An Optimized Classification System of Acute Kidney Injury for Predicting the Short-term Mortality after Open Heart Surgery; Comparison of Current Classification Systems

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Dedication

This thesis is dedicated to my parents whose love, compassion and training have always supported my dedication to mankind.

Abstract:

Epidemiologic studies need a unique operational definition of acute kidney injury (AKI) to compare outcomes. We aimed to compare prognostic value of change in serum creatinine with classification systems of AKI to predict 30-day mortality after heart surgery. From VA database, 27410 eligible patients with stable baseline kidney function who had heart surgery from 1999 to 2005 were selected. There was a graded increase in mortality from stage A to stage C of all systems. Adjusted 30-day mortality odds ratio starts to increase significantly after an acute rise $\geq$ 0.3 mg/dL of creatinine in CKD stages 1 and 2, and after 0.6 mg/dL increase in CKD stage 3. Area under ROC curve of change of creatinine from baseline was significantly higher than those of classification systems ($P<0.001$). In conclusion, compared to continuous increase of creatinine, classification systems of AKI misestimate mortality risk by collapsing predictive, clinically important data into categories.

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1) Introduction:

Over past 50 years more than 30 different definitions of acute kidney injury (AKI) have been proposed.[1] The different proposed definitions do not allow meaningful comparison of outcome in epidemiologic studies and makes the results of different trials inconsistent and as a result appropriate interventions may not be appropriately tested. Therefore, clinical studies need a valid and reliable definition of AKI so that associative studies and clinical trials aimed at either preventing or determining the complications of AKI could better be conducted and compared. In 2002, Acute Dialysis Quality Initiative proposed Risk, Injury, Failure, Loss and End-stage disease (RIFLE) for classification of AKI (table 1) using serum creatinine, GFR and urinary output changes for classification.[1, 2] In 2005, Acute Kidney injury Network (AKIN) modified the RIFLE criteria by incorporation of absolute increase of serum creatinine over a 48-hour time frame for definition of stage 1 (table 1) and removing the alternate methods of determining kidney function such as evaluation of GFR.[3] The creatinine based classification systems of these criteria are mainly defined by relative increase of serum creatinine from baseline. More recently, Waikar proposed another definition of AKI based on creatinine kinetics and absolute rather than relative increase of serum creatinine within 24 to 48 hours.[4]

Until now, several clinical studies have been identified which have attempted to validate the RIFLE classification. Among these studies, Abosaif, Ahlstrom, Cruz and Hoste[5-8] have examined mortality at different stages of

RIFLE in general intensive care units, using serum creatinine and urine output criteria. Lopes and Ostermann[9-11] have used serum creatinine criteria of this classification system in HIV and sepsis patients in general intensive care units. Kuitunen and Lin[12, 13] examined RIFLE criteria on patients undergoing cardiovascular surgery, while Coca and Lopes[14, 15] tested this system on other intensive care unit patients. Uchino applied this classification in patients who were not confined to intensive care units.[16] A common feature in methodology of these studies is comparing mortality by increase in stages of AKI. By increase in severity of AKI and subsequent graded increase in mortality at more advanced stages of RIFLE classification, all these clinical studies have uniformly showed comparable similar pattern which have been translated to the validity of RIFLE classification. However, the simple graded increase in mortality by stage of AKI may not fully portrait the performance of a classification system or its limitations.

Even, fewer studies have compared the performance characteristics of RIFLE with AKIN classification system for prediction of short-term mortality after AKI. To our knowledge, there are two reports in which ability of RIFLE and AKIN to predict short term mortality after AKI have been examined [17, 18], reported by Bagshaw and Lopes. However both of these studies have major methodological limitations. Bagshaw's study lacks baseline serum creatinine, kidney function and body weight. Since urine output criteria of RIFLE is a weight based definition, using an arbitrary number as average of weight for the whole population have certainly led to misclassification of stages of AKI in Bagshaw's

study.[17] Similarly, Lopes study lacked information on baseline serum creatinine and kidney function and has had a low sample size. There are also no studies validating the Waikar's classification with other systems. Hence, the different classification systems including RIFLE, AKIN and Waikar's classification have not been adequately examined against each other and their performance and limitations are not fully explored. Since the optimal time frame and the best markers of renal function such as change in serum creatinine or estimated GFR (eGFR) for optimally defining outcomes associated with AKI needs to be determined, this study is proposed for such a comparison.

1-1) Objectives:

Given the uncertainty in the current literature regarding the best method of AKI classification of renal function, we aimed:

1- To determine the cut-point by which the increase in serum creatinine increases the 30-day mortality after surgery at different stages of baseline kidney function.

2- To compare the prognostic value of different classification systems of AKI to predict 30-day mortality after surgery.

3- To determine which marker of AKI (change in eGFR, creatinine or both) best predicts the 30-day mortality at different stages of Risk, Injury and Failure of RIFLE classification system.

2) Methods:

2-1) Cohort construction: This study was a retrospective cohort using a representative cohort of all individuals undergoing coronary artery bypass graft surgery with or without valve replacement in Veterans Administration hospitals across the United States from September 1999 to August 2005. Inclusion criteria were patients who underwent heart surgery, had measured baseline serum creatinine within 30 days prior to the surgery, had measured creatinine within 7 days after the surgery and were followed at least for 30 days from the date of surgery. Exclusion criteria were having end stage renal disease on renal replacement therapy within 30 days prior to heart surgery, developing or recovering from AKI prior to the date of surgery and missing data on age, sex or race.

2-2) Data collection: The variables were gathered from Continuous Improvement in Cardiac Surgery Program (CICSP). From this database demographic variables, type and date of surgery as well as 30-day post operative mortality were retrieved. All serum creatinine values were obtained from the VHA national Decision Support System (DSS) database which captures all serum creatinine measurements performed in the VA system. The comorbidities were identified using inpatient outpatient administrative data in the two years prior to surgery using the Elixhauser methodology.[19] Minimum preoperative serum creatinine within 30 days prior to surgery was considered as baseline creatinine if it had been stable with less than 0.3 mg/dl variation prior to surgery. In 422

patients (1.5%) who only had one measured creatinine prior to operation their corresponding mean preoperative eGFR was 83 mL/min and therefore their serum creatinine was presumed to be at baseline. The peak post operative serum creatinine within 7 days of surgery was identified and its difference from preoperative creatinine was defined as absolute rise of creatinine after operation and was used for definition of AKI and its severity. Baseline eGFR was calculated using stable baseline creatinine prior to surgery and uncalibrated abbreviated Modification of Diet in Renal Diseases (MDRD) formula.[20] Stages of kidney function at baseline was defined using cut points recommended by Kidney Disease Outcomes Quality initiative guidelines as stages 1 and 2 (eGFR $\geq$ 60 mL/min), stage 3 (eGFR 30-59 mL/min), stage 4 (eGFR 15-29 mL/min) and stage 5 (eGFR < 15 mL/min) kidney diseases.[21] AKI was defined by different systems including RIFLE, AKIN and Waikar as shown in table 1. Accordingly, stage A refers to Risk or stage 1 of AKIN or Waikar's classification, stage B refers to Injury or stage 2 of AKIN or Waikar's classification and stage C refers to Failure or stage 3 of AKIN or Waikar's classification. $RIFLE_{cr}$ and $RIFLE_{GFR}$ were RIFLE classifications using serum creatinine and eGFR criteria, respectively. $RIFLE_{w}$ was defined as worst category of $RIFLE_{cr}$ and $RFILE_{GFR}$. In RIFLE criteria the peak serum creatinine or the lowest eGFR within 7 days after surgery was used for classification. In AKIN, in addition to relative increase as demonstrated for RIFLE criteria, the worst serum creatinine in the first 48 hours of the first increase in serum creatinine $\geq$ 0.3 mg/dL within 7 days after heart surgery was used for classification. In Waikar's criteria any acute increase in

serum creatinine meeting its definition (table 1) within a 7-day period post operation was base of classification. Primary end-point was defined as 30-day mortality starting from the date of operation.

Although the observation was made throughout a 6 year period from September 1999 to August 2005, the creatinine measurements for each patient were measured within a maximum period of 1 month prior to surgery up to seven days after surgery. Within this relatively short period of time it is a remote possibility that measurement system for each patient within the institute were the surgery was made got changed and even if at some point the measurement methodology got changed that applied to a very low percentage of patient which is unlikely to change the results of the whole sample size. Therefore, because the main basis for comparison of measured creatinine is comparison of post operative serum creatinine with baseline serum creatinine for each patient within a relatively short timeframe, our assessment is that change in methodology of measurement of serum creatinine over time is unlikely to have a significant impact on our final results.

2-3) Quality control: All the codes for calculation of new variables were checked and their accuracies were verified by the thesis supervisor. The computer generated syntax of the coding procedures is presented in appendix 14 (page 58).

2-4) Statistical analysis: Chi-square test was used to compare the categorical variables among different groups. Analysis of variance (ANOVA) was applied to detect statistically significant mean values among different groups

using Tukey-B post hoc analysis to determine the significantly different groups. Unadjusted 30-day mortality was calculated by different stages of different classification systems of AKI. For comparison of post-operative length of stay between each classification system mean ranks were calculated using Kruskal-Wallis test. Adjusted 30-day mortality odds ratio (OR) and its corresponding confidence interval was calculated using multiple logistic regression analysis for different classification systems of AKI as well as for absolute increase of serum creatinine from baseline at all levels of baseline kidney function and after adjusting with other covariates (Supplements 1 to 13). The main predictor of interest is AKI staging systems including AKIN, RIFLEcr, $RIFLE_{GFR}$, $RIFLE_{W}$, Waikar and creatinine which are presented through 6 different equations. Each classification system has three categories as defined in table 1. Assumption of linearity between three categories of each classification system is not valid. So rather than using the three categories of each system as a continuous variable, mortality in each category was compared with mortality of patients with no AKI. Similarly, for the creatinine model, creatinine was not used as a continuous variable because assumption of linearity at different levels of increase in serum creatinine is not valid. Instead, each 1 mg/dL increase in creatinine was used as a category and mortality in that category was compared with mortality in patients with no increase in creatinine as reference to allow the exploration of nonlinear relationship. The covariates for all models are age, sex, race, CHF, peripheral vascular disease, hypertension, COPD, diabetes, liver disease, obesity, weight loss and anemia. Models with stepwise inclusion of covariates were compared with

pooled models (supplements 2-13), and because the corresponding models with and without stepwise technique produced similar coefficients only results of the pooled equation are reported in the final models. To detect the cut-point in which rise in serum creatinine was associated with increase in mortality, in addition to using smoother plot graphical tools, exploratory analysis was applied to test the 30-day mortality odds ratio at different cut-points keeping patients with no increase in serum creatinine as reference. Area under receiver operating characteristics (ROC) curves corresponding to each classification system were calculated and compared with area under ROC curve of absolute increase of serum creatinine from baseline by DeLong's method [22]. For patients who have been discharged from hospital earlier than 7 days after operation or did not have daily creatinine measurements for 7 days, we performed extrapolation of linear trend of serum creatinine for available dates for each patient to estimate the serum creatinine on missing dates as a data imputation technique. The technique did not modify our associations and therefore results from data imputation are not presented.

2-5) Power calculation: Power calculation was based on comparison of area under ROC curve of 2 classification systems of AKI at alpha levels of 0.05 and 0.01, assuming a 10 percent difference in area under curves as a clinically significant difference, using Hanley's method.[23] Power calculation was performed using Power Analysis and Sample Size (PASS) 2008 software (NCSS, Kaysville, UT). All other analyses were done using SAS version 9.2 (SAS

Institute Inc., Cary, NC). This study was approved by the Minneapolis VA Medical Center human subjects committee.

3) Results:

3-1) Baseline characteristics: Initially, we identified 30664 eligible patients. In the next step, 2983 patients were excluded for evidence of developing or recovering from AKI prior to date of surgery, 249 patients for having end stage kidney disease requiring renal replacement therapy, and 22 patients for missing variables. At the end 27410 patients entered in to final analyses. Table 2 shows the distribution of study variables at study entry by baseline level of kidney function. Accordingly 83.4% of patients had a baseline eGFR ≥ than 60 mL/min, 15.8% had CKD stage 3, 0.7% had stage 4 and 0.1% of patients had stage 5 of CKD without renal replacement therapy at baseline. Age was significantly higher among stages 3 and 4 of CKD compared to other stages ($P<0.01$). Peripheral vascular diseases (PVD) and congestive heart failure (CHF) were more prevalent among stages 4 and 5 of CKD compared to other stages, but diabetes was more prevalent only in stage 5 compared to others. Distribution of sex, race, hypertension, obesity and chronic obstructive pulmonary disease (COPD) was not different among these groups. Males dominated the study and comprise more than 99% of the cohort.

3-2) Incidences of AKI and mortality by AKI classification systems: Table 3 shows incidence of AKI within 7 days after operation as well as the 30-day mortality and length of post operative hospital stay by different definitions of AKI. Accordingly the lowest AKI incidence of 18.9% was observed by $RIFLE_{cr}$

classification system. Incidence of AKI was 40.1% by other RIFLE systems, 41.5% by AKIN and 36.0% by Waikar's classification. Over-all 30-day mortality was variable by different systems ranging from 3.6 % in AKIN to 7.5% $RIFLE_{cr}$. There was a graded increase in mortality from stage A to stage C of AKI in all classification systems in patients with CKD stage 3 and better at baseline. The graded change in patients with CKD stage 4 and 5 at baseline is not shown due to low sample size and no mortality in these stages, respectively.

Table 4 shows mortality at different levels of rise in absolute increase in serum creatinine. Accordingly, in patients with CKD stage 1 and 2 at baseline, there were 8330 patients (36.4%) with $\geq$ 0.3 mg/dL increase in creatinine after operation of which 348 patients (4.2%) have dies within 1 month after operation. In patients with CKD stage 3 at baseline, there were 1182 patients (27.3%) with > 0.6 mg/dL increase in serum creatinine after operation of which 101 patients (8.5%) have died within 1 month after operation. While there have been a decrease in proportion of patient with larger increase in serum creatinine at all levels of baseline kidney function, there has been a graded increase in mortality by increase in serum creatinine (table 4).

