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Dardashti, Alain; Ederoth, Per; Algotsson, Lars; Brondén, Björn; Bjursten, Henrik

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PO Box 117
221 00 Lund
+46 46-222 00 00

Incidence, dynamics and prognostic value of Acute Kidney Injury for death after
cardiac surgery.

Alain Dardashti¹. Per Ederoth¹. Lars Algotsson¹. Björn Brondén¹. Henrik Bjursten².

¹Department of Anesthesia and Intensive Care, Clinical Sciences, Lund University, Lund, Sweden

²Department of Cardiothoracic Surgery, Clinical Sciences, Lund University, Lund, Sweden

Corresponding author:

Alain Dardashti, MD

Dept. of Anesthesia and Intensive Care.

Institute of clinical sciences

Faculty of medicine Lund University

Skane university Hospital

SE-221 85 Lund

Sweden

Tel. +46 46 17 10 00

Fax +46 46 15 86 35

E-mail: alain.dardashti@med.lu.se

Abstract

Purpose:

This study relates long-term mortality after cardiac surgery to different methods of measuring postoperative renal function, classified according to the RIFLE criteria (Risk, Injury and Failure). The dynamics of acute kidney injury (AKI) during hospital stay was studied by comparing renal function pre-operatively, at its poorest measurement and at discharge.

Methods:

5746 coronary artery bypass grafting patients were studied in a Cox analysis, over a median follow-up time of 6.0 years (range 2.5-9.5 years). Renal function was determined using the highest and discharge level of plasma creatinine by Cockcroft–Gault and Modification of Diet in Renal Disease (MDRD) formulae. AKI was classified according to the RIFLE criteria. Renal recovery was studied in a two-dimensional matrix and the impact of renal function at different time points were related to survival.

Results:

While the p-creatinine classified most patients in the non-AKI and RIFLE R, the Cockcroft–Gault and MDRD formulae classified more patients in higher RIFLE classes, and higher RIFLE classes were associated with increased long-term mortality. The effect of renal recovery on long-term survival was only in part associated with improved outcome. In addition, the poorest renal function was a stronger predictor of mortality as compared to pre-operative and discharge levels.

Conclusions:

Classification using RIFLE appears to be useful as it detects patients with renal impairment that affects long-term survival. The MDRD method seems to be the most robust method when predicting outcome, and the poorest renal function was the best predictor of outcome. Renal recovery was generally associated with better outcome.

Key Words:

Renal failure, RIFLE, Acute Kidney Injury, Survival, Cardiac Surgery.

Introduction

Acute kidney injury (AKI) is common after cardiac surgery, and incidences between 7% and 40% have been reported depending on the definition used [1-4]. AKI has well-documented negative effects on postoperative morbidity and mortality [5] as well as the length of postoperative hospital stay and costs [6]. In clinical practice, it is not obvious how this powerful predictor should be handled in a useful way.

First, almost all centres use the p-creatinine concentration for estimating glomerular renal filtration (GFR), and the shortcomings of this marker are well-known [7]. To compensate for this, different formulae have been constructed where other physiological variables are introduced. The Cockcroft-Gault (CG) and the Modification of Diet in Renal Disease (MDRD) formulae are two commonly used examples. The first expresses renal function as estimated creatinine clearance (eCrCl) and the latter as estimated glomerular filtration rate (eGFR). The MDRD formula has been widely used in studies in cardiac surgery [8-14]. P-creatinine, eCrCl and eGFR are still only estimates of true GFR.

A second challenge is that during and after cardiac surgery, renal function varies on a daily basis [15, 16]. Several authors have highlighted the observation that decreased renal function after cardiac surgery affects both short- and long-term mortality [10, 11, 17-20]. The majority of these studies have mainly focused on the poorest renal function. However, some patients with AKI recover completely during their hospital stay while others show no recovery at all. Earlier studies demonstrate conflicting results on renal recovery and long-term outcome. Therefore, there is a need for more studies on the dynamics of renal function after cardiac surgery.

The aim of this study was twofold. The primary objective was to assess the importance of time point for measuring, and consequently, the dynamics of renal recovery in relation to

long-term mortality. The secondary aim was to compare three different plasma creatinine-based assessments of renal function (i.e. absolute p-creatinine concentrations, eCrCl using the Cockcroft–Gault formula, and eGFR according to the MDRD formula) employing the RIFLE criteria in order to find the best method for renal assessment.

