

The Art Of Prediction In Renal Medicine

“Examining Determinants Of Patient Outcome
In A Low Clearance Clinic”

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During my elective period with the Hull Royal Infirmary Renal Academic Department I undertook a piece of primary research looking into predictors of outcome for patients moving through a Low Clearance Clinic. I would like to thank my supervisors Professor Sunil Bhandari and Victoria Allgar as well as all the members of the Renal academic research department for making this research possible. I would also like to thank the British Renal Association for kindly sponsoring me through their Medical Student Elective Bursary.

Background

The age standardised prevalence of chronic kidney disease (CKD) stages 3-5 is 8% and with an aging population with increasing co-morbidities such as diabetes and cardiovascular disease this is set to rise. (1) (2) In addition, there are an estimated 15000 and 5000 people on haemodialysis and peritoneal dialysis respectively in the UK and this too is rising. (3) (4) In catering to the current demand from the East Yorkshire Region there are 360 haemodialysis and 85 peritoneal dialysis patients centred primarily in Hull with satellite units in Bridlington, Grimsby, Scarborough and Scunthorpe. (5) With finite resources the challenge of the future will be whether these services can meet expanding demands.

The Traditional Low Clearance Clinic (LCC) includes Specialist Renal Nurses, Dietitians, Pharmacists, Social workers and Nephrologists and has been created to in part deal with this issue of increasing CKD and triage patients according to their risk of renal failure. Although labour intensive, the rationale behind the close monitoring of renal function, early management of associated risk factors and co-morbidities including; weight loss, low salt and phosphate diets, acidosis, optimising diabetic control and blood pressure may delay dialysis and premature death for this patient group.

Low clearance clinics not only review CKD 4-5 patients and manage the side effects of renal failure such as anaemia but also educate patients to make an informed decision about which type of renal replacement therapy (RRT) to undertake. In a growing number of patients, decisions not to have RRT are being made; instead they prefer to be supported through the palliative process. (6) Data is beginning to show that optimising patients into palliative care can have better outcomes for patients. (7)

Introduction

Although upstream interventions are aimed at improving patient outcomes, there is a caveat in preventative medicine that early intervention must be balanced against over-investigation which can cause harm, increase patient anxiety and of which elderly patients are particularly vulnerable.

Another issue about selecting the correct patients to investigate has come out of a recent drive in quality outcomes framework (QoFs) for GPs to refer patients to secondary care in CKD 3 in order to try and prevent the progression of CKD. This has sparked debate about which patients will progress to End Stage Renal Failure and whether or not this is appropriate. (8)

Indeed combined with future pressures from an increased workload, GPs and nephrologists will need to be able to appropriately stratify their patients to help target interventions more specifically and therefore cost-effectively.

The aim of this study was to demonstrate whether goal directed best clinical care in the LCC delays renal progression both to all cause mortality and requirement for RRT. As shown in **Figure 1**, we hypothesised that patients with a rapidly declining eGFR would have poorer outcomes in terms of RRT and mortality compared to those with a slower declining eGFR. Analogous to this hypothesis would be an elderly patient presenting with slow age-related decline of renal function versus a middle aged individual with uncontrolled diabetes- who would suffer a more rapid decline in eGFR. This hypothesis suggests that if we could moderate upstream patient risk factors then we would be able to improve outcomes in the future.