3-3) Post operative length of hospital stay by AKI systems: According to table 3, median post-operative lengths of hospital stay ranged from 7 to 12 days from stage A to stage C of different categorical classification systems (table 3). The least mean rank of post operative length of hospital was observed in Waikar's classification systems in all stages of A through C, as compared to other classification systems ($p < 0.01$). Table 4 shows that the median post-operative

length of hospital stay ranged from 6 to 25 days by different levels of continuous rise in serum creatinine in patient with baseline eGFR ≥ 60 mL/min, and from 7 to 28 days in patients with baseline eGFR of 30 to 59 mL/min. Accordingly, there has been a graded increase in post operative length of hospital stay by absolute increase in serum creatinine in all classification systems.

3-4) Determinations of cut-points, subgroup analysis: In figure 1, change in slope of probability of death by increase in serum creatinine is presented for different levels of CKD at baseline. Accordingly, while figure 1-A suggests a cut-point of 0.3 mg/dL increase in serum creatinine for a change in slope of probability of mortality in CKD stage 1 and 2 at baseline, figure 1-B suggests a cut-point of 0.6 for a similar change in patients with CKD stage 3 at baseline.

Similarly in figure 2, the change in slope is shown for different categories of serum creatinine at baseline. While figures 2-A and 2-B suggest a cutpoint of 0.4 and 0.2 mg/dL for baseline serum creatinine < 0.9 and 0.9 to less than 1.2 mg/dL, respectively, figure 2-C suggests a cut-point of 0.6 mg/dL for patients with baseline serum creatinine of 1.2 to less than 2 mg/dL which is compatible with the cut-point suggested for CKD stage 3 at baseline. Figure 2-D suggests a cut-point of 2.8 mg/dL for patients with baseline creatinine of 2 mg/dL and more, but this observation is based on too few cases.

Figures 3 show a subgroup analysis by different categories of covariates and comorbid conditions in patients of CKD stage 1 and 2 at baseline. Accordingly, risk of mortality in AKI defined as acute increase in serum

creatinine ≥ 0.3 mg/dL in CKD stage 1 and 2, is relatively similar in all levels of comorbid conditions and covariates. Non-significant odds ratio in females and patients with BMI < 20 kg/m^2 are likely reflection of a low sample size in those subgroups. Similarly, risk of mortality in AKI defined as an acute increase in serum creatinine > 0.6 mg/dL in CKD stage 3, is relatively similar in all levels of comorbid conditions and covariates (figure 4). Non-significant odds ratio in 'BMI < 20 kg/m^2' and 'Other races' are likely reflection of low sample size in those groups (figure 4).

3-5) Comparing mortality risk of AKI classification system with absolute increase in creatinine: Figure 5 shows the log odds of mortality from stage A to stage C of different categorical classification systems of AKI as well as by different levels of absolute rise in serum creatinine from baseline, after adjusting with sex, race, age and comorbid conditions in a multivariable model in patients with CKD stage 1 and 2 at baseline (Appendices 1 to 13). This graph suggests that there is a graded increase in mortality from stage A to stage C of all categorical classification systems, as well as by any increase in absolute change in serum creatinine ≥ 0.3 mg/dL in patients with CKD stages 1 and 2.

Figure 6 shows a similar pattern with a graded increase in mortality by increase in stages of AKI, as well as by any increase in absolute change in serum creatinine > 0.6 mg/dL from baseline in patients with CKD stage 3.

Figure 7 shows change in mortality risk by absolute change of serum creatinine within each category of RIFLEcr. Accordingly, mortality OR has increased from 2.4 in category of Risk to 29.3 in category of Failure. However,

category of Failure itself comprises of patients with minimal increased risk of mortality, to a 98 folds higher risk of mortality when compared to patients with no change in serum creatinine using absolute change in serum creatinine from baseline. Similar heterogeneity but to a lesser extent is observed within each category of Injury and Risk. On the other hand, all patients in the category of Injury have a similar risk of death to 57.3% of patients in the category of Failure (those with < 3 mg/dL increase in serum creatinine) when mortality OR is calculated by absolute increase of serum creatinine from baseline, but in spite of that they are categorized in 2 different categories of RIFLE. Similarly, 99.8% of patients in the category of Risk have similar risk of death to 95.5% of patients in the category of Injury and 10.7% of patients in the category of Failure (those with < 2 mg/dL increase in serum creatinine) when mortality OR is calculated by absolute increase of serum creatinine from baseline, but in spite of that patients fall in to 3 different categories of RIFLE. Similar pattern can be seen in patients with CKD stage 3 at baseline (Figure 8).

3-6) comparing ROC curve of different classification systems: Figure 9, shows area under ROC curves of different classification systems along with that of absolute change in serum creatinine from baseline. The area under ROC curve (SE) of post-operative increase in creatinine, Waikar's classification, AKIN, $RIFLE_{cr}$, $RIFLE_{GFR,}$ $RIFLE_{W}$ and change of eGFR are 0.76 (0.01), 0.71 (0.01), 0.72 (0.01), 0.73 (0.01), 0.73 (0.01), 0.73 (0.01) and 0.71 (0.01), respectively. Accordingly, the area under ROC curve of change in absolute change in serum creatinine was significantly greater than all other classification

systems (P<0.0001). Between the classification systems, $RIFLE_{cr}$ classification had the highest area under ROC curve compared to Waikar and AKIN (P<0.05). Although RFILEcr and RIFLEgfr were not significantly different, absolute change of eGFR showed the worst performance (tables 6-9).

3-7) Power calculation:

Report Definitions:

Power is the probability of rejecting a false null hypothesis.

N+ is the number of patients who died within 1 month after operation.

N- is the number of patients who survived the first month after operation.

AUC1' is the adjusted area under the ROC curve for a classification system of AKI.

AUC2' is the adjusted area under the ROC curve for the other classification system.

Diff' is AUC2 - AUC1. This is the adjusted difference to be detected.

Alpha is the probability of rejecting a true null hypothesis.

Power	N+	N-	AUC1'	AUC2'	Diff'	Alpha
0.8000	200	2550	0.7500	0.6750	-0.0750	0.01
0.8004	300	283	0.7500	0.6750	-0.0750	0.01
0.8007	400	196	0.7500	0.6750	-0.0750	0.01
0.8001	500	165	0.7500	0.6750	-0.0750	0.01
0.8013	600	150	0.7500	0.6750	-0.0750	0.01
0.8001	700	140	0.7500	0.6750	-0.0750	0.01
0.8003	200	193	0.7500	0.6750	-0.0750	0.05
0.8015	300	121	0.7500	0.6750	-0.0750	0.05
0.8021	400	102	0.7500	0.6750	-0.0750	0.05
0.8018	500	93	0.7500	0.6750	-0.0750	0.05
0.8022	600	88	0.7500	0.6750	-0.0750	0.05
0.8034	700	85	0.7500	0.6750	-0.0750	0.05
0.8002	300	566	0.6500	0.5850	-0.0650	0.01
0.8002	400	349	0.6500	0.5850	-0.0650	0.01
0.8005	500	284	0.6500	0.5850	-0.0650	0.01
0.8012	600	253	0.6500	0.5850	-0.0650	0.01
0.8006	700	234	0.6500	0.5850	-0.0650	0.01
0.8002	200	286	0.6500	0.5850	-0.0650	0.05
0.8009	300	210	0.6500	0.5850	-0.0650	0.05

0.8012	400	171	0.6500	0.5850	-0.0650	0.05
0.8017	500	154	0.6500	0.5850	-0.0650	0.05
0.8011	600	144	0.6500	0.5850	-0.0650	0.05
0.8015	700	138	0.6500	0.5850	-0.0650	0.05

An estimate of the number deaths prior to study is a number between 200 to 700 deaths. A sample of 200 from the deceased group needs a sample of 2550 from survivors to detect a 10% difference between the two area under ROC curves with 80% power using a two-sided z-test at significance level of 0.01, assuming AUC for the better system to be 0.75. With higher number of deaths, the required number of survivors and the total sample size has decreased. With a sample size of 27410 including 653 deaths, we are over powered to detect the clinically significant different AUCs.

4) Discussion:

In this study incidence of AKI was 18.9% by $RIFLE_{cr,}$ 36% by Waikar's classification, and about 40% by all other classification systems within 7 days after heart surgery. Our data supports the definition of AKI as an acute rise in serum creatinine ≥ 0.3 mg/dL from baseline in patients with CKD stages 1 and 2, evidenced by a significant increase in 30-day mortality starting from this point. In CKD stage 3, a 0.6 mg/dL acute rise in serum creatinine was required to observe a significant rise in mortality. Comparison of area under ROC curve of different classification systems with that of absolute increase in serum creatinine revealed significantly higher predictive value of absolute rise of serum creatinine as a continuous variable over other classification systems of AKI. Within each stage of categorical classification systems of AKI a heterogeneous pattern of mortality is observed, while patients with similar risk of death by using continuous increase of creatinine were classified in to three different stages. Mean rank of post operative length of hospital stay in all stages of Waikar's classification was significantly lower than corresponding stages of other classification systems.

Since 2005, several studies have used RIFLE classification for study of AKI.[5-8, 11-14, 16-18, 24-32] A common feature of all of these studies has been a graded increase in mortality from Risk to Failure category compared to patients without any AKI.[33] Analysis of Australian and New Zealand Intensive Care Society Adult Patient Database of 120123 patients in 57 ICUs in Australia in a 5-year period revealed an AKI incidence of 36.1%.[34] The highest incidence of AKI categories was in the category of Risk with 16.3% followed by 13.6% in Injury and 6.3% in

Failure categories. The corresponding crude hospital mortality was 17.9%, 27.7% and 33.2%, respectively. Further analysis of this cohort compared the area under ROC curve of RIFLE classification with that of AKIN.[17] There was no improvement in sensitivity and predictive value of RIFLE classification when compared to AKIN. However, there are major limitations in this study. First the baseline serum creatinine was unavailable and serum creatinine on admission was used as a proxy of baseline serum creatinine. Its other significant limitation was unavailability of patients' weight. Accordingly, the hypothetical weight of 70 kg for an average weighted person was used for the whole population to calculate the urine output criteria of RIFLE. Since the urine output criteria of RIFLE is a weight based definition using an arbitrary number for the whole population could have resulted in misclassification of stages of AKI. Furthermore it was not shown whether or not different categories of RIFLE by serum creatinine, eGFR or urine output have the same weight and or may be used interchangeably. The study performed by Antonio Lopes et al is the second largest study of comparison of RIFLE with AKIN classification. In this single center study 662 patients admitted to ICU in a 3-year period were evaluated.[18] Incidence of AKI was 43.8% with RIFLE classification as compared with 50.4% seen with AKIN classification with significantly higher mortality at higher stages of the two systems. Comparison of area under ROC curve of the two classification system did not show any significant difference in sensitivity or predictive profile of the 2 classification systems. This study although has had the individuals' weight, it had a relatively lower sample size and was similarly suffering from lack of baseline serum

creatinine as well as interchangeable use of serum creatinine and urinary output criteria.

In our study, the higher incidence of AKI in AKIN, $RIFLE_{GFR}$ and $RIFLE_{w}$ was a result of higher number of individuals classified as stage A, while in Waikar's system it was as a result of higher number of patients classified into stages B and C. The highest absolute number of death in AKIN, $RIFLE_{GFR}$, $RIFLE_{w}$ and Waikar's classifications as compared to that of RIFLEcr was the result of a higher total number of patients classified as having AKI by the former systems. Although stage A of AKIN, $RIFLE_{w}$ and $RIFLE_{GFR}$ was more sensitive to detect AKI than stage A of $RIFLE_{cr,}$ this sensitivity is offset by higher sensitivity of $RIFLE_{cr}$ to detect more AKIs at stage C, so that $RIFLE_{cr}$ has a slightly larger area under ROC curve compared to the other two systems to predict 30-day mortality after operation. However, the area under ROC curve of none of the categorical classification systems was as high as when creatinine was used as a continuous variable.

All stages of Waikar's classification system have had the lowest post-operative hospital stay as compared to other systems. It suggests that this classification system is proposing relatively healthier individuals to be classified as AKI compared to other systems. The clinical implication of this finding is that it might not have targeted the sick patients which would have been targeted by other systems otherwise, further evident by lower mortality OR observed in stages B and C of Waikar's classification system compared to other systems (figures 5 and 6). However, the conclusion on post-operative length of stay is limited by

variation in practice pattern and factors other than AKI which contribute in decision for hospital discharge.

A major limitation of categorical classification systems of AKI is misestimating the risk of mortality by collapsing a wide range of variability in risk of mortality into categories within each stage of AKI classification systems. The largest heterogeneity in risk of mortality was observed in stage C and to lesser extents in stages B and A (figures 7 and 8). Accordingly, while everybody at stage C of RIFLE is calculated to have mortality OR of 29.3 in CKD stage 1 and 2 (figure 6), some have had an OR of less than 10 and some had an OR of over 98. Therefore OR calculated by continuous rise of serum creatinine from baseline is overestimated in lower level of rise in creatinine and underestimated in higher levels of increase in serum creatinine when compared to OR within each stage of RIFLE classification system. On the other hand, patients with similar risk of death calculated by absolute increase in serum creatinine as a continuous variable were misclassified between 3 different stages of Risk, Injury and Failure when RIFLE classification was applied.

Future of diagnosis of kidney injury is based on more specific markers of tubular and renal injury. There is a general agreement that serum creatinine is neither a sensitive nor a specific marker of kidney injury, so that kidney damage might have already started few days prior to rise of serum creatinine or there may be even a rise in urea nitrogen and serum creatinine without necessarily having had kidney damage as in pre-renal states.[35, 36] Our data indicate that the categorical classification systems weaken the predictive value of serum creatinine

even further. While each 1 mg/dL increase in serum creatinine added significantly to mortality risk independent of any covariates, classification systems have blunted this effect by collapsing the data into categories. This limitation has important clinical implications. For instance, along with ignoring the continuously inclined mortality with each 1 mg/dL rise in creatinine as a result of collapsed data, the future therapeutic and preventive clinical trials may fail to detect clinically significant effect size if totally relay on classification systems.

