Supplementary Material

Addition Background, Methods and Model Building

Design and ethical considerations

We performed a retrospective observational cohort study of all patients admitted to the Royal London Hospital Adult Critical Care Unit between 1st Jan 2009 and 31st Jan 2011. Prior approval was obtained from Barts Health NHS Trust and Queen Mary University of London Joint Research Office for retrospective analysis of aggregate anonymised data collected in routine clinical practice with waiver of individual consent.

Institutional background

The Royal London Hospital is a large teaching hospital located in the East of London, UK. At the time of this study the Royal London ICU comprised an 18-bed facility admitting patients requiring mechanical ventilation and/or support of more than one organ system. Patients with acute or chronic single organ renal failure were managed on the nephrology ward and were not included in this study. In addition, many elective general surgical patients were managed in a separate surgical high dependency unit and cardiac surgery was carried out at a sister hospital. The Royal London Hospital is one of London's four major trauma centers and home to London's air ambulance. The local population of East London includes a large South Asian community with a high prevalence of chronic kidney disease; most patients defined as Asian racial background in this study were from this community. The case mix of patients included in this study was thus predominantly major trauma, emergency general surgery and patients with medical causes of multi-organ failure. Renal replacement therapy in the ICU was provided exclusively using continuous modalities.

Data collection and definitions

We screened the Royal London ICU *Intensive Care National Audit & Research Centre* (ICNARC) audit database (maintained for clinical audit and

mandatory outcome reporting) for hospitalizations containing an ICU admission lasting five days or longer with survival to acute hospital discharge. We arbitrarily chose five days of ICU admission to define a homogenous cohort with comparable exposure to critical illness to patients developing AKI. Separate hospitalizations in the same patient with intervening discharge home were treated as separate episodes. As the intention of this study was to examine the prognostic value of creatinine and estimated-GFR (eGFR) status at hospital discharge we excluded patients with prior diagnosis of end stage renal disease, renal transplant and patients who remained dependent on renal replacement therapy at time of discharge. From the ICNARC audit database we collected demographic data and illness related data: age, sex, racial background, dates of hospital and ICU stay, admitting diagnostic category (medical surgical, or trauma), and illness severity scores (Acute Physiology and Chronic Health Evaluation II - APACHE-II; Simplified Acute Physiology Score - SAPS-II and Intensive Care National Audit & Research Centre Physiology Score – ICNARC score. For each identified hospital admission, we examined the Royal London Hospital Pathology system and recorded serum creatinine results at pre-morbid baseline, during hospitalization and at post-discharge follow-up. Baseline creatinine was defined as the last available measurement from 365 days to 7 days prior to hospital admission[1]. Where baseline creatinine was not available hospital admission creatinine was used as baseline for AKI assessment within the first seven days of hospitalization. Follow-up creatinine was defined as the last available measurement obtained out in outpatients or on discharge after another hospitalization between 90 and 365 days after index hospital discharge. We then sequentially examined all creatinine values during hospital admission for maximal AKI diagnosis using the serum creatinine criteria of 2012 *Kidney Disease Improving Global Outcomes* (KDIGO) AKI criteria.[2] As well as maximal AKI category we specifically recorded creatinine values at hospital admission, at ICU admission, the peak value in hospital, at ICU discharge and at hospital discharge.

Data Analysis

Creatinine values at differing time-points are presented as boxplots,

boxes extend from 25% to 75% centiles with solid line at median. Whiskers extend to 1.5 times the interquartile range from the box. Notches[3] indicate an estimate of error in the medians so that non-overlap of notches indicates significant difference in medians at the 0.05 level (notches extend to $\pm\frac{1.58\times IQR}{\sqrt{n}}$)

