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ARTICLE *in* NEPHRON · FEBRUARY 2015

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Critically ill patients requiring acute renal replacement therapy are at increased risk of long-term renal dysfunction, but rarely receive specialist nephrology follow-up.

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Abstract

Background: Episodes of Acute Kidney Injury (AKI) have been associated with development Chronic Kidney Disease (CKD). However, follow up pathways for patients who have survived AKI complicating critical illness are not well established. We hypothesized that patients who had AKI requiring renal replacement therapy (RRT) in intensive care are at risk of CKD, but are rarely referred for nephrology follow-up at hospital discharge.

Methods: We performed a retrospective analysis of all patients who survived AKI requiring renal replacement therapy in intensive care units (ICUs) in the East London region, examining renal function at baseline, hospital discharge and 3-6 months follow-up. We excluded patients who were known to renal services prior to index admission.

Results: From 5544 critical care admissions we identified 219 patients who survived to discharge having undergone RRT for AKI that were not previously known to renal services. Of these, 124 (57%) had a creatinine measured within 3-6 months after discharge, 104 having a pre-morbid baseline for comparison. Only 26 patients (12%) received specialist nephrology follow-up. At 3-6 months follow-up estimated glomerular filtration rate was significantly lower than baseline (48 vs. 60mLs/min/1.73m² p<0.001), with the prevalence of CKD stages III-V rising from 49% to 70% (p<0.001).

Conclusions: Follow-up of patients who required RRT for AKI in ICU is inconsistent despite, evidence of a significant increase in the prevalence of CKD. There is strong

justification for development of robust pathways to identify survivors of AKI following CKD and its complications to be detected and managed.

Keywords

Acute Kidney Injury, Long-term outcomes, Chronic Kidney Disease, Critical illness

Introduction

AKI is common and serious complication of critical illness [1] with a high associated hospital mortality.[2] However, traditionally, recovery of pre-morbid renal function had been thought to occur in most of those who survive critical illness. However, when accurate determinations are made, reductions in renal function can be shown to persist long after the acute injury, consequently longer-term outcomes of patients who survive AKI are increasingly recognized as of key clinical importance.[3]

Specialist management algorithms have been developed for follow up of patients with recognized Chronic Kidney Disease (CKD),[4] however, follow-up pathways for patients who have suffered AKI complicating critical illness are not well established. Importantly, the effects of prolonged major illness can confound serum creatinine-based assessment of CKD risk at hospital discharge.[5] To document clinical need and current practice in our region we examined rates of specialist follow-up and development or progression of CKD in patients who received RRT in the ICU over a one-year period.

Methods

Design & data sources

This study was conducted as an institutionally approved service-development audit of outcomes and follow-up of severe acute kidney injury against national recommendations.[6] We performed a retrospective analysis of all adults in the East London region (UK) requiring RRT following admission to ICU from 1st January to 31st December 2011. We excluded patients previously known to a nephrology specialist with CKD, end stage renal disease or renal transplant prior to admission within the last 10 years.

East London has a population of 1.8 million served by eight NHS hospitals (9 ICUs), supported by a central nephrology service. Seven ICUs are mixed medical-surgical, one serving a level-1 trauma center, while two are specialist cardio-thoracic units. In the UK, nephrologists are not routinely involved in the decision to commence RRT, therefore in all the ICUs studied, RRT was initiated and managed solely by the intensive care team using continuous veno-veno haemofiltration or haemodiafiltration.

Patient information was collated from ICNARC (Intensive Care National Audit and Research Centre) ICU audit databases, central renal unit and local pathology electronic records. We collected demographic data, baseline renal function (last measurement, whether as a previous in-patient or as an outpatient, before seven days and up to one year prior to index hospital admission), hospital discharge creatinine, details of follow-up visits and creatinine measurements from 3 to 6 months after hospital discharge. Estimated GFR (eGFR) was calculated using the CKD-EPI four-variable creatinine equation.[7] Presumed cause of AKI was independently

assessed from clinical records by CK and MB. JP offered further review in cases of disagreement.