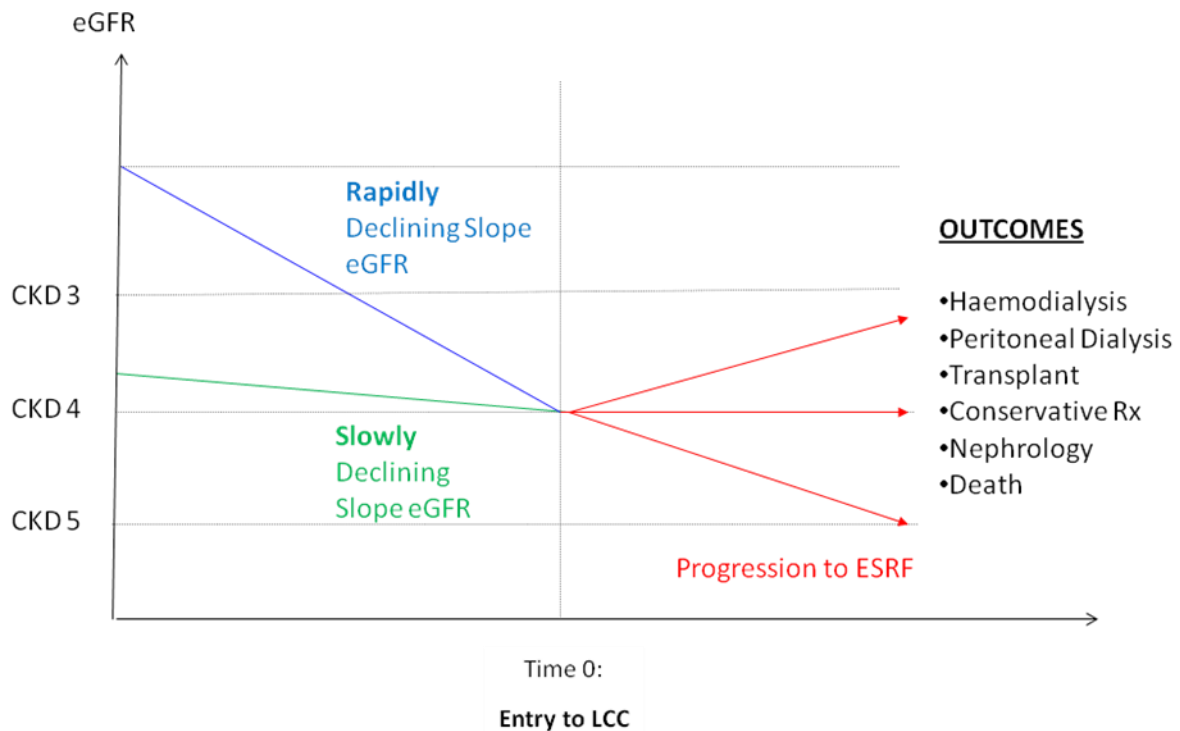


Figure 1 Error! Bookmark not defined. Rate decline in eGFR before and after entry to the LCC

Methods

A retrospective cohort study was constructed of 273 patients entering the LCC in a single centre over a 24-month period. **Figure 2**, describes the censoring process. 216 patients underwent descriptive analysis of which the baseline characteristics are included in **Table 1**. After a further round of censoring to remove those with less than 6 months follow up prior to entry into the LCC, so called “crash-landers”, 180 patients underwent survival analysis.

Potential factors considered predicative for outcome included; age on entry to LCC, sex, baseline eGFR, rate change in eGFR ($>4\text{mls/min}/1.73\text{m}^2$ per year was considered rapidly deteriorating), co-morbidity, smoking status, renal disease aetiology, haemoglobin, serum albumin and calcium phosphate levels.

To measure the effect of LCC we used a calculation based on an interrupted time series analysis and the differences in slope eGFRs before and after entry to the LCC were calculated. Values $>+1\text{ml}/\text{min}/1.73\text{m}^2$ per year were considered improvers, $<-1\text{ ml}/\text{min}/\text{m}1.73^2$ per year were considered deteriorators and $>+1$ and $<-1\text{ml}/\text{min}/1.73\text{m}^2$ per year were considered an unchanging group. As per the standardised clinic proforma, Improvers and deteriorating groups were compared in respect to systolic and diastolic blood pressure, weight and haemoglobin.

In addition, absolute differences between the slope eGFRs before and after entry into the LCC were calculated and split into quartiles and survival analysis was performed.