This study has several strengths. First, the data was gathered from all the VA hospitals across the United States in a 6-year period and therefore the generalizability of results to similar population is legitimate. Second, the large sample size has provided a high power for the analyses, except for CKD stage 4. Third, unlike other similar studies we had the baseline serum creatinine allowing determining not only the status of kidney function at baseline but also the timing of development of AKI as early as one day. Forth, the 30-day survival status was available and uniformly collected for all patients regardless of their hospital stay or discharge and therefore the 30-day mortality was calculated based on the entire sample size. There are also limitations in this study. First, urinary output was not available in our national database and therefore the urinary output components of RIFLE criteria were not tested. The subgroup of patients with CKD stage 4 was underpowered for the analyses and therefore the analyses performed on stages 1 to 3 were not performed on this stage. Overall females were underrepresented since the patient population was selected from VA in which males dominate the population. This observation was also limited to AKI after heart surgery and

generalizability to AKI following other surgeries or to medical AKIs should be verified with further research. Not all patients had daily creatinine measurements up to 7 days post operation. A potential threat is underestimation of true 7-day incidence of AKI. However, we believe that lack of daily creatinine measurement up to seven days was a reflection of patients' stability which led to physicians' decision of not requesting for daily creatinine measurement. If this is a true explanation for lack of daily creatinine measurement for everybody it is less likely to have incident AKI in unmeasured dates, unless sporadically and on rare cases which may not have a significant impact on the final results. Therefore, we feel that it is safe to conclude the reported incidence of AKI is accurate estimation of incident AKI within seven days after operation.

In conclusion, we propose the definition of AKI as an acute rise in serum creatinine $\geq$ 0.3 mg/dL from baseline within a seven day period after heart surgery in CKD stages 1 and 2, and > 0.6 mg/dL in CKD stage 3, we discourage against use of categorical classification systems of AKI, since the systems mask clinically important and predictive information by collapsing data into categories. Rather than using classification systems, we propose the absolute rise of serum creatinine from baseline as a continuous variable as a measure of severity of AKI, as long as other markers of kidney injury are in research phase and have not gained popularity in clinical practice. Along with the cut-point as a base for definition of AKI, future preventive and therapeutic clinical trials should consider absolute change of serum creatinine from baseline as a marker of severity of AKI for comparison of outcomes and efficiency of treatments.

Table 1: Comparison of RIFLE, AKIN and Waikar's criteria for classification of acute kidney injury

Stages	RIFLE, Serum creatinine or GFR	AKIN, Serum creatinine	Waikar, Serum creatinine
A	**Risk**: Increase in serum creatinine ≥ 1.5 × baseline or decrease in GFR > 25%	**Stage 1**: Increase in serum creatinine ≥ 0.3 mg/dL or increase to ≥ 150-200% (1.5 to 2.0 fold) from baseline	**Stage 1:** 0.3 mg/dL increase over 24 hours or 0.5 mg/dL increase over 48 hours
B	**Injury**: Increase in serum creatinine ≥ 2.0 × baseline or decrease in GFR > 50%	**Stage 2**: Increase in serum creatinine to > 200-300% (2.0-3.0 fold) from baseline	**Stage 2:** 0.5 mg/dL increase over 24 hours or 1.0 mg/dL increase over 48 hours.
C	**Failure**: Increase in serum creatinine ≥ 3.0 × baseline or serum creatinine ≥ 4 mg/dL with acute increase of ≥ 0.5 mg/dL or decrease in GFR > 75%	**Stage 3**: Increase in serum creatinine to > 300% (> 3 fold) from baseline or serum creatinine ≥ 4 mg/dL with acute increase of ≥ 0.5 mg/dL or initiation of RRT	**Stage 3:** 1.0 mg/dL increase over 24 hours or a 1.5 mg/dL increase over 48 hours.

RRT: Renal replacement therapy

Table 2: Baseline characteristics of patients undergoing surgery by baseline kidney function:

Variables	GFR≥60	GFR 30-59	GFR 15-29	GFR<15	Total
N (%)	22870 (83.4)	4334 (15.8)	185 (0.7)	21 (0.1)	27410 (100)
Age (years)	64.0 ± 9.3 a	69.9 ± 8.3 b	68.3 ± 9.2 b	63.6 ± 7.9 a	65.0 ± 9.4
Creatinine (mg/dL)	1.0 ± 0.2 a	1.5 ± 0.2 b	2.9 ± 0.5 c	5.7 ± 1.4 d	1.1 ± 0.3
eGFR mL/min/1.73 m^2	87.7 ± 20.0 a	50.4 ± 7.5 b	24.5 ± 4.1 c	11.4 ± 2.6 d	81.3 ± 23.5
Male (%)	22680 (99.2) a	4271 (98.5) a	182 (98.4) a	21 (100) a	27154 (99.1)
Race					
White	19257 (84.2) a	3857 (89.0) a	60 (86.5) a	17 (81.0) a	23291 (85.0)
Black	2236 (9.8)	234 (5.4)	16 (8.6)	1 (4.8)	2487 (9.1)
Others	1377 (6.0)	243 (5.6)	25 (4.9)	3 (14.3)	1632 (5.9)
Comorbid conditions:					
Hypertension (%)	19812 (86.6) a	4073 (94.0) b	179 (96.8) b	21 (100) a,b	24085 (87.9)
Diabetes (%)	9777 (42.8) a	2182 (50.3) b	112 (60.5) c	19 (90.5) d	12090 (44.1)
COPD (%)	6784 (29.7) a	1474 (34.0) b	64 (34.6) a,b	7 (33.3) a,b	8329 (30.4)
PVD (%)	5056 (22.1) a	1444 (33.3) b	86 (46.5) b	9 (42.9) a,b	6595 (24.1)
Obesity (%)	5009 (21.9) a	968 (22.3) a	48 (25.9) a	5 (23.8) a	6030 (22.0)
CHF (%)	4380 (19.2) a	1409 (32.5) b	96 (51.9) b	10 (47.6) b	5895 (21.5)

Mean ± SD or n (%), Means and rates with the same letters in each row are not statistically different. Statistical significance is considered $p < 0.01$.

Table 3: Incidence of AKI, mortality and duration of hospital stay by RIFLE, AKIN and Waikar criteria

	N= 27410	$RIFLE_{cr}$	$RIFLE_{GFR}$	$RIFLE_{w}$	AKIN	Waikar
Incidence of AKI: (%)	None (%)	22230 (81.1)	16431(59.9)	16422 (59.9)	16021 (58.5)	17551 (64.0)
	Stage A (%)	3474 (12.7)	8898 (32.5)	8829 (32.2)	10194 (37.2)	6103 (22.3)
	Stage B (%)	1122 (4.1)	1779 (6.5)	1575 (5.7)	694 (2.5)	3056 (11.1)
	Stage C (%)	584 (2.1)	302 (1.1)	584 (2.1)	501 (1.8)	700 (2.6)
	Any category (%)	5180 (18.9)	10979 (40.1)	10988 (40.1)	13389 (41.5)	10709 (36.0)
30-day mortality: (%)	None (%)	263 (1.2)	177 (1.1)	176 (1.1)	168 (1.0)	196 (1.1)
	Stage A (%)	126 (3.6)	188 (2.1)	185 (2.1)	289 (2.8)	169 (2.8)
	Stage B (%)	133 (11.9)	196 (11.0)	161 (10.2)	77 (11.1)	156 (5.1)
	Stage C (%)	131 (22.4)	92 (30.5)	131 (22.4)	119 (23.8)	132 (18.9)
	Any category (%)	390 (7.5)	476 (4.3)	477 (4.3)	485 (3.6)	457 (4.3)
Length of post operative hospital stay: Median (IQR)	None (days)	6 (5 - 9)	6 (5 - 8)	6 (5 - 8)	6 (5 - 8)	6 (5 - 8)
	Stage A (%)	8 (6 - 13)	7 (6 - 11)	7 (6 - 11)	7 (6 - 12)	7 (6 - 11)
	Stage B (%)	11 (7 - 19)	10 (7 - 19)	10 (7 - 18)	9 (7 - 18)	9 (6 -15)
	Stage C (%)	12 (7 - 26)	12 (6 - 28)	12 (7 – 26)	11 (7 – 25)	9 (6 – 18)
	Any category (days)	9 (6 – 15)	8 (6 -13)	8 (6 -13)	8 (6 -13)	8 (6 -13)

IQR: Inter-quartile range

Table 4: Mortality and incidence of AKI by level of increase in serum creatinine from baseline

Δ Cr	**Frequency (%)**	**Mortality (%)**	**Post operative length of stay, Median [IQR]**
CKD stage 1 - 2 (eGFR ≥ 60):			
< 0.3 (mg/dL)	14540 (63.6)	136 (0.9)	6 [5, 8]
0.3-1.0 (mg/dL)	7335 (32.1)	168 (2.3)	7 [6, 11]
1.1-1.9 (mg/dL)	659 (2.9)	88 (13.4)	11 [7, 18]
2.0-2.9 (mg/dL)	196 (0.9)	48 (24.5)	10 [6, 21]
3.0-3.9 (mg/dL)	70 (0.3)	19 (27.1)	12 [6, 34]
4.0-4.9 (mg/dL)	39 (0.2)	12 (30.8)	14 [8, 34]
5.0-5.9 (mg/dL)	17 (0.1)	6 (35.3)	25 [5, 34]
≥ 6 (mg/dL)	14 (0.1)	7 (50.0)	16 [8, 26]
Any cr ≥ 0.3	**8330 (36.4)**	**348 (4.2)**	**7 [6, 12]**
CKD stage 3 (eGFR, 30-59):			
< 0.6 (mg/dL)	3152 (72.7)	57 (1.8)	7 [5, 10]
0.6-1.0 (mg/dL)	609 (14.1)	21 (3.4)	9 [7, 17]
1.1-1.9 (mg/dL)	375 (8.7)	36 (9.6)	10 [7, 20]
2.0-2.9 (mg/dL)	117 (2.7)	19 (16.2)	13 [9, 27]
3.0-3.9 (mg/dL)	40 (0.9)	12 (30.0)	17 [8, 30]
4.0-4.9 (mg/dL)	22 (0.5)	5 (22.7)	16 [7, 35]
5.0-5.9 (mg/dL)	13 (0.3)	6 (46.2)	13 [8, 34]
≥ 6 (mg/dL)	6 (0.1)	2 (33.3)	28 [9, 64]
Any cr > 0.6	**1182 (27.3)**	**101 (8.5)**	**10 [7, 19]**

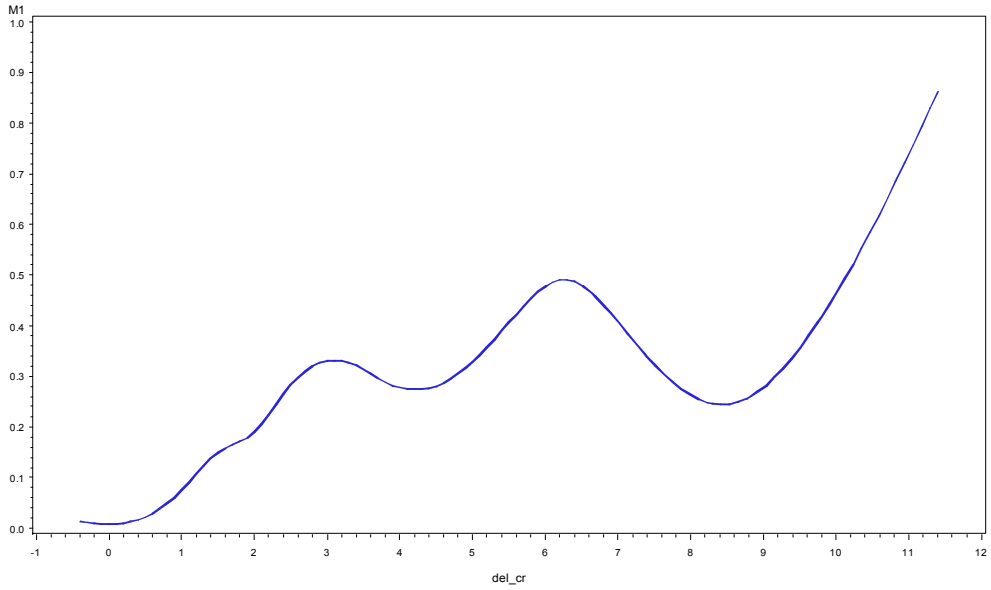
IQR: Inter quartile range

Table 5: The suggested cut points by level of CKD at baseline:

	Sample size in CKD stages 1 & 2	Suggested cut-point	Sample size in CKD stage 3	Suggested cut-point
CKD	22870	0.3	4334	0.6

Figure 1) Smoother plot of change in slope of mortality by absolute increase in serum creatinine in ***CKD stages 1 & 2*** combined (N=22870), suggesting a cut-point of 0.3 mg/dL increase in serum creatinine for change in mortality, and in serum creatinine in ***CKD stage 3*** (N=4334), suggesting a cut-point of 0.6 mg/dL increase in serum creatinine for change in mortality.