Methods

Study design

The study was approved by the local ethics committee. All patients who had undergone cardiac surgery at the Department of Cardiothoracic Surgery at the University Hospital in Lund, Sweden, from January 1st 2002 to December 31st 2008 were included.

Database management

Data were mainly collected from the hospital's quality control database, in which information is continuously collected on perioperative care during patients' hospital stay. Other sources of data were the blood bank and clinical chemistry databases at the hospital. Survival or time of death for each patient was determined from the national tax registry in May 2011, defining the follow-up period from 2.5 to 9.5 years. Where data were missing or extreme outliers were identified, patient records were read to complete the database. In cases of data mismatch between different data sources, the data were manually checked by consulting the patient's records.

After completing missing data from patient records, preoperative p-creatinine values were still missing in 104 patients. For these patients, the preoperative p-creatinine level was estimated using an imputation technique based on the p-creatinine level one day after surgery. The formula used was: $\text{Creatinine day 0} = 15.0 + (0.86 \times \text{Creatinine day 1})$, calculated by applying regression analysis to the relation between the preoperative p-creatinine level (on day 0) and the p-creatinine one day after surgery (day 1) [21, 22].

Patient inclusion and exclusion

All patients who had undergone coronary artery bypass grafting (CABG) as the sole surgical intervention between January 1st 2002 and December 31st 2008 were included. The following predetermined exclusion criteria were used: emergency operation (defined as operation within one hour of the decision to operate) (n=125, 2.1%), preoperative eGFR (MDRD) < 15 ml/min (n=20, 0.3%) and death within 7 days of operation (n=51, 0.9%) as we aimed to study long-term outcomes, and patients that die early most often suffer major cerebral or cardiac insult, and very seldom die from AKI due to available renal replacement therapies. Of a total of 5943 patients, 5746 constituted the study group after application of the exclusion criteria.

Measurements of renal function

Kidney function was based on p-creatinine levels, either the absolute p-creatinine value, eGFR[9], or the eCrCl[23]. Changes in p-creatinine, eGFR and eCrCl during the hospital stay were compared with the preoperative values (baseline value) to assess changes in kidney function. The commonly used MDRD formula used is:

$$\text{eGFR ml/min/1.73m}^2 = 32788 \times \text{p-creatinine}^{-1.154} \times \text{Age}^{-0.203} \times [1.210 \text{ if black}] \times [0.742 \text{ if female}]$$
 [9], [24].

In our population, the number of black patients is well below one percent and not recorded in journals. Therefore, we used the original formula with only that adjustment: $\text{eGFR} = 32788 \times \text{p-creatinine}^{-1.154} \times \text{Age}^{-0.203} \times [0.742 \text{ if female}]$. The Cockcroft–Gault formula used was:

$$\text{eCrCl (female) ml/min} = ([140 - \text{age}] \times \text{weight in kg} \times 1.04) / (\text{p-creatinine in } \mu\text{mol/l})$$
 or

$$\text{eCrCl (male) ml/min} = ([140 - \text{age}] \times \text{weight in kg} \times 1.23) / (\text{p-creatinine in } \mu\text{mol/l})$$
 [23].

eGFR and eCrCl values calculated on the highest concentration of post-operative p-creatinine (p-creatinine_{peak}) are denoted eGFR_{peak} and eCrCl_{peak}, respectively. In line with this, eGFR and

eCrCl values calculated on the level of p-creatinine closest to the day of discharge from hospital (p-creatinine_{discharge}) are denoted eGFR_{discharge} and eCrCl_{discharge}, respectively.

We assumed that the “peak” values corresponded to the poorest kidney function and “discharge” values to the level of kidney function at the time of discharge from hospital. All p-creatinine concentrations were determined with enzymatic colorimetric method [25] with a 1.4-1.7% co-efficient of variance. The reference method for determination of the calibrator used was ID/MS (isotope dilution / Mass spectrometry).

Definition of acute kidney injury

AKI was classified utilizing the RIFLE scale [26]. The RIFLE-staging was made according to changes in levels of kidney function measured by p-creatinine, the eGFR and eCrCl (Table 1). Urinary output data were not available, so we used only the p-creatinine-based RIFLE classifications.