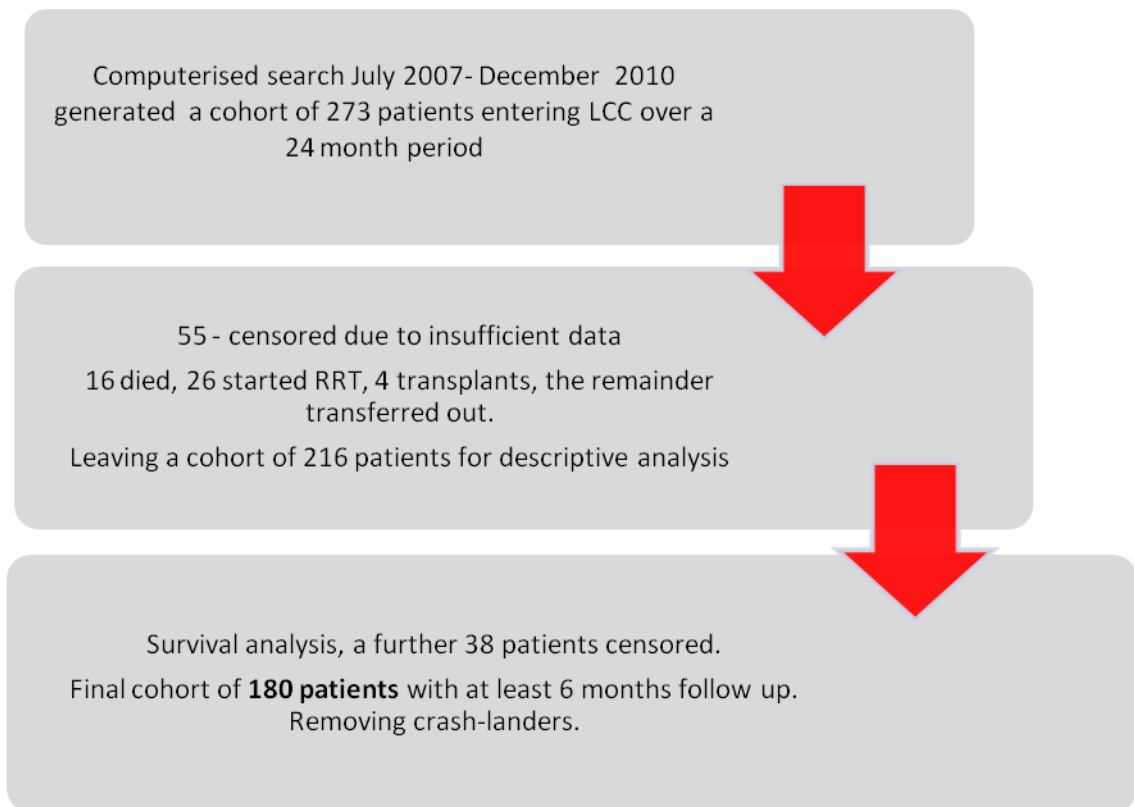


Figure 2 Censoring Process

Statistical analysis

All statistical analyses were completed on SPSS for Windows – version 19. All dependent variables are expressed as means, interquartile ranges and standard deviations. All independent variables are expressed as percentages of total study population. In comparing groups of two independent groups of variables, the non-parametric test which was chosen was a Mann-Whitney U test and a p-value of <0.05 was considered to reject the null-hypothesis.

Survival analysis was analysed using Kaplan-Meier and multivariate analysis using Cox regression analysis with mortality being a primary end-point but other secondary end-points such as time to dialysis were considered.

Predictors of mortality were determined by uni-variate, multi-variate analysis and for survival the Cox Regression and Kaplan-Meier method was used, with a negative log rank test (Mantle-Cox) to secure the p-value. A p-value of < 0.05 was considered statistically significant

Results

Baseline characteristics showed a mean age of 64 years (SD15) within a predominantly Caucasian population (99%). The mean time from a first recorded eGFR until entry to the LCC was 16.8 months (SD 11.2) with an mean baseline eGFR of 20.8 ml/min/1.73m² (SD 7.23). Mean eGFR on entry to the LCC was 13.8 ml/min/1.73m² (SD 3.68) and the mean time before a primary event (RRT, Transplant, Death, Conservative or return to management in a Nephrology Clinic) was 14 months (SD 10.1). **Table 2** shows the baseline levels of CKD.

As shown in **Table 3**, 9.2% died without primary intervention, 12% started conservative management, 10% were transferred back to Nephrology clinics, 3% were transplanted and 10.6% remain in the LCC. 55% of patients commenced RRT (119/216): 26.1% peritoneal dialysis (31/119) and 73.9% haemodialysis (88/119). The average length of time within the LCC was 14 months (SD 10.1) and of those receiving RRT 62% received this intervention within one year compared to 38% after 1 year.

Predictors of outcome prior to entry to the LCC

Shown in **Table 4** and **Figure 3**, a rapidly declining rate of eGFR prior to entry into the LCC was predictive of both those who would need haemodialysis sooner within a mean of 21 months (95% CI 17.7-25) [comparison group 31.2 months (95% CI 27.5-35.0, $p < 0.001$)] and also of mortality within an average of 26.3 months (95% CI 21.9-30.7) [comparison group 31.8 (95% CI 27.9-35.8, $p = 0.07$)].

Effects of the Clinic

The differences in slope eGFRs before and after entry to the LCC were calculated. Values $> +1$ ml/min/1.73m² per year were considered improvers, < -1 ml/min/1.73m² per year were considered deteriorators and $> +1$ and < -1 ml/min/1.73m² per year were considered an unchanging group. 63.3% of patients (114/180) improved, 34.4% deteriorated (62/118) and 2.2% (4/180) remained in the equivocal group, **Table 5**.