A) CKD stages 1 & 2 (N=22870):



B) CKD stage 3 (N=4334):

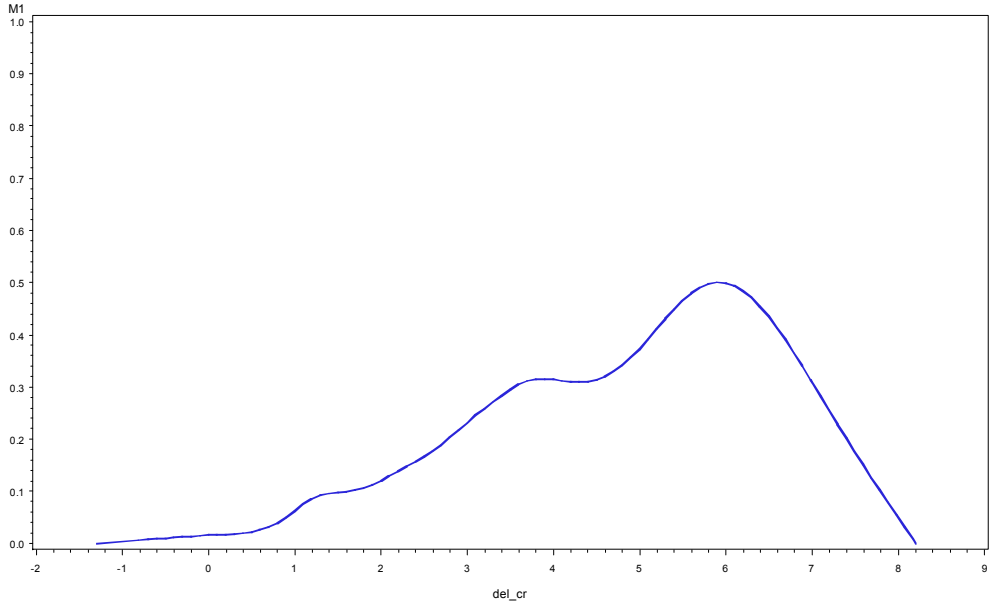
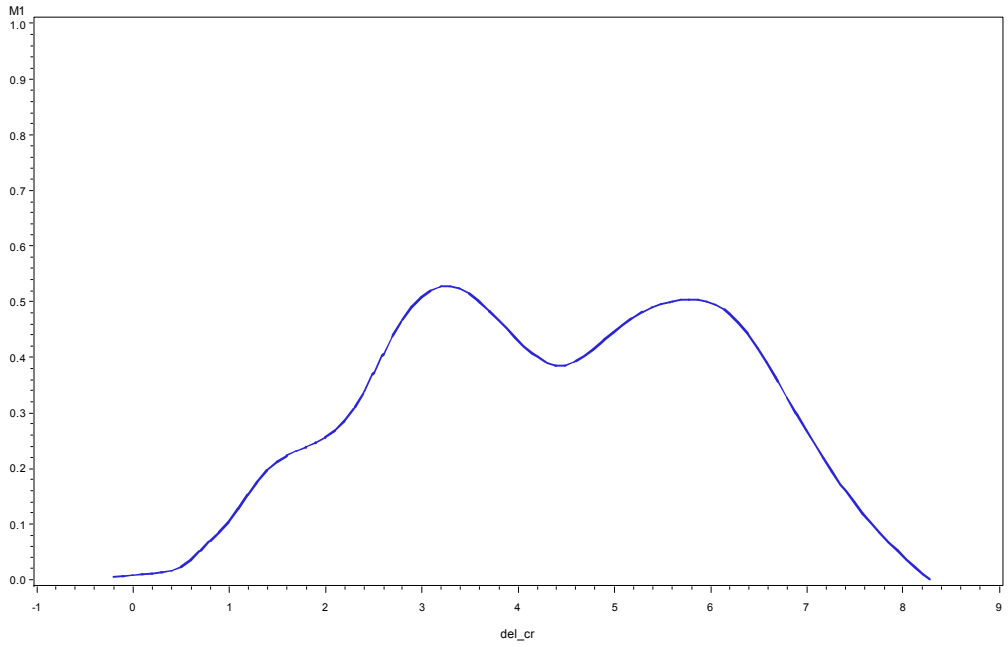
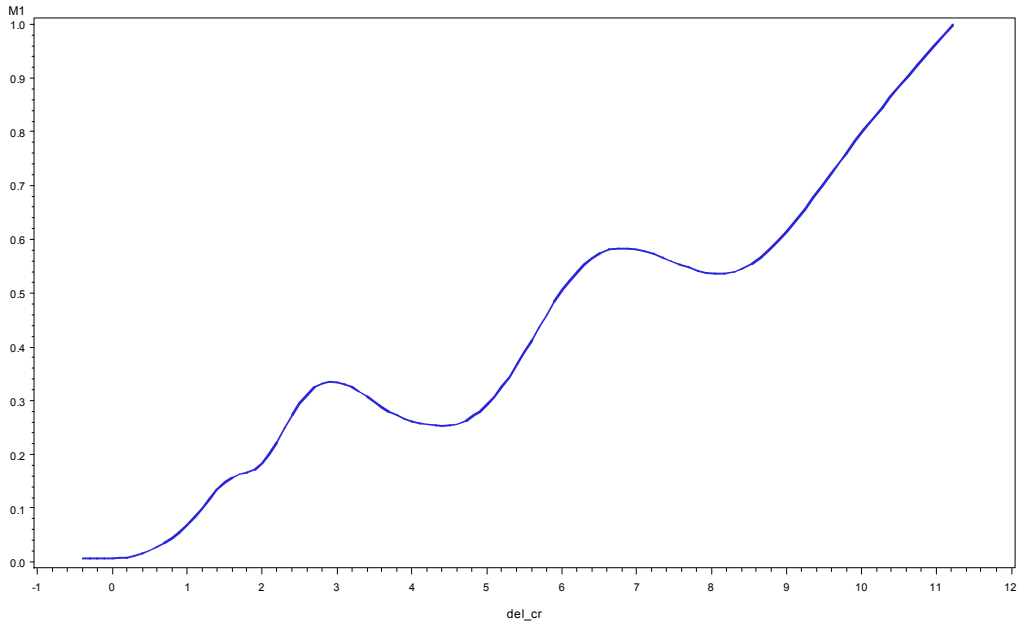


Figure 2) Smoother plot of change in slope of mortality by increase in post operative serum creatinine at different levels of baseline ***creatinine***

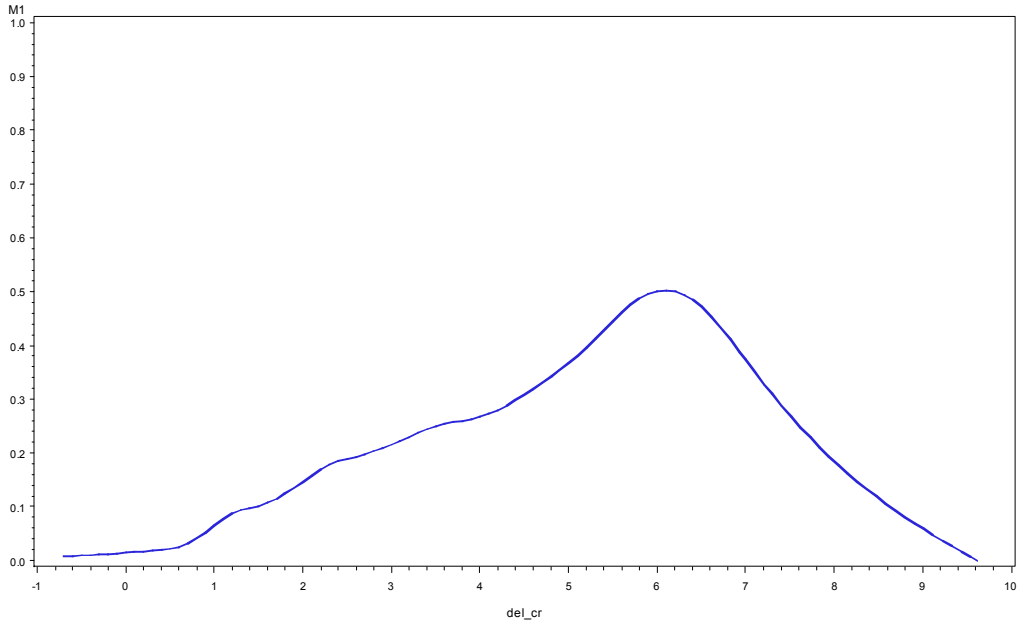
A) Baseline creatinine < 0.9 mg/dL (N=5266). Suggested cut-point = 0.4 mg/dL



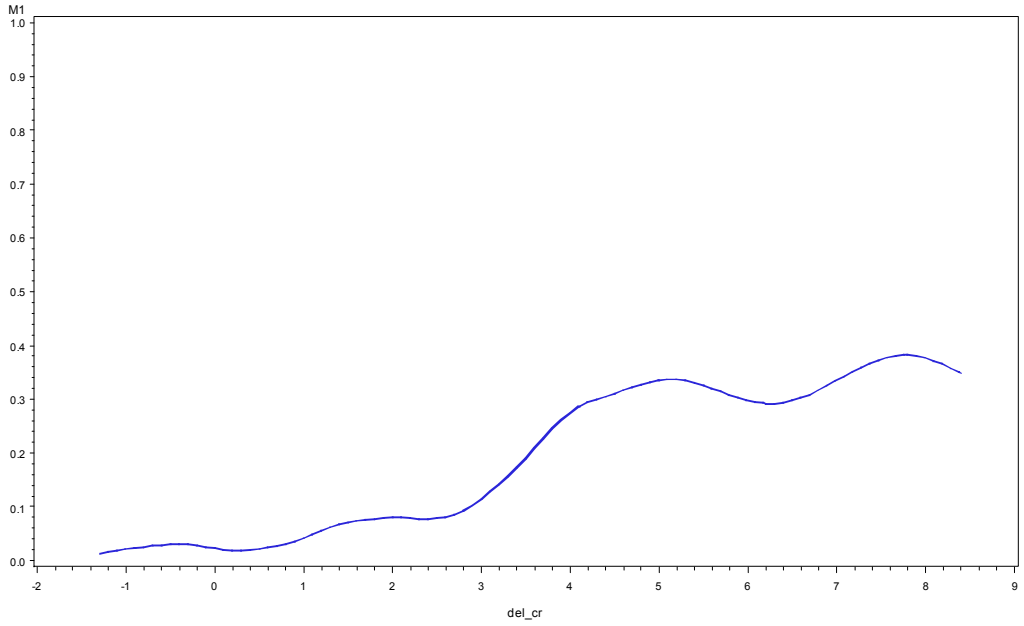
B) Baseline creatinine ≥ ***0.9 mg/dL and < 1.2 mg/dL*** (N= 14301). Suggested cut point = 0.2 mg/dL



C) Baseline creatinine ≥ ***1.2 mg/dL and < 2 mg/dL*** (N=7318). Suggested cut point = 0.6 mg/dL



D) Baseline creatinine ≥ ***2 mg/dL*** (N=525). Suggested cut point = 2.8 mg/dL



Note: SAS code to obtain the above graphs:

```
libname lib 'c:\';
data filename;
set lib.file;
run;

Goptions reset=all;
Proc Gplot data=filename;
plot M1 * del_cr;
symbol1 interpol=sm55s width=2;
run;
```

Figure 3: Subgroup analysis of change in risk of mortality in AKI by different levels of covariates in CKD stage 1 and 2 at baseline.