Statistics

Student’s t-test was used for group comparisons. Unless otherwise stated, values are presented as the mean \pm 1 standard deviation. Unadjusted Kaplan-Meier curves were used to show differences in survival between groups. A p-value of ≤ 0.05 was considered significant. The Cox proportional hazard model was used to determine which factors had an adverse outcome on long-term survival in all survival analysis. Wald statistics was used to determine the strength of a relation. The increased risk for mortality during the study period expressed as adjusted hazard ratio (HR) obtained from the multivariate Cox proportional hazard model was used to compare relative risks between groups. Based on previous studies on the subject, the following variables were entered into the Cox analysis[8, 27-29]: history of cerebrovascular disease, diabetes or chronic obstructive pulmonary disease (COPD); female gender; peripheral vascular disease; left ventricular ejection fraction (LVEF) 30-50%; LVEF <30%; age; intra-

aortic balloon pump (IABP) before surgery; IABP after surgery; previous percutaneous coronary intervention (PCI); postoperative myocardial infarction; postoperative sepsis; postoperative stroke; re-operation due to bleeding; postoperative mediastinitis or postoperative atrial fibrillation; body mass index (BMI); time on ventilator; and transfusion of red blood cells, plasma and platelets. In addition to these risk factors, measures of renal function were entered depending on which RIFLE-group of patients was being analysed and which method was used for determining RIFLE group. HRs were estimated using patients classified as non-AKI as a reference for each method used for defining AKI respectively.

Statistical analysis was performed with Statistica software, version 9.0 (Stat Soft, Inc. Tulsa, OK, USA) for most of the analyses. The R-project (version 1.13.0) software with the survival package was used to test the proportional hazard assumption for a Cox regression model fit.

To study the effect of renal recovery, a two-dimensional matrix was created in which one dimension was RIFLE_{peak} and the other RIFLE_{discharge}, based on MDRD eGFR.

To evaluate the relative strength in predicting outcome for renal function at different time points (before surgery, poorest renal function and discharge), we performed a multivariate Cox survival analysis where eGFR represented preoperative levels; poorest renal function and discharge were entered as continuous variables in our model.

Results

A total of 5746 patient were analysed over a median follow-up time of 6.0 years (range 2.5-9.5 years). The general characteristics and outcome of the cohort are presented in Table 2. The incidence of postoperative AKI (RIFLE classes R, I and F) varied depending on the method used to determine renal function. The number of patients classified as non-AKI differed depending on time point (i.e. peak or discharge) and the method of measuring renal function (i.e. p-creatinine, eCrCl or eGFR). The lowest number was found using eGFR, and the highest using p-creatinine as presented in Tables 3 and 4.

RIFLE classification based on poorest renal function

Comparing the three methods of renal function measuring, the $eGFR_{peak}$ method yielded the highest number of patients as AKI while the lowest number of patients classified as AKI was found in the p-creatinine_{peak} group. The risk of mortality during the study period, expressed as HR, increased significantly in all RIFLE classes as compared to non-AKI for all three expressions of renal function (Table 3 and Figure 1). The HR increased with more severe RIFLE class, i.e. HR for RIFLE class F>I>R>non-AKI, with $eGFR_{peak}$ F as the only exception. Using the $eGFR_{peak}$ and $eCrCl_{peak}$ led to more patients being classified as RIFLE classes R, I and F, than when p-creatinine_{peak} was used.

RIFLE classification based on renal function at discharge

More patients were classified in RIFLE classes R, I and F when using $eCrCl_{discharge}$ or $eGFR_{discharge}$ than when using p-creatinine_{discharge}. In addition, $eGFR_{discharge}$ led to more patients being classified as AKI than $eCrCl$ and p-creatinine (Table 4). HR increased progressively with more serious RIFLE class only in the $eGFR_{discharge}$ measures. Classification using p-creatinine_{discharge} and $eCrCl_{discharge}$ showed a progressive increase in hazard ratio compared to non-AKI in RIFLE classes R and I, but the value of HR decreased in RIFLE class F. With p-

creatinine_{discharge} RIFLE class F as only exception, all hazard ratios in RIFLE classes R, I and F for all three methods were significantly higher as compared to non-AKI, respectively.