Comparison of the improving and deteriorating groups is shown in **Table 6**. Haemoglobin increased on average by 0.28 g/dL per year (SD 2.77) compared to -0.90 g/dL per year (SD 2.83) in the deteriorating group. Weight decreased by -2.48 kg/year (SD 10.70) compared to -1.82 kg/year (SD 6.44) in deteriorating groups. Systolic blood pressure in the improving group dropped by -0.37 mmHg per year (SD 65.15) compared -5.83 mmHg per year (SD 111.60) in the deteriorating group. Interestingly on average the improving group were more likely to have a worse slope eGFR (-9.60 ml/min/1.73m² per year (SD 7.2)) compared to the deteriorating group prior to entry into the LCC.

Once entered into LCC

Absolute differences between the slope eGFRs before and after entry into the LCC were calculated and split into quartiles. The highest quartile of patients who maintained a decline in their respective eGFRs had a shorter time to dialysis with a mean of 24.2 months (95% CI 20.9-27.5, SE 1.7) [comparison group 30.4 months (95% CI 26.1-34.7, SE 2.2, $p = 0.03$)] but showed no difference in mortality (**Figure 4**). Indeed even after adjusting for potential confounders of comorbidities such as smoking, diabetes, left ventricular hypertrophy, anaemia, vascular disease and cancer a Cox-regression model showed no significant difference in mortality ($p = 0.384$). However, given that the average yearly cost of haemodialysis is £30,000; delaying dialysis by 6 months would confer a cost saving of £15,000 per patient by reducing the overall rate decline in slope eGFR.

Conclusions

Our study shows that management of patients within a low clearance clinic setting improves markers of severity of renal disease such as haemoglobin and eGFR however there was no overall benefit in mortality conferred by the clinic. However it is important to remember that crash-landers were censored from the analysis, there was relatively short follow up and further analysis would

have to adjust from lead time bias. Another retrospective cohort trial, with the majority of patients in CKD5, has shown that although no difference was shown in any of the biological data they collated (serum calcium, phosphate and albumin) they had improved rates of survival in their multidisciplinary clinic compared to their standard nephrology clinic. (9) In our study, it is fair to say that a significant proportion of our patients with inadequate length of follow up and rapidly declining renal function had died prior to entry into a low clearance clinic. There is an assumption that as acute presenters these would have benefited little within the clinic and conferred little benefit to the overall mortality seen.

Importantly, we have demonstrated that the clinic can delay the need for dialysis by reversing the rate decline of renal function. This reflects work in the randomised prospective multicentre Canadian Prevention of Renal and Cardiovascular Endpoints Trial (CanPREVENT) that has shown this intervention cost-effective. (10)

Traditionally nephrologists have always viewed the eGFR within the clinical context; indeed there is now emerging interest in the rate decline of eGFR being predictive of mortality and factored into risk prediction tools. (11) (12) Trusts have been advocating referral based a trend of declining eGFR however this has yet been incorporated into a model. (13) We suggest that a risk model based on rate decline of eGFR could be incorporated into pre-existing models based on biological data at a point in time. (14)

In summary, we have shown that a LCC does impact the rate of decline of eGFR and that it is a cost-effective intervention. In addition pre-LCC rate of eGFR decline predicted outcome in relation to RRT and mortality. These patients may require more attention and early identification to further reduce mortality in the future.

Limitations

I am aware of the selection bias that occurs when censoring however I have tried to ameliorate this by including a brief follow up analysis (approximately half of the patients censored starting renal replacement therapy and approximately a third dying combined with the short follow up it is fair to say that these represent a sicker proportion of patients).

Finally what I have learnt from this experience...

Undertaking a piece of primary research has certainly enriched my undergraduate experience in medicine. It has given me tools in which to apply critical thinking in my day to day work with a healthy pinch of scepticism. It has caused me to ask questions such as; "is this really an efficacious treatment?", "what are the potential harms?" and "what would happen if we stopped this course of action?" In addition it has exposed me to an environment where I have met new colleagues with a diverse and stimulating array of research interests and points of view.

The key to the success of much in research mirrors what is needed in any professional working environment. From needing to persevere when answers are not forthcoming, networking with the people around you who may know an easier way of doing something and having a good working relationship with your supervisors who ultimately provide shape and balance to what you are doing.

I would full-heartedly recommend undertaking a piece of primary research to all medical students, not just because it looks great on your CV, but will give you an understanding of where the limits of medicine are and the boundaries to overcome.