Data Analysis

Analysis was performed using R: A language and environment for statistical computing (<http://www.R-project.org>). Continuous variables are reported as median (range) and compared by Mann Whitney-U or Wilcoxon signed rank tests, categorical variables were compared using Fisher Exact or McNemar tests. Statistical significance was defined by a two-sided p value of <0.05. Simple linear regression was used to investigate the relationship between discharge and follow-up eGFR with calculation of the coefficient of determination (Pearson r^2). To assess whether changes between repeated observations could be explained by *regression to the mean* the regression line was compared against a predicted regression line, derived from modeling repeated eGFR measurements using a high-end estimate for the coefficient of variation (CV) of 20%.

Results

There were 5544 ICU admissions in 2011, 781(14%) patients received renal replacement therapy (RRT), of these 261 survived to hospital discharge and were not known to renal services (Figure 1). Distribution of cases between ICUs is shown in Supplementary Table 1.

Within three months of hospital discharge 22 died, seven commenced maintenance renal replacement therapy, eight were re-admitted to hospital and five moved out of region (Figure 1), leaving 219 patients where outpatient assessment of

CKD status would be possible. 182/219 (83%) were offered a hospital follow-up appointment; 142/182 (78%) attended their appointment, but only 78 of those (55% of those attending) had their creatinine measured at this visit. Twenty-six patients (12%) were reviewed in nephrology out-patients and creatinine was checked in all of these patients. Median time to first hospital appointment with any clinician was 6 weeks (range 1-32).

Despite the low frequency of creatinine measurement at first outpatient visit, 124 patients (57%) had a creatinine checked between 3-6 months after hospital discharge, either at another hospital visit or in primary care, providing results that could be used for CKD assessment. The demographics of patients with and without post-discharge creatinine results are shown in Table 1. Having a 3-6 month creatinine measurement was associated with lower pre-morbid eGFR (60 v 67 ml/min/1.73m²; p=0.04) and a higher proportion of baseline CKD (53 (51%) v 38 (28%); p<0.001). Trauma was less frequent and obstruction more frequent in those who had follow-up creatinines.

There was no significant difference between creatinine measurements (121 (27-617) vs. 124 (40-645)µmol/L, p=0.13) or eGFR (46.5 (5-147) vs. 49.5 (2-142) ml/min/1.73m²; p=0.2) at hospital discharge compared to 3-6 months later. However, linear regression analysis between discharge and follow up eGFR suggested significant variation in individual eGFR measurements during follow-up (r²=0.59). Overall, the regression equation suggested that eGFR values higher than 49ml/min/1.73m² tended to decrease during follow-up, while values lower than this tended to increase, this effect was larger than the predicted regression to the mean

effect from repeated eGFR measurements, suggesting actual changes in eGFR were occurring during the follow-up period (Figure 2).

In the sub-group of 104 patients who had baseline, hospital discharge and follow up creatinine measurements, baseline creatinine was significantly lower than at hospital discharge creatinine and 3-6 months later (99 (51-398) versus 120 (27-617) or 126 (40-641) $\mu\text{mol/L}$ respectively, $p < 0.0001$ for both). Similarly eGFR was higher at baseline than at discharge or follow-up (60 (12-141) v 45 (5-142) and 48 (2-128) ml/min/1.73m^2 respectively, $p < 0.0001$ for both). Consequently, prevalence of CKD III (eGFR < 60) rose significantly from 49% at baseline to 70% at 3-6 months (Table 2). There was a tendency for eGFR to decrease from baseline to follow-up across the whole range of baseline renal function, with a regression line lying consistently below the line of identity (Figure 3).

Discussion

Summary of findings

We focused on a cohort of patients not previously known to renal services surviving to hospital discharge after receiving RRT in ICU. As expected, there were high rates of adverse outcomes after hospital discharge, 14% dying, requiring maintenance RRT or being re-hospitalized within 3 months of hospital-discharge. In our cohort of patients developing RRT requiring AKI we observed a high prevalence of pre-morbid CKD (51%), in line with the well-described role of CKD as the strongest baseline risk factor for development of AKI.[3,8,9]

Of the 219 patients available for follow-up only 12% were referred to a nephrologist. When seen by non-nephrologists only 55% had creatinine measured at

their first follow-up. When measured, the prevalence of CKD III, or greater, rose from 49 to 70% after critical illness and proportion with CKD IV or V more than doubled, highlighting the importance of follow-up for these patients. Falls in eGFR after critical illness were seen at all levels of baseline function, but were unpredictable between individuals (Fig. 3) suggesting it may be difficult to prospectively select high risk patients for progression of CKD at baseline.