Dynamics of renal recovery and its impact on survival

A two-dimensional matrix in which one dimension was RIFLE_{peak} and the other was RIFLE_{discharge}, both based on eGFR, was constructed to demonstrate the effect of recovery (Table 5). The HR for long-term mortality for all postoperative AKI (RIFLE classes R, I and F) with or without recovery was 1.56 (CI 1.37-1.77, $p < 0.001$). The hazard ratio for patients with any degree of AKI who showed complete recovery to non-AKI was 1.42 (CI 1.21-1.66, $p < 0.001$). The hazard ratio for patients with any degree of remaining AKI at discharge was 1.69 (CI 1.44-1.99, $p < 0.001$). Long-term mortality HR for patients who recovered to non-AKI at discharge was not increased if eGFR_{peak} had been RIFLE R. However, if eGFR_{peak} classified the patients as RIFLE I or F, it resulted in an increased HR, where RIFLE_{peak} I had an HR 1.58 (CI 1.18-2.10, $p = 0.002$), and those classified as RIFLE_{peak} F had an HR 2.53 (CI 1.84-3.48, $p < 0.001$).

Relative importance of renal function at different time points

In a separate survival analysis where the three values of eGFR for preoperative (eGFR_{pre-operative}) levels, levels for poorest renal function (eGFR_{peak}) and levels at discharge (eGFR_{discharge}) were entered separately, the eGFR_{peak} levels contributed the most to the model and were thus the most predictive for outcome. The HR for eGFR_{pre-operative} was 0.99 ($p < 0.0001$, Wald=32.91), the HR for eGFR_{discharge} was 0.98 ($p < 0.0001$, Wald=44.98) and the HR for eGFR_{peak} was 0.98 ($p < 0.0001$, Wald=80.16).

To further clarify which time for renal measurement is the most important, all three variables (eGFR_{preoperative}, eGFR_{discharge} and eGFR_{peak}) were forced in a separate Cox analysis, and only the eGFR_{peak} values remained significant with a HR 0.98 ($p < 0.0001$, Wald=41.4). The values

for $eGFR_{\text{discharge}}$ changed to HR 1.0 ($p=0.3$, Wald=1.1), and the values for preoperative $eGFR$ changed to HR1.0 ($p=0.6$, Wald=0.25).

Discussion

In this large single-centre cohort of patients with no history of chronic kidney failure undergoing coronary artery bypass surgery, we aimed at assessing different methods of evaluating postoperative AKI with the RIFLE system and correlating them to long-term mortality. The $eGFR_{\text{peak}}$ value was a much stronger predictor of death than the $eGFR_{\text{preoperative}}$ or $eGFR_{\text{discharge}}$. The highest number of patients was classified as AKI with the $eGFR$ method. Patients with a recovered renal function at discharge had a normalized HR if their AKI was classified as RIFLE R, but a remaining increased mortality risk if they had recovered from RIFLE I or F.

Both time point for measuring and the dynamics of renal recovery seem important as the poorest renal function appears vastly superior in predicting survival. An analysis was performed where $eGFR$ from three different time points (preoperative, peak and discharge) were entered separately into the Cox regression model, followed by another analysis where all $eGFR$ measures were entered at the same time. The results were the same in both analyses, where $eGFR_{\text{peak}}$ was indisputably the strongest predictor (HR 0.98, $p<0.0001$, Wald=41.4). This corresponds to a risk increase of 2% for every ml/min decrease in $eGFR_{\text{peak}}$. To our knowledge this has not been reported before. Looking at the RIFLE-classification in Tables 3 and 4, we see that peak levels rather than discharge levels detect more patients in higher risk-

classes (I and F). Moreover, patients at the lower R risk-class had a lower HR. Therefore, our RIFLE analysis confirms the strength of peak levels.