Log-transformed linear regression

We performed linear regression analyses to examine the influences of AKI and critical illness on hospital discharge creatinine or follow-up creatinine using natural log transformation of the dependent variable and explanatory covariates. Log-transformation was chosen as a better potential fit to the physiology of creatinine excretion and AKI. In log-transformed regression covariates and factors result in multiplicative rather than additive changes in the dependent variable. This relationship is in keeping with decreases in muscle mass related to illness duration and severity, which would be expected to result in a proportional decrease in steady state serum creatinine. Similarly as AKI is categorized as a fold- rather than absolute- increase in serum creatinine it is most appropriately modeled as a multiplicative relationship with serum creatinine in the recovery phase. To illustrate, in a log regression equation (Eq. 1) x is the dependent variable, y a continuous covariate, z a categorical variable taking value 0 or 1 for absence or presence of the category, A and B the regression coefficients, and C the intercept.

$$\log(x) = A\times\log(y) + B\times z + C \quad (1)$$

Solving this equation for x results in the following relationship with the dependent variable where e is the base of the natural logarithm (Eq. 2). Note when z=0, e^{Bz} = 1.

$$x = y^A \times e^{Bz} \times e^C \quad (2)$$

To generate a final model we performed stepwise forward and backward

selection based on minimization of the *Akaike An Information Criterion* in the optimal model. We considered the following co-variates and factors in our initial model: age, sex, racial background, diagnostic category, baseline or admission creatinine, illness severity scores, AKI category and duration of hospitalization. We assessed for multicollinearity by calculation of variance inflation factors, multicollinearity was considered to be significant if the square root of the variance inflation factor was >2. Similar methods were used to build a predictive model for baseline:hospital-discharge creatinine ratio.

Table S1: log-log Regression model based on admission creatinine

	Dependent variable:
	log(Hospital Discharge Creatinine)
log(Hospital Admission Cr)	0.339***
	(0.028)
Male Sex	0.106***
	(0.029)
log(Age)	0.093***
	(0.033)
White/Other Race	$Reference$
Black Race	0.079*
	(0.041)
Asian Race	0.136***
	(0.039)
log(Hospital Length of Stay)	−0.138***
	(0.019)
log(ICNARC Physiology Score)	−0.119***
	(0.041)
Trauma	$Reference$
Surgical	0.061*
	(0.036)
Medical	0.129***
	(0.034)
No AKI	$Reference$
AKI-1	0.103***
	(0.034)
AKI-2	0.096**
	(0.047)
AKI-3	0.304***
	(0.041)
Constant	−0.196
	(0.175)
Observations	700
R^2	0.39
Adjusted R^2	0.38
Regression coefficients shown with standard error in parenthesis	*p<0.1; **p<0.05; ***p<0.01

Table S1 (previous page): Regression model based on hospital admission creatinine as a surrogate for baseline in 700 patients. *log(hospital admission creatinine)*, *log(hospital length of stay)*, *sex*, *age*, *racial background*, *admitting diagnostic category* and *AKI category* were retained in our final model predicting *log(discharge creatinine)*. Increasing hospital stay was significantly associated with lower hospital discharge creatinine, for example in a typical patient (a white, male, trauma patient, age 49, ICNARC score 19 and admission creatinine 0.95mg/dl), with hospital length of stay 36 days (the population median) this model predicts a 42% (95% CI 38-45%) fall in hospital discharge creatinine from admission in the absence of AKI. AKI-3 would then confer a 35% increase (25-47%) increase in discharge creatinine over that predicted without AKI. In this model AKI-1 and AKI-2 were also significantly associated with higher hospital discharge creatinine predicting a 10% increase. The effects of hospital length of stay and AKI-3 in this model are comparable to that in the model based on baseline creatinine in 160 patients (Main article, Table 3 col1).

Creatinine	Observed Admission	Modelled Baseline	Observed Discharge
Mean	0.840	0.841	0.586
Standard Deviation	0.229	0.229	0.152
Median	0.837	0.843	0.588
25% centile	0.690	0.670	0.467
75% centile	0.992	0.972	0.679
p vs. Admission	-	0.97	<0.001

Table S2: Model validation. Population statistics for observed admission creatinine in test set of patients where admission creatinine would be expected to be similar to baseline compared with model-predicted baseline creatinine, with values for observed discharge creatinine in the same patients for comparison. Distribution were compared using the Kolmogorov-Smirnov test.

