5-13)	10.5(6-14.2)	0.005
Haemoglobin (g/dl)>11	80.4%	59%	0.02
PTH pg/ml	219 (2-1381)	228(19-1238)	0.8
PTH <200	26 (56%)	20 (52%)	0.9
Potassium (mEq/L)	4.5(2.9-7)	4.7(3-7.4)	0.08
Creatinine (mg/dl)	7.1(3.2-11.8)	7.5(3.7-12.78)	0.2
eGFR	7(4-19)	7(4-16)	0.5

Note: Serum creatinine in mg/dl may be converted to μmol/L by multiplying by 88.4; urea in mg/dl to mmol/L by multiplying by 0.357, PTH in pg/ml to pmol/L by multiplying by 0.105

Table V: Laboratory variables at clinic assessment immediately before start of dialysis.

	EmG (n=44)	EG (n=44)	
	Median (range)	Median (range)	p
Urea	84 (32-156)	84 (39-149)	0.7
Creatinine	6.07 (2.89-13.4)	7.29 (3.38-12.6)	<0.001
eGFR	9.5 (4-20)	7.5 (4-20)	0.003
Potassium	4.8 (3.7-7.3)	4.8 (3.4-6.4)	0.8
Bicarbonate	23 (13-33)	22.5 (11-32)	0.6
Haemoglobin	10.4 (7.6-14)	10.9 (6.7-15.9)	0.1
Ferritin	79.9 (7.5-669)	87.5 (7.6-400)	0.4
CRP	11 (3-200)	4 (3-44)	0.03
Calcium mg/dl	8.4 (7.2-11.5)	9.2 (7.6-11.3)	0.005
Calcium(corrected)	9.5 (8-11.6)	9.6 (7.9-11.7)	0.1
Phosphate mg/dl	5.6 (3.3-9.6)	5.9 (2.3-8.7)	0.8
Total protein g/dl	6.2 (5-7.7)	6.3 (4.7-7.6)	0.3
Albumin g/dl	3.1 (2.3-4.3)	3.5 (2.3-4.4)	<0.001

CRP*: Number of observations, EmG 42, EG 37
Note: Serum creatinine in mg/dl may be converted to μmol/L by multiplying by 88.4; urea in mg/dl to mmol/L by multiplying by 0.357, calcium in mg/dl to mmol/L by multiplying by 0.25, phosphate in mg/dl to mmol/L by multiplying by 0.323, protein and serum albumin in g/dl to g/ L by multiplying by 10

Table VI: Laboratory variables 3 months before start of dialysis.

		EmG		EG	
	n	Median (range)	n	Median (range)	p
Haemoglobin	46	10.4 (7.8-14)	44	11 (8.2-15.9)	0.06
Albumin	44	3.2 (1.7-4.7)	43	3.6 (2.8-4.2)	<0.001
CRP	41	21 (3-312)	19	5 (3-56)	0.08
Bicarbonate	43	23 (15-31)	41	23 (15-27)	0.6
eGFR	46	11 (6-30)	44	9 (5-29)	<0.001

To assess the significance of raised inflammatory markers further, laboratory variables were analysed three months in advance of requiring first RRT in both groups. EmG patients had significantly low serum albumin (p<0.001) and better preserved eGFR (p<0.001). They also had higher CRP and low Hb though difference didn't reach to statistical significance (Table VI). There was no difference observed in the two groups for the rate of decline in the renal functions in the preceding six months before requiring first RRT. The majority of diabetic patients started dialysis as an emergency (75% vs. 25% P=0.008).

Subgroup analysis of all diabetic patients known for more than six months showed that those who started dialysis as an emergency were significantly more anaemic compared to the diabetic patients who started dialysis as planned outpatient treatment (median Hb 9±0.28 vs. 11.4± 0.49, p=0.001).

To investigate whether patients who lived further from the dialysis unit were more likely to start dialysis as an inpatient, we measured the distance from each patient's home to the main dialysis unit and didn't find any difference between the two groups(p=0.07). Numbers of patients living within 10 mile radius of hospital were 55% in EmG vs. 40% in EG and 44% vs. 60% outside 10 mile radius in each group respectively.