Tables and Graphs

Table 1

Baseline characteristics [mean and standard deviation (SD)]

Factor	Statistics	Patient numbers
Age (years)	64 years (15)	216
Age >65 (%)	56%	120
Ethnicity: Caucasian%	99%	213
Male gender (%)	57%	124
Clinical diagnosis		
Diabetic nephropathy (%)	20%	43
Hypertension/Reno-vascular disease (%)	5%	13
Glomerulonephritis (%)	31%	67
Diagnosis Unknown (%)	29%	61
Other	15%	32
Smoking		
Current smokers (%)	17%	37
Ex-smokers (%)	12%	25
Non-smokers	71%	154
LVH	11%	24
Diabetes mellitus	28%	61
Co-morbidity		
Ischaemic heart disease (%)	26%	56
Cerebrovascular accident (CVA) (%)	14%	30
Peripheral vascular disease (%)	13%	29
Chronic obstructive pulmonary disease (COPD) (%)	8%	17
Cancer (%)	15%	32
Peripheral Oedema	29%	62

Table 2

Baseline level of CKD on Referral and entry into the LCC

Characteristics	Initial Referral	On entry to LCC
Average eGFR (ml/min/1.73m ²)	20.8 (SD 7.23)	13.8 (SD 3.68)
Percentage CKD 3	11% (24/216)	<1% (1/216)
Percentage CKD 4	68% (146/216)	29% (63/216)
Percentage CK5	21% (46/216)	70% (152/216)

Table 3

Outcomes by Proportion

OVERALL RESULTS		
Average time from first LCC appointment to Last (Including all outcomes: RTT, Death, TP, Return to nephrology clinic or beginning conservative management)	13.97 months	SD 10.1
Average time after censoring those returning to conservative/ management in nephrology clinic	14.9 months	SD 10.3
CONSERVATIVE		
Proportion of conservatively managed patients	12%	(26/216)
Average time until considered for conservative management	9.88 months	SD 9.33
Proportion of conservative management patients deceased	54%	(14/26)
Average number of months from decision of conservative management to death	8.14 months	SD 6.01
PATIENTS RETURNING TO NEPHROLOGY CLINICS		
Proportion of patients returning to nephrology	10%	(21/216)
Average time until considered to return to nephrology	12.8 months	SD 9
Proportion of patients managed in nephrology deceased	24%	(5/21)
Average time, months, decision of nephrology management to death	15.25	SD 6.7
DIALYSIS PATIENTS		
Percentage of patients ending on RRT (Haemo/PD)	55%	(119/216)
Percentage of patients on initial haemodialysis	73.9%	(88/119)
Percentage of patients on initial PD	26.1%	(31/119)
Percentage of patients finally on HD	76%	(91/119)
Avg. number of months before starting RRT after entering LCC	12.33 months	SD 8.64
REFERRAL FROM LCC TO RRT TIME		
<1 month (%)	1%	1/119
0/12–12/12 months (%)	61%	73/119
>12/12 months (%)	38%	45/119

Table 4

Table showing pre-LCC Kaplan-Meier Survival Times for Haemodialysis and Mortality

PRE-LCC: COMPARING RAPID AND SLOW DECLINING EGFR AND TIME TO DEATH AND RRT		
Comparison Groups Time to Haemodialysis:	31.2 months	(95%CI 27.5-35.0, SE 1.9)
Rapidly Declining entry to LCC Time to haemodialysis:	21 months	(95% CI 17.7-25.0, SE 1.9)
Comparison groups: Months to death	31.8	(95% CI 27.9-35.8, SE 2.0)
Rapid declining entry to LCC months to death	26.3 months	(95% CI 21.90-30.7, SE 2.2)

Crash Landers removed before analysis.

Table 5

Proportion of Improvers, Deteriorating and Equivocal group members

	FREQUENCY	PERCENT
Improvers	114	63.3
Deteriorating	62	34.4
Equivocal Group	4	2.2

Improver ($>+1\text{ml}/\text{min}/1.73\text{m}^2$ per year), Deteriorating ($<-1\text{ml}/\text{min}/1.73\text{m}^2$ per year), Equivocal groups (within $1\text{ml}/\text{min}/1.73\text{m}^2$ per year either way)

Table 6.