We found no significant difference between eGFR at hospital discharge and at 3-6 months follow up. Both increases and decreases in eGFR can occur after hospital discharge as a result of recovery, or further deterioration, in true GFR or recovery of muscle mass. In the 124 patients with discharge and follow-up eGFR the coefficient of determination was 0.59, implying that over 40% of the variation in follow-up eGFR could not be accounted for by variation in discharge eGFR. Higher eGFR values tended to decrease and lower values to increase (Fig. 2), an effect that was larger than could be accounted for by regression to the mean between repeated measurements. Patients with lower eGFR at discharge may have more potential for continued renal recovery, while increase in muscle mass may be more likely in those with higher discharge eGFR. However, in individual patients, substantial increases or decreases in follow-up eGFR were seen across most of the range of discharge eGFR (Fig 2). It is therefore difficult to predict who requires follow-up at hospital discharge and specifically a higher eGFR at discharge should not be taken as universally reassuring.

Strengths and limitations

This study represents a comprehensive description of the follow-up of severe AKI complicating critical illness in a populous geographical area. As all acute health care in our region is provided by the National Health Service hospitals we can be confident of capturing almost all acute RRT episodes.

As a retrospective analysis this study has limitations. Follow-up data is incomplete, however, the paucity of follow-up is an important finding in its own right. Rates of pre-morbid CKD and creatinine levels at ICU discharge were lower in the group who had no follow-up, however approximately half these patients still had an eGFR of <60 at hospital discharge, suggesting significant potential for CKD in these patients.

However, it is likely that estimates of creatinine generation implicit in eGFR equations are poorly calibrated to critically ill AKI patients, who experience significantly decrease creatinine generation [10,11] not only during their illness but also at the time of hospital discharge and then weeks into their recovery; eGFR could therefore significantly over-estimate true GFR in many survivors of critical illness for a significant period after the acute illness.[5] Use of CKD-EPI eGFR in this study is pragmatic, it is a simple clinical tool by clinician to assess AKI recovery and, in the absence of measured GFR, gives a lower limit for the prevalence of CKD. It is thus likely that the prevalence of true GFR below 60 or 30 in our population is higher than that indicated by eGFR, particularly at hospital discharge; however this would only strengthen our findings and recommendations.

Finally patterns of AKI follow-up we have observed may be specific to environments like the UK, many European Nations and Australia where CRRT is prescribed and provided by the ICU clinical team. In this setting nephrology

consultation is usually only undertaken if there are specific indications, or need for ongoing RRT following recovery from critical illness. This practice pattern has the advantage of rapid 24h access to RRT in the critically ill and integration of CRRT into integrated multi-organ support overseen by an intensivist, however it does require specific referral for long-term follow-up. We did not study patients outside the ICU who received intermittent haemodialysis (IHD) for AKI as a single organ failure in renal units, where follow up may be more comprehensive. All RRT provided in the ICU this study was CRRT, however as recent evidence suggests that renal outcomes are if anything worse with first use of IHD for AKI in the ICU [12] our findings regarding development and progression of CKD would be expected to be more significant in setting where IHD is used in the ICU.

In support of our findings, a large retrospective analysis of US Veterans Administration Hospitals patients found that only a minority of nearly 4000 AKI-survivors were referred for nephrology follow-up, despite the a likely higher level of specialist nephrology consultation in the ICU in a US healthcare environment.[13] The study analysed persistent renal dysfunction 30 days after the peak AKI and found despite a 60% prevalence of CKD prior to the renal injury, only 8.5% (10.6% of AKI III survivors) were referred to a nephrologist for follow up.