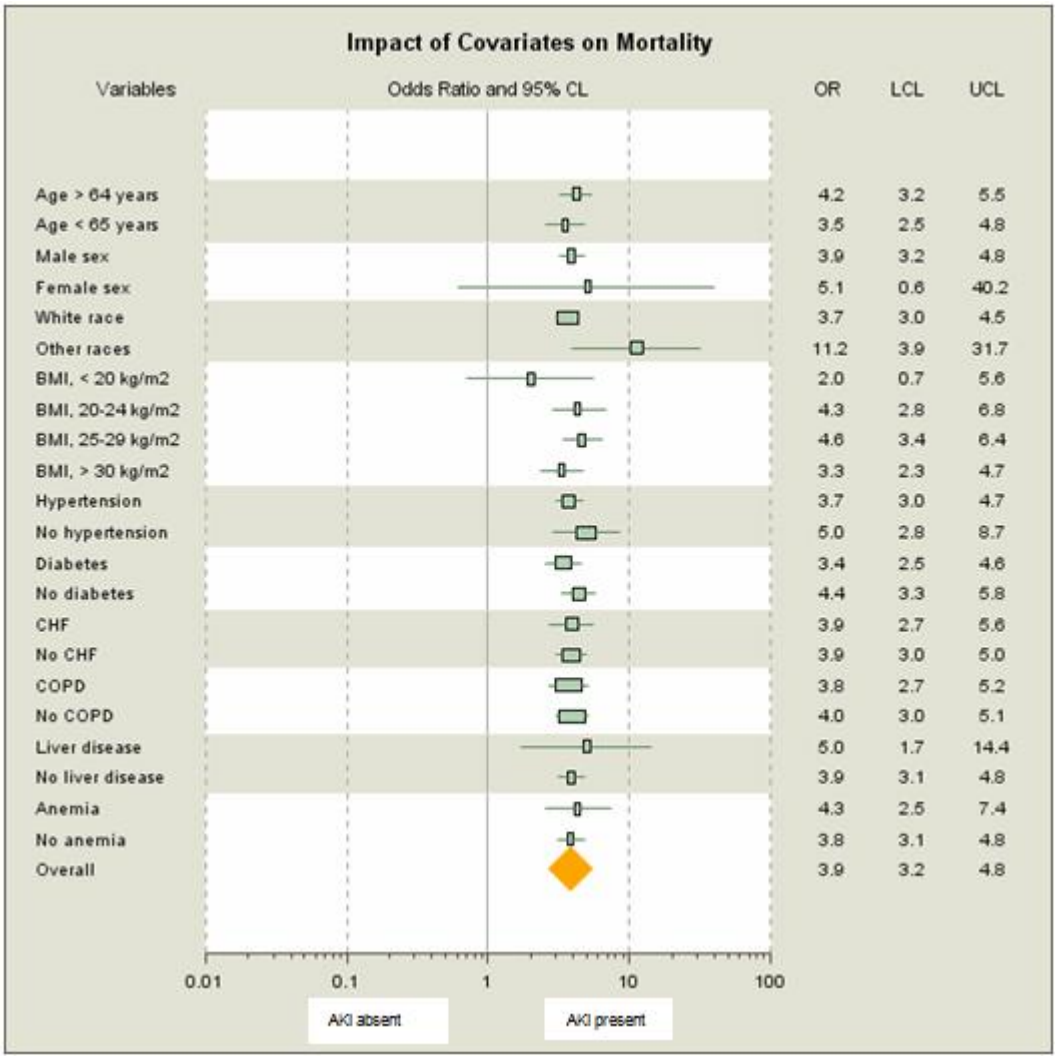
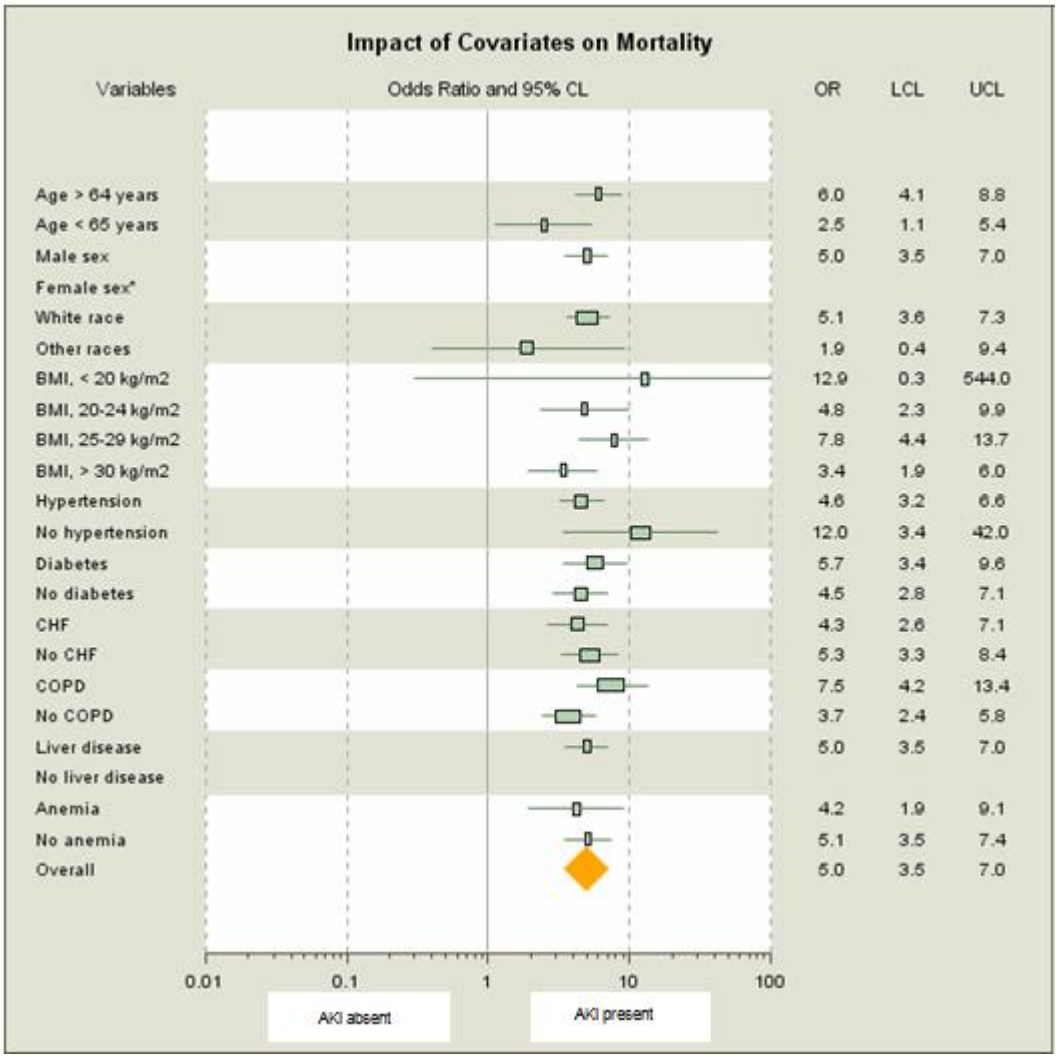
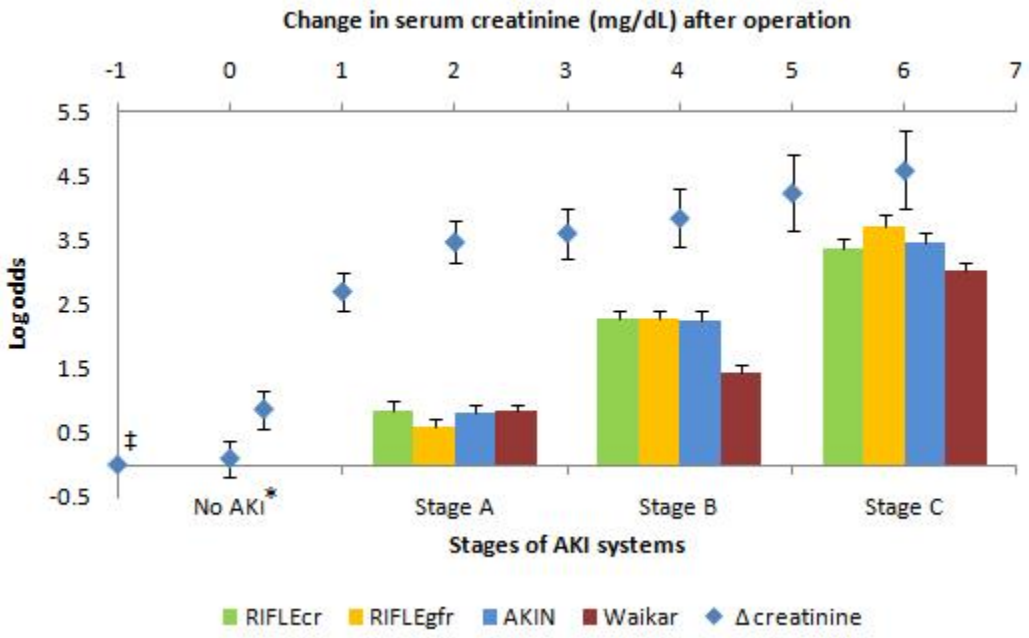


Figure 4: Subgroup analysis of change in risk of mortality in AKI by different levels of covariates in CKD stage 3 at baseline.



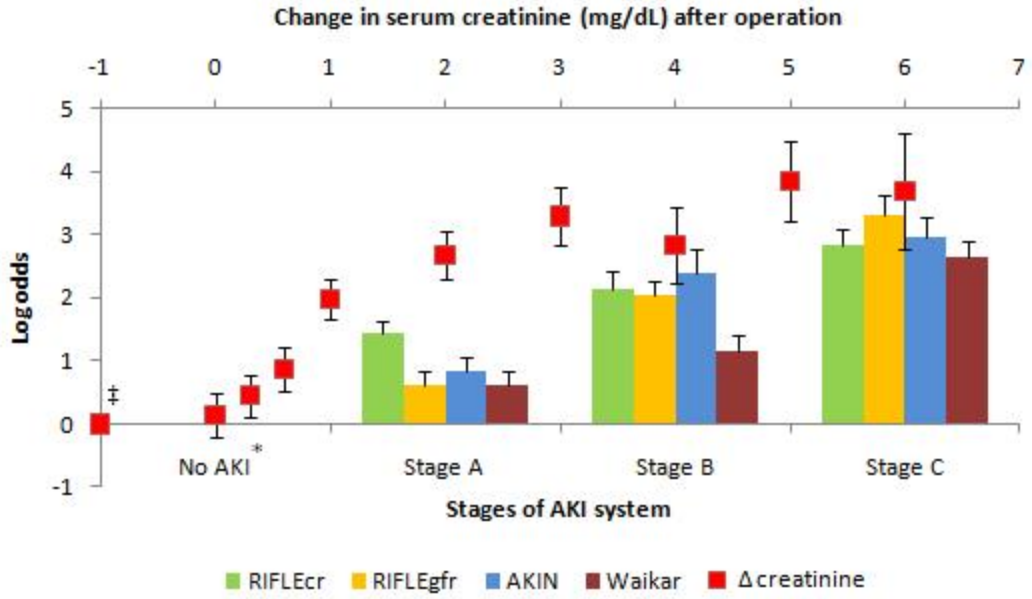
Note: Odds ratio in female sex and no liver disease are not calculated due to low sample size.

Figure 5: Log odds ratio (SE) of 30-day post operative mortality by different stages of AKI classification systems (primary horizontal axis) as well as by different levels of absolute increase of serum creatinine from baseline (secondary horizontal axis) in patients with stage 1 and 2 of CKD at baseline.



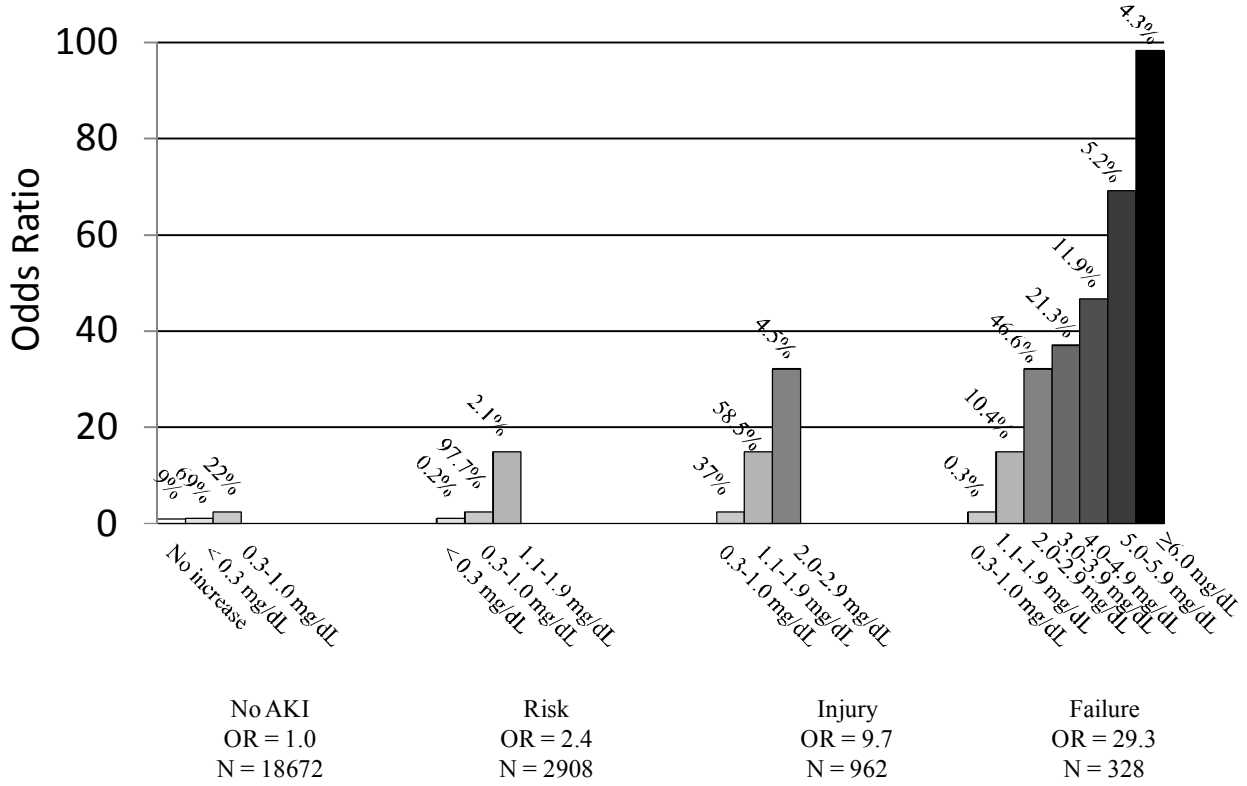
Note: *: $p < 0.001$ compared to other stages; ‡: $p < 0.005$ compared rise in creatinine of 0.3 mg/dL and above. For all equations log odds is calculated after adjusting with age, sex, race, hypertension, diabetes, obesity, peripheral vascular disease, congestive heart failure, anemia, unintentional weight loss, and chronic obstructive lung disease for all models.

Figure 6: Log odds ratio (SE) of 30-day post operative mortality by different stages of AKI classification systems (primary horizontal axis) as well as by different levels of absolute increase of serum creatinine from baseline (secondary horizontal axis) in patients with stage 3 of CKD at baseline.