Table S3: log-log Regression Models for Follow-up Creatinine

	Dependent variable:	
	log(Follow-up Creatinine)	
	(1)	(2)
log(Hospital LOS)	-0.073^{**}	-0.196^{***}
	(0.030)	(0.048)
White/Other	*Reference*	*Reference*
Black	-0.009	0.324^{**}
	(0.062)	(0.144)
Asian	0.165^{***}	0.209^{**}
	(0.060)	(0.093)
log(Hospital Discharge Cr.)	0.658^{***}	
	(0.047)	
log(Baseline Cr.)		0.777^{***}
		(0.089)
No AKI	*Reference*	*Reference*
AKI-1	0.066	0.085
	(0.057)	(0.119)
AKI-2	0.082	0.394^{***}
	(0.078)	(0.124)
AKI-3	0.128^{**}	0.407^{***}
	(0.060)	(0.101)
Constant	0.258^{**}	0.430^{**}
	(0.106)	(0.175)
Observations	221	96
R^2	0.63	0.68
Adjusted R^2	0.61	0.65
Regression coefficients shown with standard error in parenthesis	*p<0.1; **p<0.05; ***p<0.01	

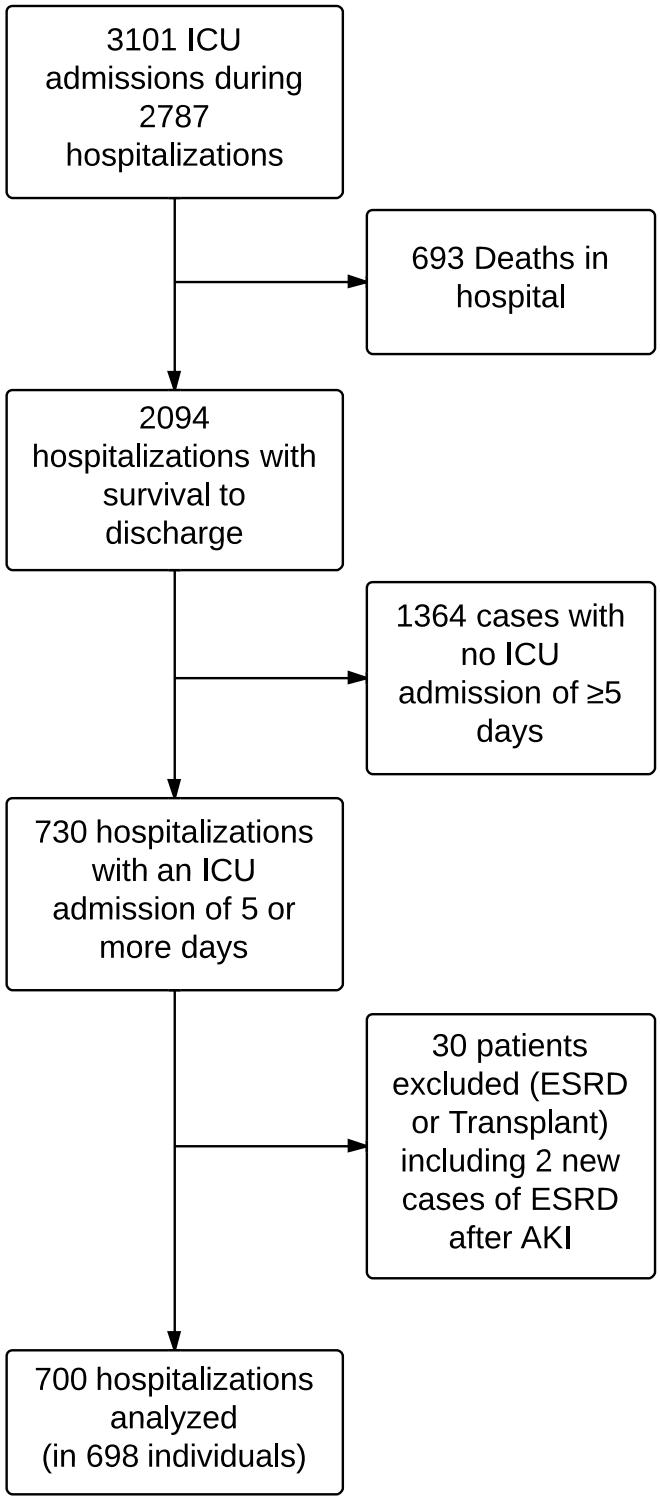

Fig. S1: Flow diagram for case selection of 700 cases considered amongst 3101 ICU admissions during 2009-11.

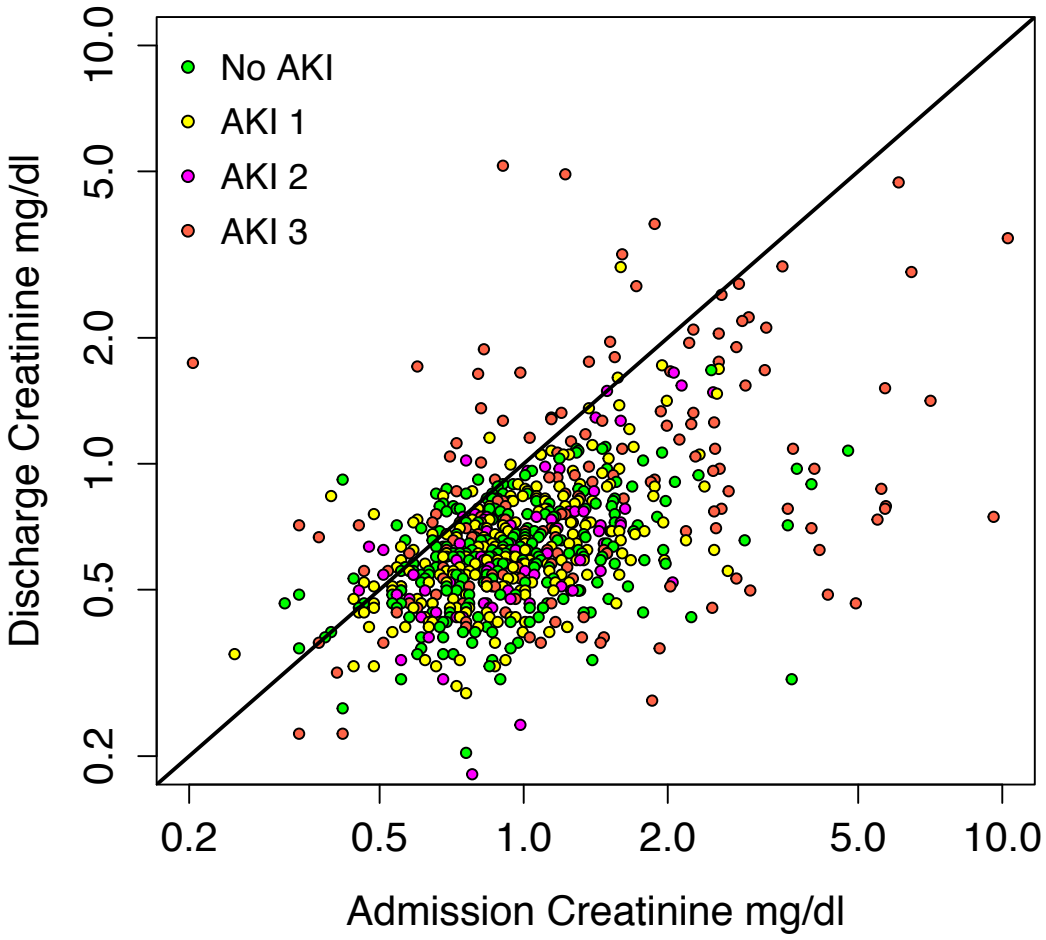

Fig S2: Hospital discharge serum vs. hospital admission creatinine in 700 hospitalizations (log scales). A large majority of discharge values fall below admission values across all values of admission creatinine and both in patients with AKI and without. Peak AKI category in hospital is shown.