Implications and future research

It is now well established that AKI is major risk factors for the development and progression of CKD [14-16], even with apparent recovery to baseline function.[17,18] Furthermore CKD after AKI has been associated with increased risk of death and cardiovascular morbidity.[19,20]

Evidence exists from a Canadian Study that contact with a renal physician after severe AKI (as opposed to with a cardiologist or general practitioner) may improve outcomes in patients that are not already known to a Renal service.[21] Targeted follow-up and simple medical interventions recommended for patients with CKD could modify long-term outcomes. A recent UK health economic analysis has suggested that *post-discharge* healthcare costs attributable to inpatient-AKI in 2010–11 would be £179 million, primarily due to increased incidence of CKD and need for RRT.[22] It has been estimated that prescription of ACE-inhibitors or Angiotensin Receptor Blockers to patients with CKD could save £470 per patient in UK healthcare costs over 5yrs by prevention of cardiovascular and other complications of CKD progression.[23]

Despite this potential financial gain, and evidence of poor follow up rates in two other similar health economies, we have found very low rates of systematic renal follow-up after RRT-requiring AKI in the ICU, and that it is difficult to predict, at the time of hospital discharge, whether renal function will subsequently improve, stabilize or worsen. In light of our findings, we suggest an algorithm (Fig. 4) as a guideline for follow up for patients surviving severe AKI. While, as we've discussed, use of eGFR, has significant drawbacks, it is the existing methodology used to compare renal function at discharge and during follow-up, potentially supplemented by more formal assessment of true GFR in selected patients. This pathway would provide a platform to study the true epidemiology of CKD after AKI and the effects of intervention on long-term health and healthcare costs. Follow-up would place an additional burden on renal services of ~190 patients/year in our region for patients

requiring RRT, but potentially greater if this pathway was applied to patients experiencing less severe AKI. Thus we emphasize the early recognition and treatment of CKD after AKI, which if stable can be subsequently monitored and managed in primary care.

Conclusions

After critical illness complicated by severe AKI, it is difficult predict in which patients renal function will improve, stabilize or worsen. Despite severe-AKI, only 36% of patients who could have potentially undergone reassessment of renal function after 3 months did so, and only 12% received specialist renal follow-up. In those whose renal function was reassessed, prevalence of CKD was significantly increased. There is thus a strong justification for a specialist follow-up pathway for patients experiencing significant AKI complicating critical illness.

Acknowledgements

We are grateful to Ms. Gail Marshall, ICNARC Audit Lead, The Royal London Hospital for assistance in providing local ICNARC data.

Conflicts and Disclosures

The results presented in this paper have not been published previously in whole or part, except in abstract format.

JRP has received consultancy and speakers fees from Baxter Gambro Inc and institutional developmental support fro Nikkiso Co Ltd, both manufacturers of continuous renal replacement therapy technology.

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Table 1: Baseline demographics of all 261 patients with AKI requiring RRT who were not previously known to nephrology services. CKD is defined by eGFR<60 by the CKD-EPI equation. Medians with ranges presented. Between group comparisons by Mann-Whitney U test or Fisher's Exact Test as appropriate.

	Patients with AKI requiring RRT who had a Cr measurement 3-6 months post discharge	Patients with AKI requiring RRT but did not have a Cr measurement 3-6 months post discharge	P-value
Number	124	137	
Age (Range)	66 (21 – 88)	64 (18 – 90)	NS
Male (%)	78 (69)	82 (60)	NS
Ethnicity (%)			
White British	85 (69)	93 (68)	NS
White Other	7 (6)	7 (5)	NS
Black	7 (6)	13 (9)	NS
South Asian	22 (17)	23 (17)	NS
Other	3 (2)	1 (1)	NS
Reason for Admission (%)			
Medical	73 (58)	73 (53)	NS
Emergency Surgery	25 (20)	33 (24)	NS
Elective Surgery	25 (20)	24 (18)	NS
Trauma	2 (2)	7 (5)	<0.001
Baseline Renal Function			
N available (%)	104 (84)	98 (72)	0.007
N of those with CKD (%)	53 (51)	38 (38)	< 0.001
Creatinine (mmol/L)	99 (51 – 398)	91 (43 – 546)	NS
eGFR (ml/min/1.73m ²)	60 (12 – >90)	67 (36 – >90)	0.04
Discharge Renal Function			
Creatinine (mmol/L)	121(27-617)	94 (33-806)	0.03
eGFR (ml/min/1.73m ²)	47 (5- >90)	62 (5- >90)	0.03
Presumed Cause of AKI (%)			
Autoimmune	0 (0)	3 (1.5)	NS
Cardiogenic	24 (19)	25 (18)	NS
Contrast induced	2 (1.5)	2 (1.5)	NS
Hemodynamic	17 (14)	14 (10)	NS
Ischaemic	0 (0)	2 (1.5)	NS
Metabolic	512 (10)	14 (10)	NS
Obstruction	12 (10)	1 (1)	< 0.001
Rhabdomyolysis	0 (0)	6 (4)	NS
Sepsis	55 (44)	67 (49)	NS
Unable to determine	2 (1.5)	2 (1.5)	NS