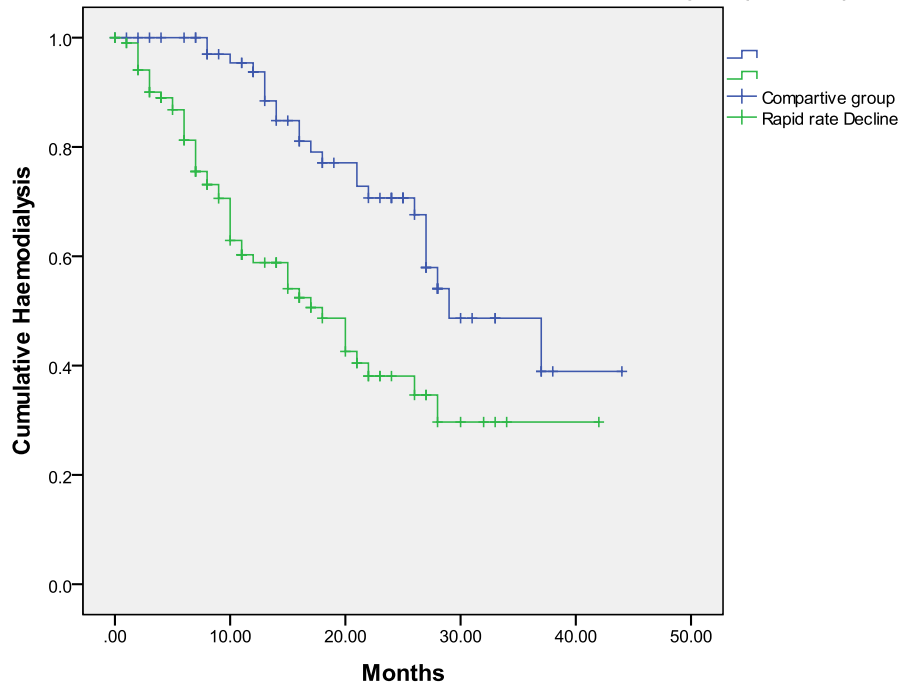
Comparison of independent variables by groups of improvers and deteriorating

Difference in change (Δ) of independent variables over time	Improvers (n=114)		Deteriorating (n=62)		Significance value
	Mean	SD	Mean	SD	
Δ Hb (g/dl per year)	.28	2.77	-.90	2.83	0.035
Δ Systolic BP (mmHg per year)	-.4	65.1	-5.8	111.6	0.825
Δ Diastolic BP (mmHG per year)	-2.7	29.9	-7.3	43.1	0.365
Δ Weight (kg per year)	-2.48	10.70	-1.82	6.44	0.632
Rate change in EGFR prior to entry to LCC	-9.69	7.20	-1.85	3.05	0.000
Rate change in eGFR once in the LCC	-1.42	4.06	-5.63	3.67	0.000

Independent variables significance calculated with Mann-Whitney U test. Levels of <0.05 considered as statistically significant

Figure 3

Comparing groups with a rate change EGFR of $>4\text{mls/min/m}^2\cdot\text{year}^{-1}$ with those with a slower decline and their time to Haemodialysis ($p<0.001$)



Rapid rate decline on entry to LCC vs comparative slopes and Mortality ($p=0.075$)