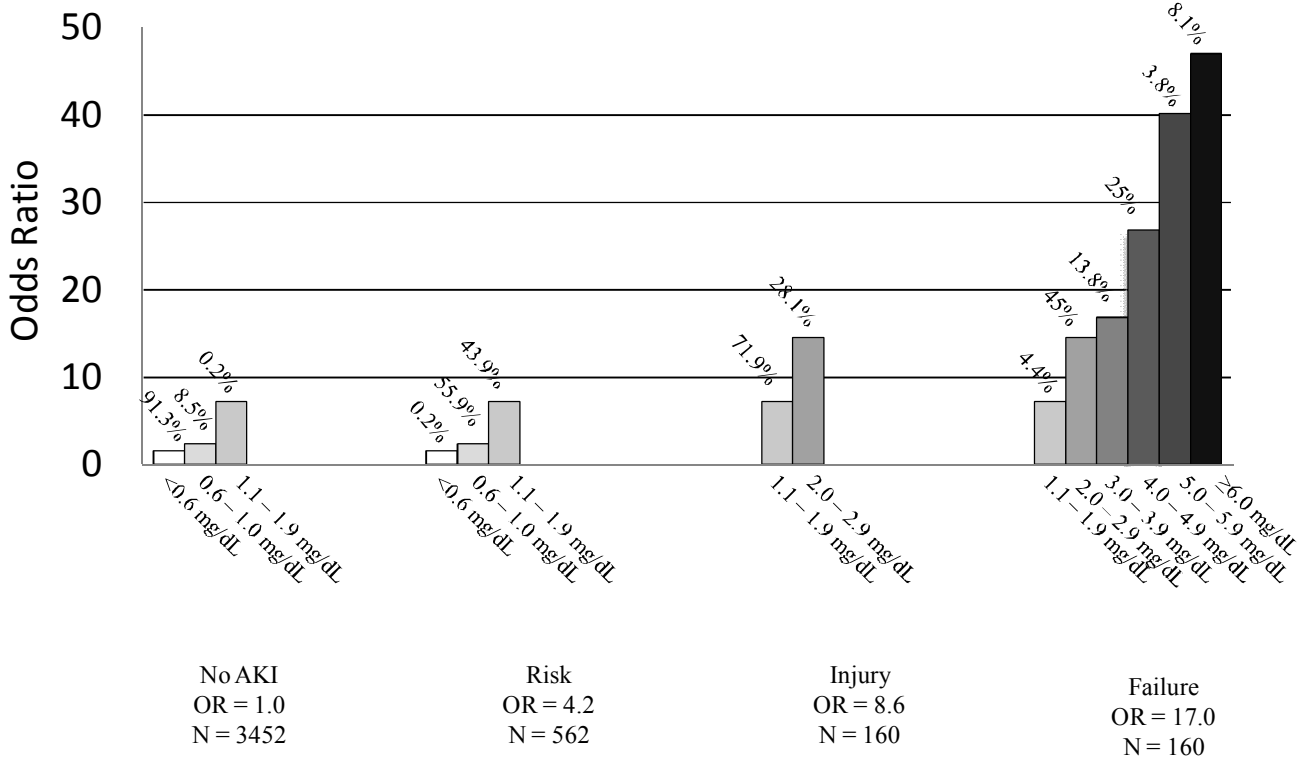
Note: *: $p < 0.02$ compared to other stages; ‡: $p < 0.02$ compared rise in creatinine of 0.6 mg/dL and above. For all equations log odds is calculated after adjusting with age, sex, race, hypertension, diabetes, obesity, peripheral vascular disease, congestive heart failure, anemia, unintentional weight loss, and chronic obstructive lung disease for all models.

Figure 7: Heterogeneity of mortality OR within each category of RIFLE in CKD stage 1 and 2



Note: Frequency distribution of patients within each stage of AKI is presented above each column.

Figure 8: Heterogeneity of mortality OR within each category of RIFLE in CKD stage 3



Note: Frequency distribution of patients within each stage of AKI is presented above each column.

Figure 9 : Comparison of area under ROC curves of changes of serum creatinine (del_cr) and GFR (del_gfr) from baseline, AKIN, RIFLE and Waikar criteria in AKI after heart surgery

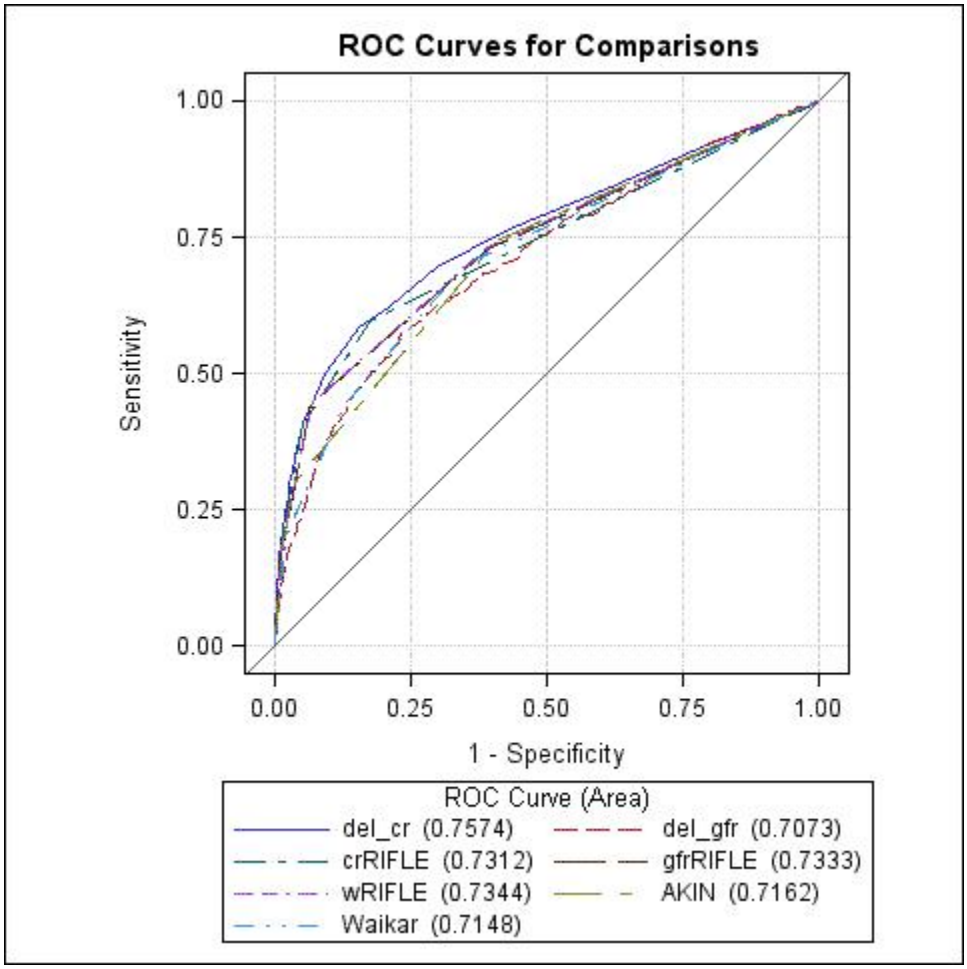


Table 6: Area under ROC curve of different classification systems of AKI

ROC	Area	Standard Error	95% Confidence Limits
del_cr	0.7574	0.0114	0.7351 to 0.7797
del_gfr	0.7073	0.0114	0.6850 to 0.7295
crRIFLE	0.7312	0.0104	0.7107 to 0.7517
gfrRIFLE	0.7333	0.0108	0.7121 to 0.7546
wRIFLE	0.7344	0.0108	0.7131 to 0.7556
AKIN	0.7162	0.0103	0.6959 to 0.7364
Waikar	0.7148	0.0106	0.6940 to 0.7355

Table 7: Difference of area under ROC curve of different AKI systems with absolute increase in creatinine

	Standard Estimate	Error	95% Confidence Limits	P value
del_gfr - del_cr	-0.0501	0.00643	-0.0627 to -0.0375	<.0001
crRIFLE - del_cr	-0.0262	0.00641	-0.0388 to -0.0136	<.0001
gfrRIFLE - del_cr	-0.0241	0.00524	-0.0343 to -0.0138	<.0001
wRIFLE - del_cr	-0.0230	0.00514	-0.0331 to -0.0129	<.0001
AKIN - del_cr	-0.0412	0.00608	-0.0531 to -0.0293	<.0001
Waikar - del_cr	-0.0426	0.00656	-0.0555 to -0.0297	<.0001

Table 8: Difference of area under ROC curve of different AKI systems with Waikar's system

	Standard Estimate	Error	95% Confidence Limits	P value
del_gfr - Waikar	-0.00753	0.00935	-0.0259 to 0.0108	0.4209
crRIFLE - Waikar	0.0164	0.00709	0.00251 to 0.0303	0.0206
gfrRIFLE - Waikar	0.0185	0.00724	0.00436 to 0.0327	0.0104
wRIFLE - Waikar	0.0196	0.00719	0.00551 to 0.0337	0.0064
AKIN - Waikar	0.00137	0.00534	-0.00908 to 0.0118	0.7969

Table 9: Difference of area under ROC curve of different AKI systems with crRIFLE system

	Standard Estimate	Error	95% Confidence Limits	P value
del_gfr - crRIFLE	-0.0239	0.00794	-0.0395 to -0.0084	0.0026
gfrRIFLE-crRIFLE	0.00214	0.00605	-0.00971 to 0.014	0.7231
AKIN - crRIFLE	-0.0150	0.00670	-0.0282 to -0.0019	0.0249
Waikar - crRIFLE	-0.0164	0.00709	-0.0303 to -0.0025	0.0206

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8) Appendix 1: The multiple logistic regression models using AKI stages as predictor, 30-day mortality as response, and othe varaibles as covariates. AKI stages defined by AKIN, RIFLEs and Waikar classification have 3 catgories each, as defined in table 1. The models to predict 30-day mortality for each classification systems are:

Mortality by AKIN classification system = AKIN + age + sex + race + CHF + Peripheral vascular disease + HTN + COPD + diabetes + liver disease + obesity + weight loss + Anemia

Mortality by RIFLEcr classification system = RIFLEcr + age + sex + race + CHF + Peripheral vascular disease + HTN + COPD + diabetes + liver disease + obesity + weight loss + Anemia

Mortality by RIFLE$_{GFR}$ classification system = RIFLE$_{GFR}$ + age + sex + race + CHF + Peripheral vascular disease + HTN + COPD + diabetes + liver disease + obesity + weight loss + Anemia

Mortality by RIFLE$_{W}$ classification system = RIFLE$_{W}$ + age + sex + race + CHF + Peripheral vascular disease + HTN + COPD + diabetes + liver disease + obesity + weight loss + Anemia

Mortality by Waikar classification system = Waikar + age + sex + race + CHF + Peripheral vascular disease + HTN + COPD + diabetes + liver disease + obesity + weight loss + Anemia

Mortality by Creatinine classification system = Creatinine + age + sex + race + CHF + Peripheral vascular disease + HTN + COPD + diabetes + liver disease + obesity + weight loss + Anemia

Note: Each of the above models are calculated seperately for CKD stage 1 and 2 combined, as well as for CKD stage 3, with and without setpwise inclusion of significant covariates as shown in appendices 2 to 13.

Appendix 2: Independent association of stages of AKIN by ctagories of CKD to predict 30-day mortality

Variables in the Equation

			B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
CKD 1 & 2	Step [a]	AGE	.044	.005	.000	1.045	1.034	1.056
		male	-.756	.405	.062	.470	.212	1.039
		white	.206	.171	.230	1.228	.878	1.718
		CHF	.702	.102	.000	2.017	1.651	2.464
		PeriVasc	.398	.104	.000	1.488	1.214	1.825
		HTN	-.204	.143	.154	.815	.616	1.079
		COPD	.183	.100	.067	1.200	.987	1.460
		Diabetes	.008	.099	.938	1.008	.829	1.224
		LiverDs	.690	.251	.006	1.993	1.219	3.260
		Obesity	.027	.118	.822	1.027	.815	1.294
		WtLoss	.226	.199	.257	1.253	.849	1.850
		Anemia	-.151	.132	.253	.860	.664	1.114
		AKIN			.000			
		AKIN(1)	.822	.113	.000	2.275	1.822	2.842
		AKIN(2)	2.254	.162	.000	9.525	6.934	13.083
		AKIN(3)	3.453	.157	.000	31.597	23.235	42.970
		Constant	-5.497	.563	.000	.004		

a. Variable(s) entered on step 1: AGE, male, white, CHF, PeriVasc, HTN, COPD, Diabetes, LiverDs, Obesity, WtLoss, Anemia, AKIN.

Variables in the Equation

		B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
CKD 3	Step[a] AGE	.033	.011	.003	1.034	1.012	1.057
	male	-.260	.732	.722	.771	.183	3.239
	white	.382	.414	.357	1.465	.650	3.301
	CHF	.523	.174	.003	1.687	1.198	2.374
	PeriVasc	.280	.173	.106	1.323	.942	1.857
	HTN	-.560	.291	.054	.571	.323	1.011
	COPD	.222	.174	.200	1.249	.889	1.755
	Diabetes	-.302	.177	.087	.739	.523	1.045
	LiverDs	.364	.568	.521	1.439	.473	4.378
	Obesity	-.069	.217	.749	.933	.610	1.427
	WtLoss	-.842	.527	.110	.431	.153	1.209
	Anemia	-.209	.209	.318	.811	.538	1.223
	AKIN			.000			
	AKIN(1)	.832	.217	.000	2.299	1.504	3.514
	AKIN(2)	2.402	.364	.000	11.041	5.414	22.517
	AKIN(3)	2.962	.299	.000	19.344	10.758	34.781
	Constant	-4.648	1.185	.000	.010		

a. Variable(s) entered on step 1: AGE, male, white, CHF, PeriVasc, HTN, COPD, Diabetes, LiverDs, Obesity, WtLoss, Anemia, AKIN.

Appendix 3: Independent association of stages of AKIN by ctagories of CKD to predict 30-day mortality after adjusting for other variables using stepwise seletion of statistically significant variables.

Variables in the Equation

			B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
CKD 1& 2	Step 6[a]	AGE	.044	.005	.000	1.045	1.034	1.056
		CHF	.709	.100	.000	2.032	1.670	2.472
		PeriVasc	.400	.103	.000	1.492	1.220	1.824
		LiverDs	.672	.250	.007	1.958	1.200	3.193
		AKIN			.000			
		AKIN(1)	.815	.113	.000	2.259	1.810	2.820
		AKIN(2)	2.254	.161	.000	9.527	6.951	13.056
		AKIN(3)	3.444	.156	.000	31.309	23.063	42.502
		Constant	-6.139	.361	.000	.002		
CKD 3	Step 5[b]	AGE	.036	.011	.001	1.036	1.015	1.058
		CHF	.486	.168	.004	1.626	1.170	2.261
		HTN	-.645	.286	.024	.525	.300	.919
		AKIN			.000			
		AKIN(1)	.808	.216	.000	2.244	1.470	3.425
		AKIN(2)	2.315	.358	.000	10.128	5.021	20.431
		AKIN(3)	2.893	.293	.000	18.039	10.152	32.056
		Constant	-4.680	.820	.000	.009		

a. Variable(s) entered on step 5: LiverDs.

b. Variable(s) entered on step 4: HTN.

c. Variable(s) entered on step 2: Diabetes.