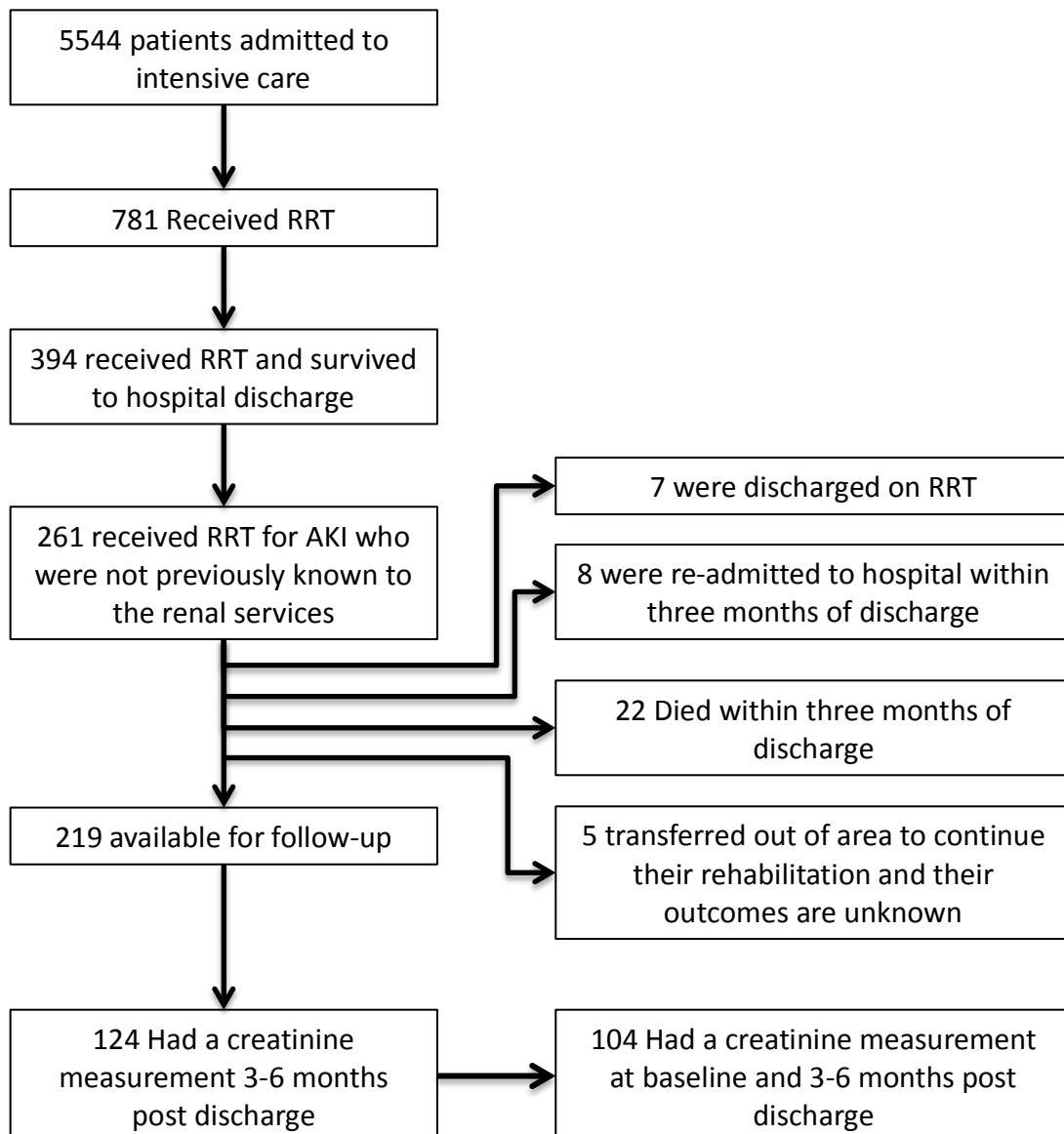
Table 2. CKD categories before and after AKI requiring renal replacement therapy in the 104 patients with baseline, hospital discharge and follow up creatinine measurements. Comparisons by McNemar's test for proportion of patients in stated AKI category or greater (note formally CKD status cannot be diagnosed until renal dysfunction has persisted for 3 months)