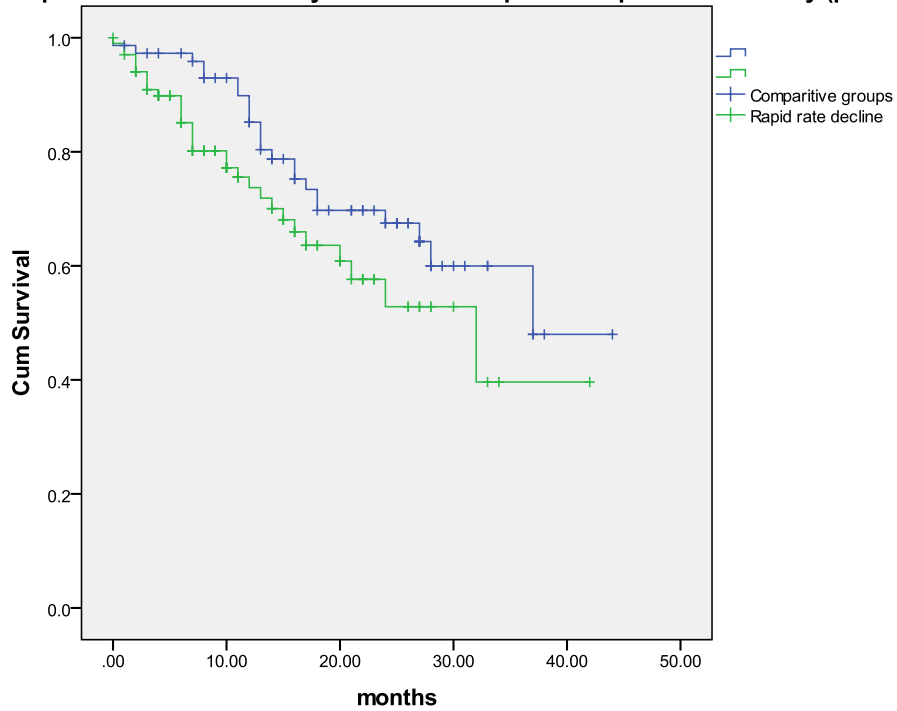
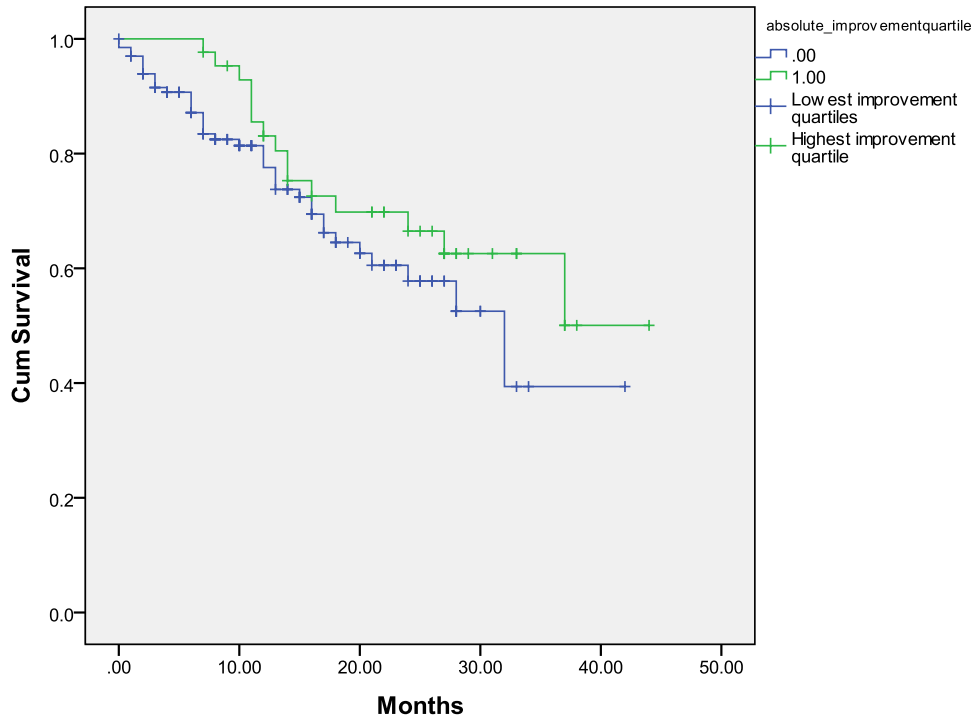
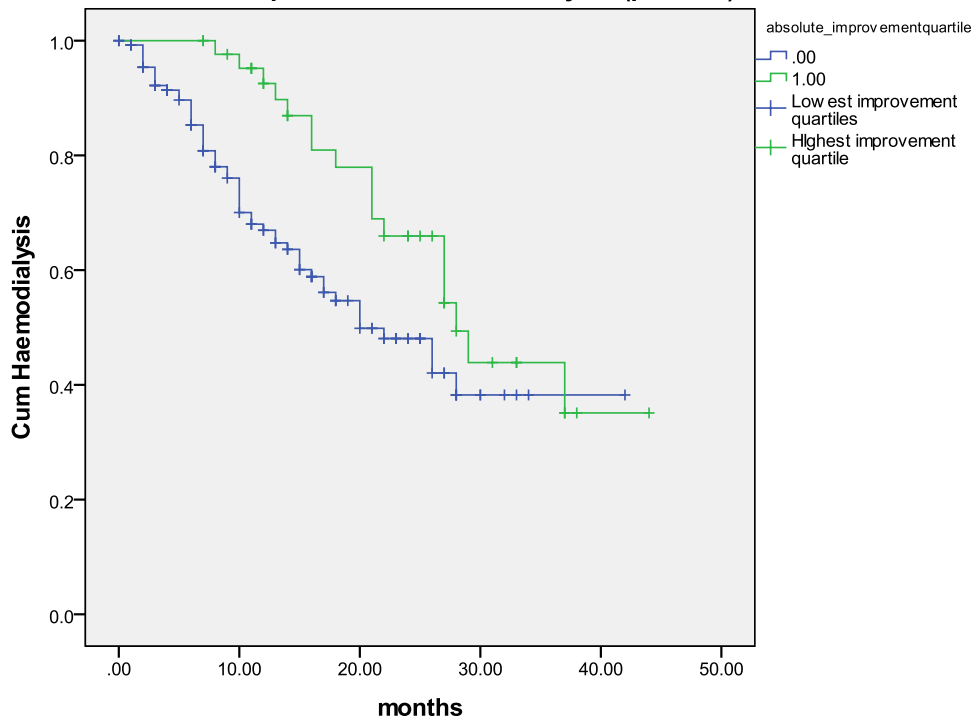