Tables VII A & VII B: Multivariate analysis of variables obtained 3 months in advance to first dialysis.

VII A

Number of observations =87			
	Odds Ratio	95% conf. interval	p-value
Sex	0.57	0.21 - 1.54	0.2
Diabetes	4.93	1.62 - 14.98	0.005
Albumin <35	0.25	0.62 - 1.08	0.06
Albumin = 35	0.149	0.395 - 0.561	0.005

VII B

Number of observations=60			
	Odds Ratio	95% conf. interval	p-value
Sex	0.42	0.11 – 1.60	0.2
Diabetes	5.88	1.32 - 26.22	0.02
CRP=5-30	0.66	0.16 - 2.70	0.5
CRP=>30	5.57	0.94 - 32.95	0.05

In multivariate analysis of a number of variables obtained 3 months before starting dialysis, only a diagnosis of diabetes and a CRP >30 were independent risk factors for starting dialysis as an emergency. Having an albumin >35 was associated with a reduced risk of having an emergency start to dialysis (Table VII A & VII B).

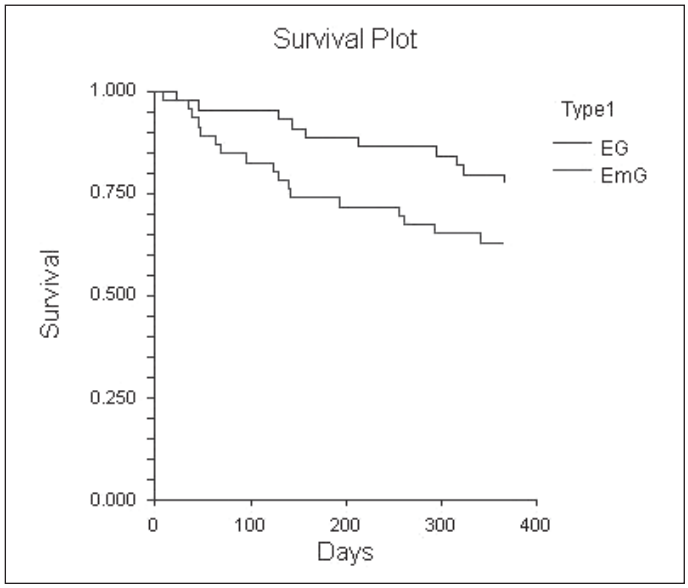

Figure 3: *Kaplan-Meier survival curves comparing survival in the Emergency (EmG) and Elective group (EG)*

There was no significant survival difference between the two groups (p=0.08), although the numbers were small. Compared to the EG, the survival in EmG was 82% (71- 93) vs. 95% (CI 0.89-1.0) at 95 days and 63 % (CI 49-76) vs. 77 % (CI 67- 89) at 12 months-Figure 3. Different causes of death are as listed in Table VIII.

Table VIII: Causes of death.

	EmG(n=46)	EG(n=44)
Cardiac	3	2
Cerebrovascular disease	1	0
Infection related	4	3
Malignancy	3	2
*Other causes	3	1
Treatment withdrawal	3	2
Total deaths	17 (37%)	10 (23%)

*Other cause:
EmG; 2 due to mesenteric infarction, 1 due to calcific uraemic arteriopathy
EG; 1 due to bowel perforation
(Deaths due to infections with MSSA (2) and MRSA (1) only occurred in the EmG)

DISCUSSION

Ideally, all patients and particularly those known to the renal services should start dialysis in a planned way as an outpatient. However this study shows that despite regular follow up in clinic, half of all patients known to the renal unit for at least 6 months started dialysis as an inpatient in an emergency situation. This remained unexplained by age, gender, BMI, underlying renal diagnosis, associated co-morbidities; distance lived from the renal unit and frequency of clinic follow up. However, 75% of all patients with diabetes mellitus as their underlying renal disease started dialysis as an emergency.