CKD stage	Baseline	Hospital discharge		3 – 6 month follow up		
	N	N	p vs. baseline (for CKD stage or greater)	N	p vs. baseline (for CKD stage or greater)	p vs. discharge (for CKD stage or greater)
0, I, II	51 (49%)	30 (29%)	-	31 (30%)	-	NS
IIIa	24 (23%)	23 (22%)	<0.001	25 (24%)	<0.001	NS
IIIb	22 (21%)	29 (28%)	<0.001	32 (31%)	<0.001	NS
IV	4 (4%)	17 (16%)	<0.001	10 (10%)	0.008	NS
V	3 (3%)	5 (5%)	NS	6 (6%)	NS	NS

Figures

Figure 1: Flow chart of patient analysis

(RRT = Renal Replacement Therapy)



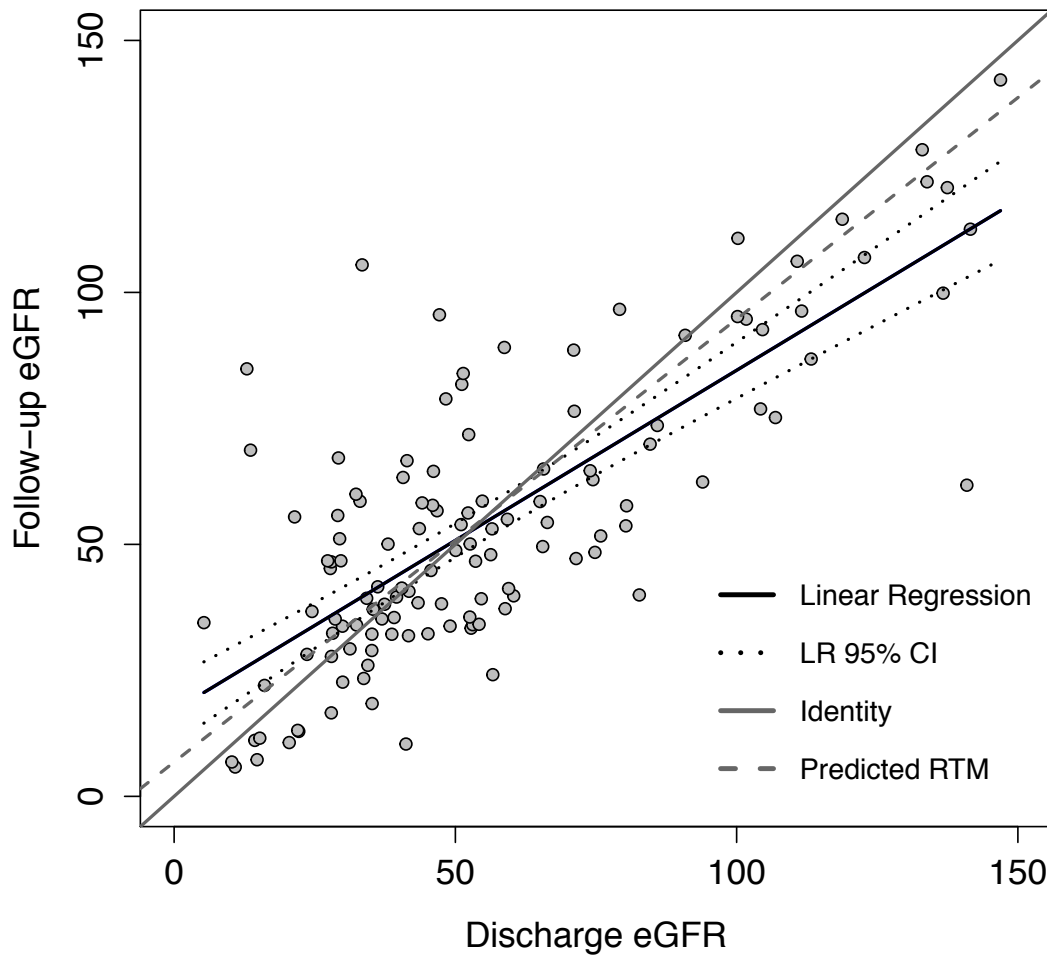