Figure 4

Absolute change in EGFR once entered into LCC comparisson of highest quartile vs other quartiles survival p=0.229



Absolute change in eGFR. Comparisson of Highest quartile change vs other quartiles and time to dialysis (p=0.028)



References

- 1 Stevens PE, O'Donoghue DJ, de Lusignan S, Van Vlymen J, Klebe B, Middleton R, Hague N, New J and Farmer CK. Chronic kidney disease management in the United Kingdom: NEOERICA project. *Kidney Int* 2007; 72: 92-9,
2. Byrne C, Steenkamp R, Castledine C, Ansell D and Feehall J. UK Renal Registry 12th Annual Report (December 2009): Chapter 4 UK ESRD Prevalent Rates in 2008: National and centre-specific analyses. *Nephron Clin Pract* 2010; 115 [Suppl 1]:c41–c67
3. Feest TG, Rajamahesh J, Byrne C et al. Trends in adult renal replacement therapy in the UK: 1982-2002. *QJM* 2005; 98: 21-28
4. NHS Choices: Dialysis. NHS [internet]. n.d. [Accessed 2012 Jan 05]. Available from: [HYPERLINK "http://www.nhs.uk/conditions/Dialysis/Pages/Introduction.aspx?url=Pages/what-is-it.aspx"](http://www.nhs.uk/conditions/Dialysis/Pages/Introduction.aspx?url=Pages/what-is-it.aspx)
<http://www.nhs.uk/conditions/Dialysis/Pages/Introduction.aspx?url=Pages/what-is-it.aspx>
5. Renal Units in the UK. Renal association [internet] n.d. [Accessed 2012 Jan 05]. Available from: [HYPERLINK "http://www.renal.org/unit/?c=hull"](http://www.renal.org/unit/?c=hull) <http://www.renal.org/unit/?c=hull>
6. Murray S, Kendall M, Boyd K. Illness trajectories and palliative care. *BMJ* 2005;330:1272.1
- 7.: Russon L, Mooney A. Audit: Integrating Palliative Care within a Low Clearance Clinic is Associated with Improved Outcomes. Leeds Teaching Hospital. [Accessed 2012 Jan 05]. Available from: [HYPERLINK "http://www.kidneycare.nhs.uk/"](http://www.kidneycare.nhs.uk/) <http://www.kidneycare.nhs.uk/>
8. Spence D. Bad medicine: chronic kidney disease. *BMJ* 2010;340:c3188
9. Fenton A, Sayar Z, Dodds A, Dasgupta I. Multidisciplinary Care Improves Outcome of Patients with Stage 5 Chronic Kidney Disease *Nephron Clin Pract* 2010;115:c283-c288
10. Hopkins RB, Garg AX, Levin A, Molzahn A, Rigatto C, Singer J, Soltys G, Soroka S, Parfrey PS, Barrett BJ, Goeree R. Cost effectiveness analysis of a randomized trial comparing care models for chronic kidney disease. [HYPERLINK "http://www.ncbi.nlm.nih.gov/pubmed/21617091"](http://www.ncbi.nlm.nih.gov/pubmed/21617091) \o "Clinical journal of the American Society of Nephrology : CJASN." *Clin J Am Soc Nephrol.* 2011 Jun;6(6):1248-57.
11. Al-Aly Z, Zeringue A, Fu J, Rauchman MI, McDonald JR, El-Achkar TM, Balasubramanian S, Nurutdinova D, Xian H, Stroupe K, Abbott KC, Eisen S. [HYPERLINK "http://www.ncbi.nlm.nih.gov/pubmed/20947634"](http://www.ncbi.nlm.nih.gov/pubmed/20947634) Rate of kidney function decline associates with mortality. *J Am Soc Nephrol.* 2010;21(11):1961-9.
12. Tangri N, Stevens LA, Griffith J, Tighiouart H, Djurdjev O, Naimark D, Levin A, Levey AS. [HYPERLINK "http://www.ncbi.nlm.nih.gov/pubmed/21482743"](http://www.ncbi.nlm.nih.gov/pubmed/21482743)
A predictive model for progression of chronic kidney disease to kidney failure. *JAMA.* 2011 20;305(15):1553-9
13. Renal Guidelines- Adults with Chronic Kidney Disease. The East Midlands Renal Network Guidelines. Sep 2009. [Accessed 2012 Jan 05]. Available from: <http://www.emrn.org.uk/>

14. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. *JAMA*. 2011;305