Timing of referral to the nephrologist is crucial in the management of CKD patients. Most studies in the past had used 3-4 months as a definition of late referral for dialysis (1, 2, 3 and 5). In a survey of Canadian nephrologists, a majority thought 4-12 months in advance of RRT would be adequate interval to prepare patients (7). On the basis of our local experience, six months in advance of RRT was felt to be a reasonable length of time for patient's preparation. Good practice guidelines by the National Service Framework UK recommend referral 12 months in advance of anticipated start of dialysis (8). Fifty-five percent of our study cohort was known to us for more than 12 months and a significant proportion (47%) still started dialysis as an emergency. This further raise the question whether even

12 months is adequate period to prepare patients for smooth initiation of dialysis.

Overall (in both groups), 50% of patient had permanent access at the time of first dialysis which is similar to the national average as reflected in the recent Renal Registry report (6). Similar results been reported in other studies from UK (5, 9) and Canada (10). However, the majority of EmG patients (74%) started dialysis with temporary access and had more infection related deaths due to MRSA and MSSA. Survival at 3 and 12 months after starting dialysis was worse in the EmG but not significantly different from that in the EG. Subjects in the EmG were also less likely to have had been reviewed by the pre-dialysis education team.

There were at least 13(28%) unavoidable admissions in EmG where the physician could have done very little to prevent an urgent start of dialysis. Eight patients had acute on chronic renal failure and two had poor compliance with clinic attendance and treatment. Three patients transformed their dialysis modality from planned peritoneal dialysis (PD) to haemodialysis (HD) at very late stage and required admission; two patients changed their mind when presented acutely to have dialysis instead of previously planned conservative care.

The timing of dialysis initiation has remained a controversial area (11, 12 and 13) and most recommendations have not been evidence based. More recently, results by Cooper et al from IDEAL study, a randomized controlled trial, showed no improvement in survival or clinical outcome for planned early initiation of dialysis in patients with stage five chronic kidney disease (14). The median eGFR at the start of dialysis treatment in our study was 7mls/min/1.73 m^2 in both groups which is similar to the median eGFR reported by the UK Renal Registry at the start of RRT in UK from 2000-2005 (6).

Our study has number of limitations; it is a retrospective analysis from a single centre with some missing variables. Although both groups were closely matched but compared to the EG, there were significantly higher percentage of diabetics in the EmG. The study sample was also relatively small with an element of lead time bias affecting the survival analysis.

So, can we forecast emergency initiation of dialysis in well known CKD patients? Apart from diabetic patients it seems difficult to identify patient characteristics which may predict in advance unplanned start of RRT. In addition, Subgroup analysis of diabetic patients showed that among them, anaemic patients were at higher risk of initiating dialysis in emergency. These findings suggest that it may be desirable to consider even earlier initiation of RRT in diabetic patients before they become symptomatic and similarly concentrate on their anaemia management.

Renal function and its rate of decline seem of no predictive value 3-6 months in advance of requiring dialysis when serial eGFR readings were plotted against time. However, another important finding in our study has been association of high CRP and low albumin (at last clinic appointment and 90 days before first RRT) with inpatient start of RRT. Inflammation in CKD patients seems to be multifactorial in origin(15,16), number of studies have demonstrated that increased CRP in CKD population predicting worse outcome related to all cause and to cardiovascular mortality (17,18). Low serum albumin has also been shown as independent risk factor for all-cause mortality in predialysis (CKD stage 3 and 4) patients and related with poor outcome when noted at the start of RRT (19, 20). Randomised controlled studies probably can shed further light on importance of the raised inflammatory markers and their association with emergency start of RRT.

CONCLUSION

Despite active follow up under specialist nephrology care for at least 6 months, 51% of patients starting haemodialysis did so as an emergency requiring hospital admission. These patients were less well prepared in terms of dialysis education and permanent vascular access and tended to have a less favourable outcome. Further analysis of the data showed that referral to the nephrologists even 12 months in advance of requiring dialysis may not be adequate period for all patients to have smooth initiation of RRT.

Apart from diabetes mellitus, raised CRP and low albumin may identify patients with CKD stage 5 who possibly can benefit from an earlier start of dialysis. Such an approach however would require formal testing in a randomised controlled study.

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