Figure 2: Relationship between eGFR at discharge and at 3-6 month follow-up after RRT-requiring AKI in 124 patients. Higher eGFRs at discharge tended to decline at follow-up while lower eGFRs tended to increase, but the extent was highly variable between patients. Linear regression (LR) line is shown with 95% confidence interval (CI). Regression equation: Follow-up = $0.68 \times \text{Baseline} + 16$, $r^2=0.59$. Line of identity and predicted *regression to the mean* (RTM) effect with repeated observations are also shown, changes in eGFR above and below the mean are larger than that effected from RTM alone.

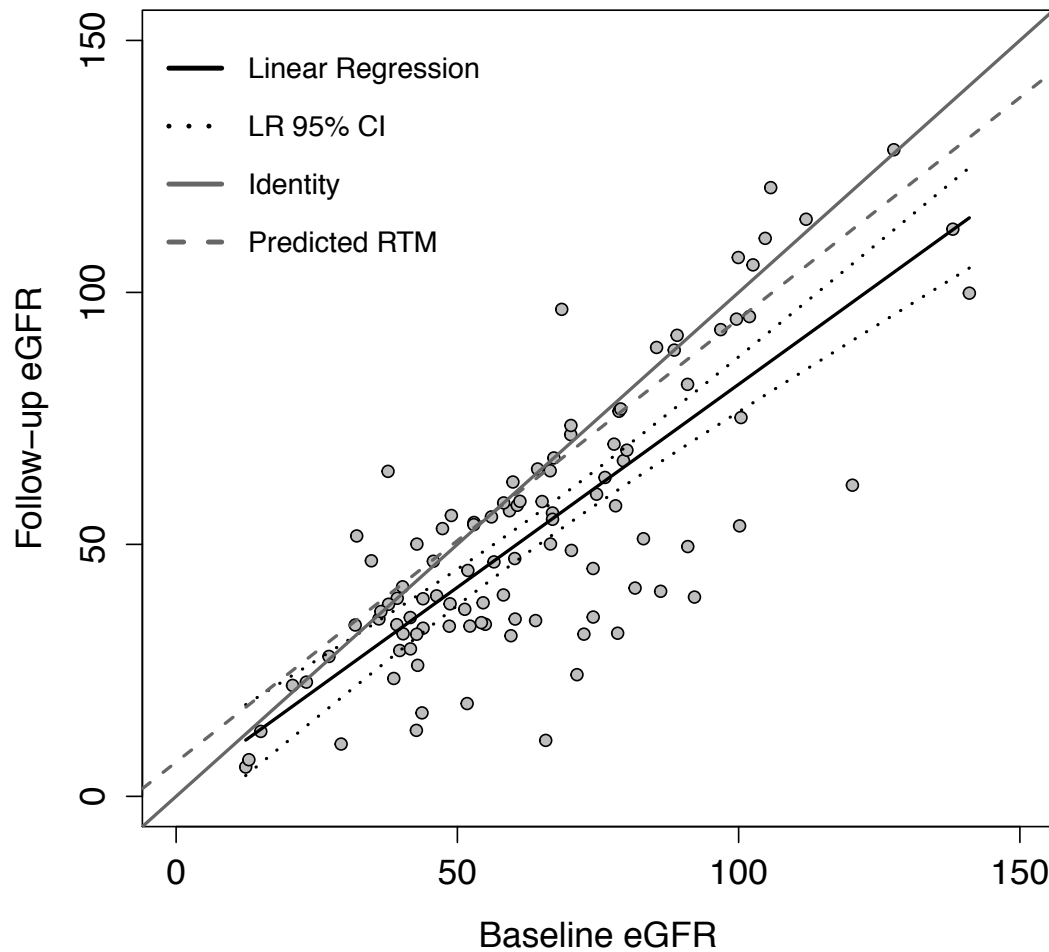
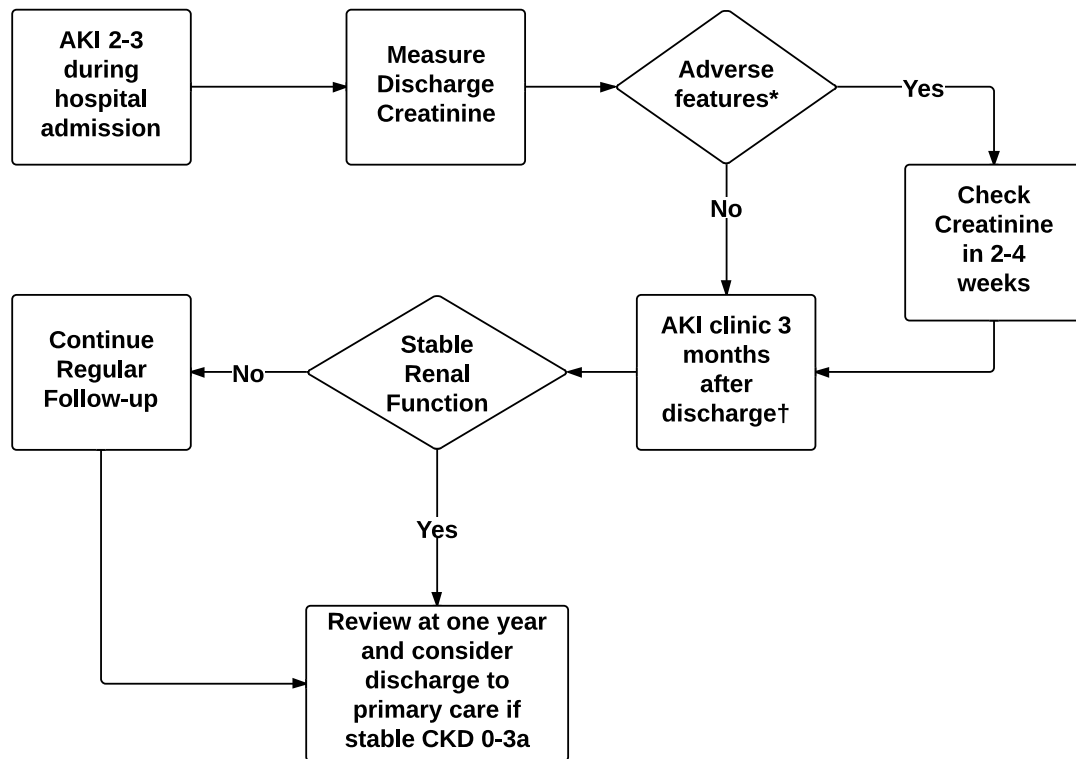