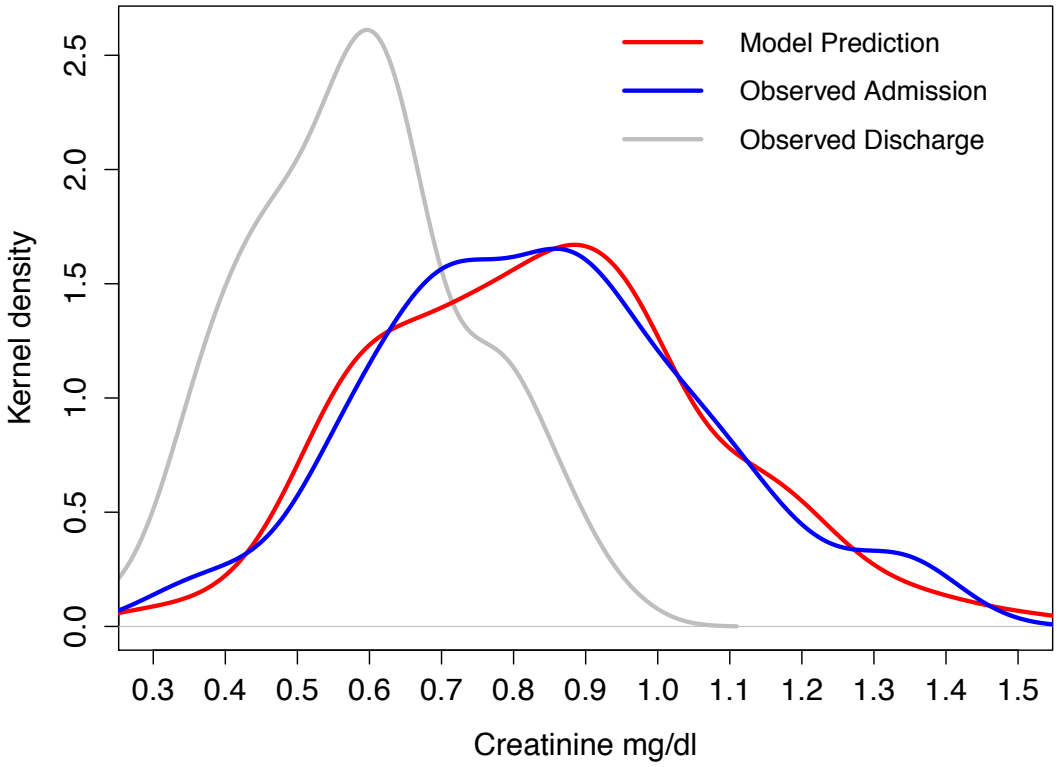

Fig S3: Model validation. Smoothed density (probability distribution) of observed admission creatinine in test set of patients with no AKI and creatinine<1.4 on admission and distribution of model-predicted baseline (pre-morbid) creatinine, with distribution of observed discharge creatinine used for modelling provided for comparison. Population statistics for these datasets are shown in Table S2.