Appendix 4: Independent association of stages of RIFLEcr by ctagories of CKD to predict 30-day mortality

Variables in the Equation

			B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
CKD 1 & 2	Step 1[a]	AGE	.042	.005	.000	1.043	1.032	1.054
		male	-.681	.408	.095	.506	.227	1.126
		white	.181	.172	.293	1.198	.855	1.679
		CHF	.670	.103	.000	1.954	1.597	2.391
		PeriVasc	.403	.105	.000	1.497	1.219	1.838
		HTN	-.200	.144	.166	.819	.618	1.086
		COPD	.180	.100	.074	1.197	.983	1.457
		Diabetes	-.006	.100	.949	.994	.817	1.208
		LiverDs	.598	.253	.018	1.818	1.107	2.984
		Obesity	.010	.119	.930	1.010	.801	1.275
		WtLoss	.200	.200	.316	1.222	.826	1.807
		Anemia	-.172	.133	.195	.842	.649	1.092
		crRIFLE			.000			
		crRIFLE(1)	.853	.132	.000	2.346	1.810	3.042
		crRIFLE(2)	2.271	.127	.000	9.693	7.557	12.434
		crRIFLE(3)	3.376	.149	.000	29.265	21.864	39.171
		Constant	-5.272	.564	.000	.005		

a. Variable(s) entered on step 1: AGE, male, white, CHF, PeriVasc, HTN, COPD, Diabetes, LiverDs, Obesity, WtLoss, Anemia, crRIFLE.

Continue:

			B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
CKD 3	Step 1[a]	AGE	.027	.011	.013	1.028	1.006	1.050
		male	-.066	.740	.929	.936	.220	3.987
		white	.465	.417	.265	1.592	.703	3.603
		CHF	.493	.177	.005	1.637	1.158	2.314
		PeriVasc	.251	.175	.151	1.285	.913	1.810
		HTN	-.566	.293	.053	.568	.320	1.007
		COPD	.198	.175	.258	1.219	.865	1.719
		Diabetes	-.398	.179	.026	.672	.473	.955
		LiverDs	.201	.571	.725	1.222	.399	3.740
		Obesity	-.078	.218	.720	.925	.603	1.418
		WtLoss	-.901	.531	.090	.406	.144	1.150
		Anemia	-.286	.212	.177	.751	.496	1.137
		crRIFLE			.000			
		crRIFLE(1)	1.426	.214	.000	4.161	2.738	6.323
		crRIFLE(2)	2.150	.275	.000	8.581	5.007	14.707
		crRIFLE(3)	2.832	.238	.000	16.987	10.647	27.104
		Constant	-4.302	1.189	.000	.014		

a. Variable(s) entered on step 1: AGE, male, white, CHF, PeriVasc, HTN, COPD, Diabetes, LiverDs, Obesity, WtLoss, Anemia, crRIFLE.

Appendix 5: Independent association of stages of RIFLEcr by ctagories of CKD to predict 30-day mortality after adjusting for other variables using stepwise seletion of statistically significant variables.

Variables in the Equation

			B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
CKD 1 & 2	Step 6[a,,b]	AGE	.041	.005	.000	1.042	1.031	1.053
		CHF	.673	.101	.000	1.959	1.608	2.388
		PeriVasc	.401	.103	.000	1.493	1.219	1.828
		LiverDs	.576	.252	.022	1.779	1.086	2.916
		crRIFLE			.000			
		crRIFLE(1)	.850	.132	.000	2.339	1.806	3.030
		crRIFLE(2)	2.271	.126	.000	9.684	7.564	12.399
		crRIFLE(3)	3.366	.148	.000	28.960	21.671	38.701
		Constant	-5.874	.362	.000	.003		
CKD 3	Step 6[a,,b]	AGE	.027	.011	.012	1.027	1.006	1.049
		CHF	.493	.172	.004	1.638	1.169	2.295
		crRIFLE			.000			
		crRIFLE(1)	1.438	.213	.000	4.213	2.776	6.394
		crRIFLE(2)	2.118	.272	.000	8.317	4.877	14.182
		crRIFLE(3)	2.798	.235	.000	16.410	10.364	25.985
		Constant	-3.757	.831	.000	.023		
		HTN	-.605	.288	.036	.546	.310	.960
		Diabetes	-.423	.176	.016	.655	.464	.925

a. Variable(s) entered on step 5: LiverDs.

b. Variable(s) entered on step 5: HTN.

c. Variable(s) entered on step 2: Diabetes.

Appendix 6: Independent association of stages of $RIFLE_{GFR}$ by ctagories of CKD to predict 30-day mortality

Variables in the Equation

			B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
CKD 1 & 2	Step 1[a]	AGE	.042	.005	.000	1.042	1.032	1.054
		male	-.677	.408	.097	.508	.228	1.131
		white	.215	.172	.213	1.239	.884	1.738
		CHF	.684	.103	.000	1.981	1.619	2.424
		PeriVasc	.401	.105	.000	1.494	1.217	1.834
		HTN	-.191	.144	.186	.826	.623	1.096
		COPD	.172	.100	.087	1.187	.975	1.446
		Diabetes	.000	.100	.995	.999	.822	1.215
		LiverDs	.606	.253	.017	1.833	1.117	3.008
		Obesity	-.009	.119	.942	.991	.786	1.251
		WtLoss	.217	.200	.278	1.242	.840	1.837
		Anemia	-.181	.133	.173	.834	.643	1.082
		gfrRIFLE			.000			
		gfrRIFLE(1)	.601	.125	.000	1.823	1.428	2.329
		gfrRIFLE(2)	2.285	.129	.000	9.829	7.626	12.668
		gfrRIFLE(3)	3.718	.170	.000	41.166	29.487	57.473
		Constant	-5.425	.563	.000	.004		

a. Variable(s) entered on step 1: AGE, male, white, CHF, PeriVasc, HTN, COPD, Diabetes, LiverDs, Obesity, WtLoss, Anemia, gfrRIFLE.

Continue:

			B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
CKD 3	Step 1[a]	AGE	.029	.011	.008	1.030	1.008	1.052
		male	.040	.746	.957	1.041	.241	4.496
		white	.287	.412	.486	1.332	.594	2.988
		CHF	.476	.176	.007	1.610	1.140	2.274
		PeriVasc	.281	.175	.108	1.324	.940	1.865
		HTN	-.493	.294	.094	.611	.343	1.088
		COPD	.204	.176	.245	1.227	.870	1.730
		Diabetes	-.364	.179	.041	.695	.490	.986
		LiverDs	.254	.578	.661	1.289	.415	4.001
		Obesity	.000	.218	.998	.999	.652	1.532
		WtLoss	-.910	.530	.086	.402	.143	1.136
		Anemia	-.211	.210	.315	.810	.537	1.222
		gfrRIFLE			.000			
		gfrRIFLE(1)	.615	.213	.004	1.849	1.218	2.807
		gfrRIFLE(2)	2.050	.222	.000	7.771	5.033	11.999
		gfrRIFLE(3)	3.297	.334	.000	27.024	14.039	52.020
		Constant	-4.527	1.206	.000	.011		

a. Variable(s) entered on step 1: AGE, male, white, CHF, PeriVasc, HTN, COPD, Diabetes, LiverDs, Obesity, WtLoss, Anemia, gfrRIFLE.

Appendix 7: Independent association of stages of $RIFLE_{GFR}$ by ctagories of CKD to predict 30-day mortality after adjusting for other variables using stepwise seletion of statistically significant variables.

Variables in the Equation

		B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
CKD 1 & 2	Step 6[a] AGE	.041	.005	.000	1.042	1.031	1.053
	CHF	.684	.101	.000	1.982	1.626	2.416
	PeriVasc	.397	.103	.000	1.488	1.215	1.822
	LiverDs	.580	.252	.021	1.786	1.090	2.926
	gfrRIFLE			.000			
	gfrRIFLE(1)	.596	.125	.000	1.814	1.421	2.316
	gfrRIFLE(2)	2.278	.128	.000	9.757	7.587	12.548
	gfrRIFLE(3)	3.706	.169	.000	40.684	29.194	56.695
	Constant	-5.995	.361	.000	.002		
CKD 3	Step 5[b] AGE	.028	.011	.010	1.028	1.007	1.050
	CHF	.495	.172	.004	1.640	1.171	2.297
	Diabetes	-.397	.174	.023	.672	.478	.947
	gfrRIFLE			.000			
	gfrRIFLE(1)	.609	.212	.004	1.838	1.213	2.787
	gfrRIFLE(2)	2.019	.219	.000	7.534	4.903	11.576
	gfrRIFLE(3)	3.352	.330	.000	28.548	14.954	54.499
	Constant	-4.443	.803	.000	.012		

a. Variable(s) entered on step 5: LiverDs.

b. Variable(s) entered on step 4: Diabetes.

c. Variable(s) entered on step 2: Obesity.

Appendix 8: Independent association of stages of $RIFLE_W$ by ctagories of CKD to predict 30-day mortality

Variables in the Equation

			B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
CKD 1 & 2	Step 1[a]	AGE	.042	.005	.000	1.042	1.032	1.053
		male	-.707	.406	.082	.493	.222	1.094
		white	.207	.172	.230	1.230	.878	1.723
		CHF	.676	.103	.000	1.966	1.607	2.404
		PeriVasc	.391	.105	.000	1.478	1.204	1.814
		HTN	-.203	.144	.158	.816	.615	1.082
		COPD	.175	.100	.080	1.192	.979	1.451
		Diabetes	-.008	.100	.934	.992	.816	1.206
		LiverDs	.603	.253	.017	1.828	1.114	2.999
		Obesity	-.010	.118	.930	.990	.785	1.248
		WtLoss	.213	.199	.286	1.237	.837	1.828
		Anemia	-.174	.133	.190	.840	.648	1.090
		wRIFLE			.000			
		wRIFLE(1)	.602	.125	.000	1.826	1.430	2.333
		wRIFLE(2)	2.254	.132	.000	9.528	7.355	12.344
		wRIFLE(3)	3.520	.159	.000	33.793	24.749	46.141
		Constant	-5.423	.561	.000	.004		

a. Variable(s) entered on step 1: AGE, male, white, CHF, PeriVasc, HTN, COPD, Diabetes, LiverDs, Obesity, WtLoss, Anemia, wRIFLE.

Continue:

			B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
CKD 3	Step 1[a]	AGE	.029	.011	.007	1.030	1.008	1.052
		male	-.036	.744	.961	.964	.225	4.141
		white	.467	.416	.262	1.596	.706	3.608
		CHF	.491	.176	.005	1.634	1.158	2.306
		PeriVasc	.263	.174	.130	1.301	.925	1.830
		HTN	-.517	.291	.076	.597	.337	1.055
		COPD	.233	.174	.181	1.263	.897	1.777
		Diabetes	-.370	.178	.038	.691	.487	.980
		LiverDs	.212	.570	.710	1.236	.404	3.782
		Obesity	-.062	.217	.773	.939	.614	1.437
		WtLoss	-.901	.528	.088	.406	.144	1.144
		Anemia	-.282	.211	.181	.754	.499	1.140
		wRIFLE			.000			
		wRIFLE(1)	.621	.213	.004	1.860	1.225	2.824
		wRIFLE(2)	1.883	.254	.000	6.570	3.994	10.807
		wRIFLE(3)	2.759	.247	.000	15.781	9.726	25.604
		Constant	-4.770	1.194	.000	.008		

a. Variable(s) entered on step 1: AGE, male, white, CHF, PeriVasc, HTN, COPD, Diabetes, LiverDs, Obesity, WtLoss, Anemia, wRIFLE.

Appendix 9: Independent association of stages of $RIFLE_W$ by ctagories of CKD to predict 30-day mortality after adjusting for other variables using stepwise seletion of statistically significant variables.

Variables in the Equation

			B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
CKD 1 & 2	Step 6[a,,b]	AGE	.041	.005	.000	1.042	1.031	1.053
		CHF	.676	.101	.000	1.967	1.614	2.396
		PeriVasc	.387	.103	.000	1.472	1.202	1.803
		LiverDs	.579	.252	.021	1.784	1.090	2.923
		wRIFLE			.000			
		wRIFLE(1)	.597	.125	.000	1.816	1.423	2.318
		wRIFLE(2)	2.247	.131	.000	9.462	7.320	12.232
		wRIFLE(3)	3.506	.158	.000	33.301	24.435	45.383
		Constant	-7.630	.361	.000	.000		
CKD 3	Step 6[a,,b]	AGE	.029	.011	.007	1.029	1.008	1.051
		CHF	.500	.171	.004	1.649	1.178	2.307
		wRIFLE			.000			
		wRIFLE(1)	.625	.213	.003	1.868	1.232	2.834
		wRIFLE(2)	1.855	.252	.000	6.392	3.899	10.478
		wRIFLE(3)	2.723	.243	.000	15.228	9.456	24.525
		Constant	-5.468	.817	.000	.004		
		HTN	-.569	.286	.047	.566	.323	.992
		Diabetes	-.394	.175	.025	.675	.478	.951

a. Variable(s) entered on step 5: LiverDs.

b. Variable(s) entered on step 5: HTN.

c. Variable(s) entered on step 2: Diabetes.