Figure 3: Relationship between eGFR at baseline and at 3-6 month follow-up after RRT-requiring AKI in 104 patients. Overall, there was a consistent trend to reduction in eGFR at follow-up, but the extent was highly variable between patients. Linear regression (LR) line is shown with 95% confidence interval (CI). Regression equation: Follow-up = $0.81 \times \text{Baseline} + 1$, $r^2=0.63$. Line of identity and predicted *regression to the mean* (RTM) effect with repeated observations are also shown.

Figure 4: A proposed pathway for follow up of patients who survive an episode of AKI 2 or 3 (as per KDIGO criteria) whilst in hospital.



* Adverse features suggesting need for early follow-up include a significant increase in serum creatinine from pre-morbid baseline to discharge (new overt CKD or unrecovered AKI) or the presence of significant renal impairment (suggested as a serum creatinine of $>175\mu\text{mol/L}$ (2mg/dl) or $\text{eGFR} <30\text{ml/min/1.73m}^2$). Consider formal measurement of GFR or Creatinine Clearance in patients with prolonged critical illness or significant loss of muscle mass.

† Patients with specific features including persistent haematuria or proteinuria (Urine Protein:Creatinine Ratio $>100\text{ mg/mmol}$), proven or suspected glomerulonephritis, refractory hypertension, familial renal disease, recurrent or extensive nephrolithiasis, or likely progression to ESRD within 1 year should be referred directly to the appropriate specialist nephrology clinic.