The results of the survival analysis based on the renal function estimated from the highest postoperative level of p-creatinine ($p\text{-creatinine}_{\text{peak}}$) were similar to those reported in previous studies [10, 11, 17], where increasing renal dysfunction/RIFLE class resulted in increasing risk of long-term mortality. For instance, Hobson et al. [10] also using $p\text{-creatinine}_{\text{peak}}$, showed increasing HRs with higher RIFLE classes. Thus, our data seem to confirm the results of previous studies. We also studied the predictive value of renal function measures at discharge from hospital for long-term survival. Our data indicated poorer survival with increasing degree of renal dysfunction, where the MDRD formulae predicted increasing risks of more serious RIFLE classes, while the $p\text{-creatinine}$ value did not predict an increase in HR for every RIFLE class (Table 4). On the other hand, the $p\text{-creatinine}_{\text{discharge}}$ value was demonstrated to be of statistically much lower strength in predicting death, so the clinical value of the $p\text{-creatinine}_{\text{discharge}}$ estimates is therefore limited. Our findings are in concordance with previous studies, where an association between renal function and long-term mortality has been shown [19, 30]. It has also been shown that the magnitude and duration of post cardiac surgery AKI is proportional to long-term mortality [1, 10, 11, 31].

The use of eGFR and eCrCl in conjunction with AKI has been questioned, and caution for the use of these estimates in the context of AKI has been advocated [32-34] given that these estimations have been developed for patients with chronic kidney disease and a $p\text{-creatinine}$ in steady state, which is not the case in an AKI scenario. However, these estimates have previously been used in conjunction with post cardiac surgery AKI [8, 10, 28]. A higher sensitivity for RIFLE classes Risk and Injury in cardiac surgery has also been suggested using eGFR compared with $p\text{-creatinine}$ [33]. A similar finding was made in the present study where the $p\text{-creatinine}_{\text{peak}}$ value was evaluated. The number of patients classified as AKI was

higher in the eGFR group than in the p-creatinine and eCrCl groups. Another important piece of the puzzle was findings in a recent study from our group, where different estimates of renal function versus iohexol clearance in cardiac surgery were evaluated, that found that MDRD eGFR was better than Cockcroft Gault eCrCl in estimating clearance in postoperative patients [16]. Taken together, in our opinion MDRD eGFR seems to be a robust biomarker for GFR in cardiac surgery patients under non steady state conditions. In addition, this study supports that both eCrCl and eGFR were superior to crude p-creatinine in identifying patients with AKI after CABG surgery, and eGFR was slightly superior to eCrCl.

The poorest renal function postoperatively and the renal function at discharge from hospital can be combined in order to assess the impact of these changes in renal function on survival. RIFLE classes based on MDRD eGFR were used to create a two-dimensional matrix with peak and discharge RIFLE class. MDRD eGFR was used because this method, in our opinion, reflected renal function better than eCrCl and p-creatinine, as discussed above. When analysing the effect of total recovery from any degree of AKI to non-AKI at discharge, the results were beneficial in terms of survival compared with patients without RIFLE R recovery. This is in accordance with previous studies [1, 4, 10, 11, 19, 31]. Notably, this was not true for the groups that had been in RIFLE groups I and F at the poorest level, with a remaining HR proportional to the worse degree of AKI. A similar result has been presented previously by Mehta et al., reporting a slightly increased long-term mortality in the group showing partial recovery from acute renal failure (HR 1.58 vs. 1.42) [4]. Loef et al. reported an increase in long-term mortality in patients with AKI, irrespective of postoperative renal recovery [19]. Although stratifying the patients into groups according to their RIFLE class provides more information about the effect of recovery, depending on the degree of AKI at peak p-creatinine level and the degree of recovery at discharge, the groups become smaller thus increasing the uncertainty in the analysis. However, studying the two-dimensional

analysis, we can see that long-term mortality HR for all non-AKI patients at discharge was directly proportional to the AKI level at RIFLE_{peak} for these patients.