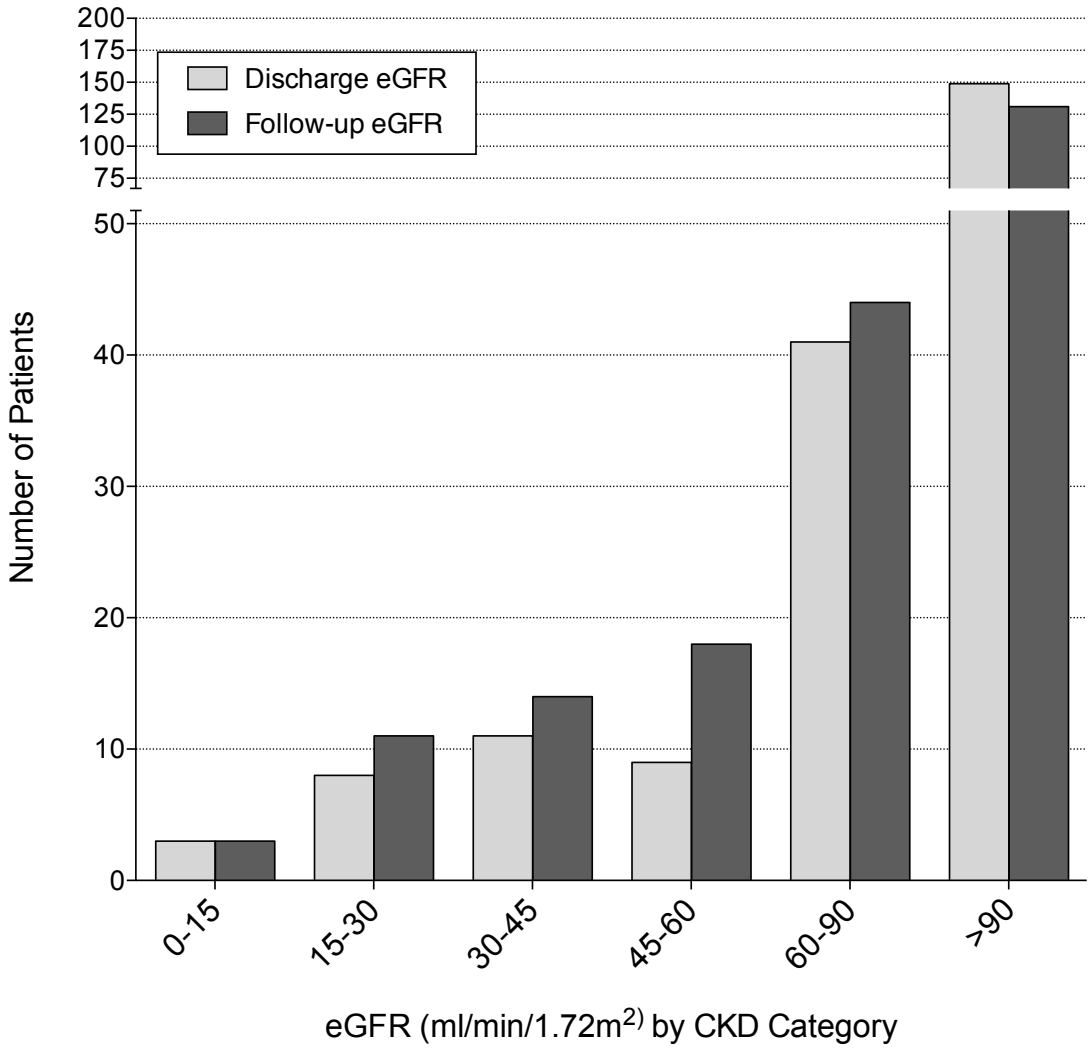

Fig S4: CKD diagnosis bases on hospital discharge eGFR and 3-12 month follow-up eGFR in 221 patients. There were significantly more patients with eGFR<60ml/min/1.73m^2 at follow-up than at hospital discharge, McNemar's test p=0.009.

References

1. Siew, ED, Ikizler, TA, Matheny, ME, Shi, Y, Schildcrout, JS, Danciu, I, Dwyer, JP, Srichai, M, Hung, AM, Smith, JP, Peterson, JF: Estimating baseline kidney function in hospitalized patients with impaired kidney function. *Clin J Am Soc Nephrol,* 7**:** 712-719, 2012.

2. Kidney Disease: Improving Global Outcomes (KDIGO): KDIGO Clinical Practice Guideline for Acute Kidney Injury. Section 2: AKI Definition. *Kidney Int Suppl,* 2**:** 19-36, 2012.

3. McGill, R, Tukey, JW, Larsen, WA: Variations of Box Plots. *The American Statistician,* 32**:** 12-16, 1978.