One of the strengths of this study is the database, which contains information on many perioperative variables such as laboratory results and transfusion data. In addition, many variables had a high completion rate, with more than 99% complete data follow up. Moreover, the present study includes only CABG patients, whereas several other studies have included a mixed population [31, 35]. The lack of baseline p-creatinine in using the RIFLE classification [10] has been highlighted as a limitation [32]. Preoperative p-creatinine levels were missing in only 1.8% of our subjects, and we used an imputation technique based on the p-creatinine level on the first postoperative day, which has a correlation estimate of 0.89 [21]. In a post-hoc analysis, we checked the demographics for the patients who had their pre-operative creatinine imputed. These patients had a slightly higher Euroscore (5.6 vs. 4.8) and a higher frequency of pre-operative IABP (3% vs. 11%) but did not differ in any other characteristic. We did not take into account the time to recovery in our analysis, although this may be a factor influencing long-term survival, as reported by Brown et al. [1]. Although the study comprises more than 5000 individuals, the numbers of patients in the more serious classes of renal dysfunction are relatively small, especially in the two-dimensional matrix. This could lead to an overparameterization, which subsequently will lead to a risk of over- or underestimation of the HRs in these small groups. Other limitations are single-center, retrospective study, lack of data on urinary output and the inherent weaknesses of the MDRD and CG formula, such as extreme body weight, low GFR and age of the cohort. A more accurate measure of GFR would further strengthen the results of a study of this type. Today, p-creatinine is the most commonly used marker for renal function despite its shortcomings, but cystatin-c has recently been suggested as a better marker [16].

In concordance with previous studies, we can conclude that renal function plays a pivotal role in long-term outcome in cardiac surgery. The dynamics of renal function during hospital stay is also an important factor, where recovery seems to be beneficial, and until better serum markers for renal function are found, eGFR based on the MDRD formula seems to yield the most reliable results. The present study also suggests that the poorest measured postoperative renal function is the most predictive for mortality.

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Conflicts of interest

Henrik Bjursten has a vested interest in ErySave AB. Lars Algotsson lectures for Orion Pharma AB and Abbott Scandinavia AB. The other authors have no conflicts of interest to report.

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Tables

Table 3. Relative risk of mortality (expressed as adjusted hazard ratio) after CABG surgery depending on RIFLE class at poorest measured renal function (RIFLE_{peak}) during hospital stay. The three methods used to measure renal function were: 1) p-creatinine, 2) the Cockcroft-Gault formula for creatinine clearance and 3) Modification of Diet in Renal Disease (MDRD) formulae. P-values refer to comparison with non-AKI.

		Non-AKI	R	I	F
1	P-creatinine n=5742	5092 (88.7%)	1.57 (1.31-1.89)	1.62 (1.13-2.33)	1.90 (1.32-2.74)
			[p<0.000001]	[p=0.009435]	[p=0.000600]
			463 (8.1%)	103 (1.8%)	84 (1.5%)
2	Cockcroft-Gault eCrCl n=5735	4147 (72.3%)	1.32 (1.13-1.56)	1.53 (1.23-1.90)	2.03 (2.03-2.53)
			[p= 0.000716]	[p=0.000145]	[p<0.000001]
			942 (16.4%)	327 (5.7%)	319 (5.6%)
3	MDRD eGFR n=5742	3855 (67.1%)	1.29 (1.09-1.51)	1.85 (1.51-2.27)	1.85 (1.85-2.26)
			[p=0.002536]	[p<0.000001]	[p<0.000001]
			1051 (18.3%)	400 (7.0%)	436 (7.6%)

Table 4. Relative risk of mortality (expressed as hazard ratio) during follow-up depending on RIFLE class at discharge (RIFLE_{discharge}). The three methods used to measure renal function were: 1) p-creatinine, 2) the Cockcroft–Gault formula for creatinine clearance and 3) MDRD eGFR.

		Non-AKI	R	I	F
1	P-creatinine	5579 (97.2%)	1.90 (1.39-2.87) [p=0.000050]	2.07 (1.09-3.92) [p=0.025779]	1.15 (0.57- 2.33) [p=0.693115]
	n=5742		123 (2.1%)	24 (0.4%)	16 (0.3%)
2	Cockroft-Gault	5116 (89.2%)	1.37 (1.13-1.67) [p=0.001363]	2.00 (1.40-2.86) [p=0.000160]	1.60 (1.12-2.28) [p=0.010398]
	eCrCl n=5735		442 (7.7%)	89 (1.6%)	88 (1.5%)
3	MDRD eGFR	4920 (85.7%)	1.45 (1.21-1.74) [p=0.000045]	1.75 (1.30-2.37) [p=0.000275]	1.94 (1.43-2.63) [p=0.000018]
	n=5742		561 (9.8%)	143 (2.5%)	118 (2.0%)

Table 5. Relative risk of mortality (expressed as hazard ratio) during follow-up depending on the combination of RIFLE class at discharge (RIFLE_{discharge}) and poorest measured renal function (RIFLE_{peak}). Renal function was measured by MDRD eGFR.

	Non-AKI peak	R peak	I peak	F peak
Non-AKI at discharge	3855 (67.1%)	1.18 (0.98-1.43) <i>P</i> =0.085694 723 (12.6%)	1.58 (1.18-2.10) <i>P</i> =0.001975 204 (3.6%)	2.53 (1.84- 3.48) <i>P</i> <0.00001 139 (2.4%)
R at discharge		1.49 (1.16-1.91) <i>P</i> =0.001891 328 (5.7%)	2.17 (1.59-2.96) <i>P</i> <0.00001 125 (2.2%)	1.19 (0.80-1.76) <i>P</i> =0.382464 107 (1.9%)
I at discharge			1.95 (1.27-3.00) <i>P</i> =0.002285 71 (1.2%)	1.82 (1.18-2.81) <i>P</i> =0.007228 72 (1.3%)
F at discharge				2.07 (1.50-2.85) <i>P</i> =0.000008 118 (2.1%)

Figure legend

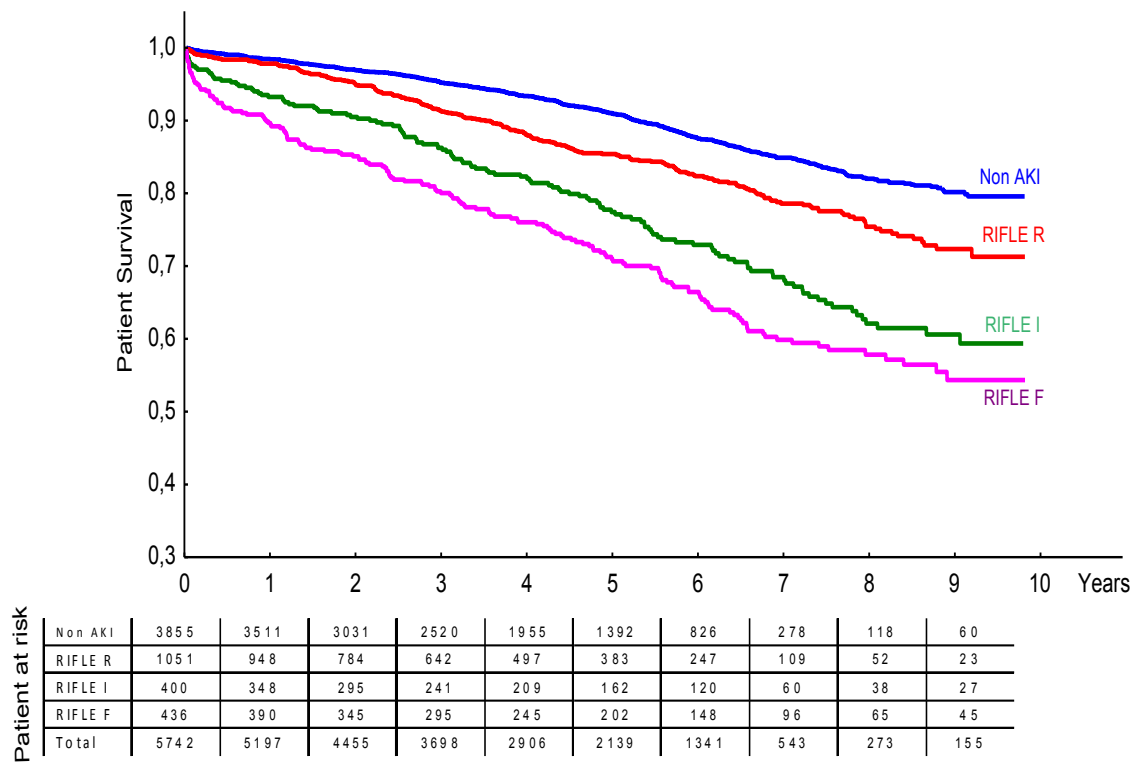


Figure 1: Unadjusted Kaplan–Meier plot depicting the survival of patients depending on level of AKI stratified by the RIFLE classification based on MDRD $eGFR_{peak}$ calculations.