Appendix 10: Independent association of stages of Waikar by ctagories of CKD to predict 30-day mortality

Variables in the Equation

			B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
CKD 1 & 2	Step 1[a]	AGE	.046	.005	.000	1.047	1.036	1.058
		male	-.917	.399	.021	.400	.183	.873
		white	.247	.170	.147	1.280	.917	1.787
		CHF	.637	.101	.000	1.891	1.550	2.306
		PeriVasc	.406	.103	.000	1.501	1.227	1.836
		HTN	-.240	.142	.092	.787	.595	1.040
		COPD	.207	.099	.036	1.230	1.013	1.493
		Diabetes	.007	.098	.946	1.007	.830	1.220
		LiverDs	.631	.249	.011	1.879	1.154	3.059
		Obesity	.052	.117	.653	1.054	.839	1.325
		WtLoss	.286	.195	.142	1.331	.908	1.951
		Anemia	-.137	.130	.294	.872	.676	1.126
		Waikar			.000			
		Waikar(1)	.831	.121	.000	2.295	1.810	2.910
		Waikar(2)	1.428	.129	.000	4.171	3.241	5.367
		Waikar(3)	3.015	.148	.000	20.398	15.250	27.285
		Constant	-5.689	.555	.000	.003		
CKD 3	Step 1[a]	AGE	.034	.011	.002	1.035	1.013	1.057
		male	-.090	.744	.904	.914	.213	3.927
		white	.437	.409	.286	1.547	.694	3.450
		CHF	.466	.175	.008	1.594	1.132	2.245
		PeriVasc	.260	.173	.134	1.297	.923	1.821
		HTN	-.581	.292	.047	.559	.315	.991
		COPD	.212	.174	.222	1.236	.879	1.737
		Diabetes	-.309	.176	.079	.734	.520	1.037
		LiverDs	.386	.563	.493	1.471	.488	4.430
		Obesity	-.102	.217	.639	.903	.590	1.382
		WtLoss	-.778	.522	.136	.459	.165	1.278
		Anemia	-.221	.209	.291	.802	.532	1.208
		Waikar			.000			
		Waikar(1)	.603	.238	.011	1.828	1.146	2.916
		Waikar(2)	1.165	.240	.000	3.204	2.001	5.131
		Waikar(3)	2.652	.251	.000	14.178	8.661	23.210
		Constant	-5.292	1.178	.000	.005		

a. Variable(s) entered on step 1: AGE, male, white, CHF, PeriVasc, HTN, COPD, Diabetes, LiverDs, Obesity, WtLoss, Anemia, Waikar.

Appendix 11: Independent association of stages of Waikar by ctagories of CKD to predict 30-day mortality after adjusting for other variables using stepwise seletion of statistically significant variables.

Variables in the Equation

			B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
CKD 1 & 2	Step 8[a]	AGE	.045	.005	.000	1.046	1.036	1.057
		male	-.924	.398	.020	.397	.182	.866
		CHF	.628	.100	.000	1.874	1.540	2.280
		PeriVasc	.388	.102	.000	1.474	1.206	1.800
		COPD	.203	.099	.040	1.225	1.010	1.486
		LiverDs	.612	.248	.013	1.844	1.135	2.996
		Waikar			.000			
		Waikar(1)	.823	.121	.000	2.278	1.798	2.887
		Waikar(2)	1.413	.128	.000	4.110	3.199	5.281
		Waikar(3)	2.991	.147	.000	19.915	14.920	26.583
		Constant	-5.624	.522	.000	.004		
3.00	Step 6[b]	AGE	.034	.010	.001	1.034	1.013	1.056
		CHF	.476	.170	.005	1.610	1.153	2.249
		HTN	-.606	.288	.036	.546	.310	.960
		Diabetes	-.340	.174	.050	.712	.506	1.000
		Waikar			.000			
		Waikar(1)	.597	.238	.012	1.817	1.139	2.897
		Waikar(2)	1.140	.239	.000	3.125	1.955	4.996
		Waikar(3)	2.644	.249	.000	14.075	8.632	22.950
		Constant	-4.832	.817	.000	.008		

a. Variable(s) entered on step 7: COPD.

b. Variable(s) entered on step 5: Diabetes.

c. Variable(s) entered on step 1: Obesity.

Appendix 12: Independent association of different levels of absolute increase of serum creatinine by ctagories of CKD to predict 30-day mortality

Variables in the Equation

		B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
Step 1[a]	AGE	.041	.005	.000	1.042	1.031	1.053
	male	-.877	.410	.032	.416	.186	.929
	white	.231	.173	.182	1.260	.898	1.768
	CHF	.677	.103	.000	1.968	1.607	2.410
	PeriVasc	.395	.105	.000	1.485	1.208	1.824
	HTN	-.211	.145	.146	.810	.610	1.076
	COPD	.186	.101	.065	1.205	.989	1.468
	Diabetes	-.012	.101	.907	.988	.811	1.204
	LiverDs	.623	.255	.015	1.865	1.131	3.076
	Obesity	.007	.120	.954	1.007	.796	1.273
	WtLoss	.241	.201	.229	1.273	.859	1.886
	Anemia	-.222	.134	.097	.801	.616	1.041
	delcr_cat44			.000			
	delcr_cat44(1)	.097	.294	.740	1.102	.620	1.959
	delcr_cat44(2)	.849	.291	.003	2.338	1.322	4.134
	delcr_cat44(3)	2.626	.305	.000	13.825	7.606	25.126
	delcr_cat44(4)	3.473	.328	.000	32.226	16.935	61.324
	delcr_cat44(5)	3.615	.394	.000	37.163	17.171	80.430
	delcr_cat44(6)	3.846	.457	.000	46.798	19.098	114.676
	delcr_cat44(7)	4.234	.589	.000	69.015	21.756	218.934
	delcr_cat44(8)	4.588	.611	.000	98.258	29.676	325.334
	Constant	-4.320	.573	.000	.013		

a. Variable(s) entered on step 1: AGE, male, white, CHF, PeriVasc, HTN, COPD, Diabetes, LiverDs, Obesity, WtLoss, Anemia, delcr_cat44.

Continue:

Variables in the Equation

		B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
CKD stage 3	AGE	.027	.011	.014	1.028	1.005	1.050
Step 1[a]	male	-.095	.744	.899	.909	.211	3.913
	white	.561	.416	.178	1.753	.775	3.962
	CHF	.457	.177	.010	1.579	1.115	2.235
	PeriVasc	.247	.176	.162	1.280	.906	1.808
	HTN	-.604	.295	.041	.546	.306	.975
	COPD	.209	.177	.239	1.232	.871	1.743
	Diabetes	-.402	.180	.026	.669	.470	.952
	LiverDs	.248	.571	.665	1.281	.418	3.922
	Obesity	-.057	.220	.796	.945	.614	1.454
	WtLoss	-.841	.527	.111	.431	.153	1.212
	Anemia	-.264	.212	.213	.768	.507	1.164
	delcr_cat5			.000			
	delcr_cat5(1)	.143	.354	.687	1.153	.576	2.307
	delcr_cat5(2)	.449	.335	.180	1.567	.813	3.019
	delcr_cat5(3)	.871	.345	.012	2.390	1.214	4.704
	delcr_cat5(4)	1.977	.321	.000	7.219	3.846	13.550
	delcr_cat5(5)	2.678	.372	.000	14.556	7.024	30.164
	delcr_cat5(6)	3.290	.446	.000	26.847	11.195	64.383
	delcr_cat5(7)	2.823	.596	.000	16.824	5.236	54.053
	delcr_cat5(8)	3.850	.635	.000	46.993	13.538	163.116
	delcr_cat5(9)	3.692	.917	.000	40.127	6.650	242.117
	Constant	-4.113	1.199	.001	.016		

a. Variable(s) entered on step 1: AGE, male, white, CHF, PeriVasc, HTN, COPD, Diabetes, LiverDs, Obesity, WtLoss, Anemia, delcr_cat5.

Appendix 13: Independent association of different levels of absolute in serum creatinine by ctagories of CKD to predict 30-day mortality after adjusting for other variables using stepwise seletion of statistically significant variables.

Variables in the Equation

		B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
Step 7[a]	AGE	.041	.005	.000	1.042	1.031	1.053
	male	-.889	.409	.030	.411	.184	.917
	CHF	.678	.101	.000	1.970	1.615	2.403
	PeriVasc	.391	.104	.000	1.478	1.206	1.812
	LiverDs	.603	.254	.018	1.827	1.109	3.008
	delcr_cat44			.000			
	delcr_cat44(1)	.090	.293	.760	1.094	.615	1.945
	delcr_cat44(2)	.833	.290	.004	2.300	1.302	4.065
	delcr_cat44(3)	2.592	.304	.000	13.356	7.362	24.228
	delcr_cat44(4)	3.451	.328	.000	31.524	16.587	59.912
	delcr_cat44(5)	3.562	.393	.000	35.217	16.289	76.137
	delcr_cat44(6)	3.795	.456	.000	44.478	18.213	108.623
	delcr_cat44(7)	4.229	.587	.000	68.617	21.721	216.763
	delcr_cat44(8)	4.635	.606	.000	103.022	31.426	337.735
	Constant	-4.215	.541	.000	.015		

a. Variable(s) entered on step 6: male.

Continue:

Variables in the Equation

		B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
CKD stage 3 Step 6[a]	AGE	.026	.011	.014	1.027	1.005	1.049
	CHF	.462	.173	.008	1.587	1.131	2.227
	HTN	-.654	.291	.024	.520	.294	.919
	Diabetes	-.426	.177	.016	.653	.461	.925
	delcr_cat5			.000			
	delcr_cat5(1)	.118	.353	.738	1.125	.563	2.249
	delcr_cat5(2)	.439	.334	.189	1.551	.805	2.986
	delcr_cat5(3)	.865	.345	.012	2.376	1.209	4.667
	delcr_cat5(4)	1.925	.319	.000	6.856	3.667	12.821
	delcr_cat5(5)	2.618	.368	.000	13.714	6.661	28.233
	delcr_cat5(6)	3.250	.442	.000	25.788	10.840	61.346
	delcr_cat5(7)	2.766	.583	.000	15.891	5.072	49.787
	delcr_cat5(8)	3.962	.628	.000	52.566	15.363	179.855
	delcr_cat5(9)	3.710	.913	.000	40.840	6.816	244.709
	Constant	-3.478	.834	.000	.031		

a. Variable(s) entered on step 5: Diabetes.

Appendix 14: The computer generated syntax of coding procedures of the classification systems of AKI and new other variables including eGFR:

Coding RIFLE by creatinine:

```
COMPUTE crRIFLE=0. EXECUTE.
IF (MaxCr0_7 >= 1.5 * MinPreopCr) crRIFLE=1. EXECUTE.
IF (MaxCr0_7 >= 2 * MinPreopCr) crRIFLE=2. EXECUTE.
IF (MaxCr0_7 >= 3 * MinPreopCr | (MaxCr0_7 >= 4 & MaxCr0_7 - MinPreopCr >= 0.5))
crRIFLE=3. EXECUTE.
```

Calculating GFR:

```
IF  (male = 1 & white = 1) bgfr=186* (MinPreopCr)**-1.154 * age**-0.203. EXECUTE.
IF  (male = 1 & white = 1) gfr0=186* (cr0)**-1.154 * age**-0.203. EXECUTE.
IF  (male = 1 & white = 1) gfr1=186* (cr1)**-1.154 * age**-0.203. EXECUTE.
IF  (male = 1 & white = 1) gfr2=186* (cr2)**-1.154 * age**-0.203. EXECUTE.
IF  (male = 1 & white = 1) gfr3=186* (cr3)**-1.154 * age**-0.203. EXECUTE.
IF  (male = 1 & white = 1) gfr4=186* (cr4)**-1.154 * age**-0.203. EXECUTE.
IF  (male = 1 & white = 1) gfr5=186* (cr5)**-1.154 * age**-0.203. EXECUTE.
IF  (male = 1 & white = 1) gfr6=186* (cr6)**-1.154 * age**-0.203. EXECUTE.
IF  (male = 1 & white = 1) gfr7=186* (cr7)**-1.154 * age**-0.203. EXECUTE.
IF  (male = 0 & white = 1) gfr0=186* (cr0)**-1.154 * age**-0.203 * 0.742. EXECUTE.
IF  (male = 0 & white = 1) gfr1=186* (cr1)**-1.154 * age**-0.203 * 0.742. EXECUTE.
IF  (male = 0 & white = 1) gfr2=186* (cr2)**-1.154 * age**-0.203 * 0.742. EXECUTE.
IF  (male = 0 & white = 1) gfr3=186* (cr3)**-1.154 * age**-0.203 * 0.742. EXECUTE.
IF  (male = 0 & white = 1) gfr4=186* (cr4)**-1.154 * age**-0.203 * 0.742. EXECUTE.
IF  (male = 0 & white = 1) gfr5=186* (cr5)**-1.154 * age**-0.203 * 0.742. EXECUTE.
IF  (male = 0 & white = 1) gfr6=186* (cr6)**-1.154 * age**-0.203 * 0.742. EXECUTE.
IF  (male = 0 & white = 1) gfr7=186* (cr7)**-1.154 * age**-0.203 * 0.742. EXECUTE.
IF  (male = 0 & white = 0) bgfr=186* (MinPreopCr)**-1.154 * age**-0.203 * 0.742 * 1.212.
EXECUTE.
IF  (male = 0 & white = 1) bgfr=186* (MinPreopCr)**-1.154 * age**-0.203 * 0.742. EXECUTE.
IF  (male = 0 & white = 0) gfr0=186* (Cr0)**-1.154 * age**-0.203 * 0.742 * 1.212. EXECUTE.
IF  (male = 0 & white = 0) gfr1=186* (Cr1)**-1.154 * age**-0.203 * 0.742 * 1.212. EXECUTE.
IF  (male = 0 & white = 0) gfr2=186* (Cr2)**-1.154 * age**-0.203 * 0.742 * 1.212. EXECUTE.
IF  (male = 0 & white = 0) gfr3=186* (Cr3)**-1.154 * age**-0.203 * 0.742 * 1.212. EXECUTE.
IF  (male = 0 & white = 0) gfr4=186* (Cr4)**-1.154 * age**-0.203 * 0.742 * 1.212. EXECUTE.
IF  (male = 0 & white = 0) gfr5=186* (Cr5)**-1.154 * age**-0.203 * 0.742 * 1.212. EXECUTE.
IF  (male = 0 & white = 0) gfr6=186* (Cr6)**-1.154 * age**-0.203 * 0.742 * 1.212. EXECUTE.
IF  (male = 0 & white = 0) gfr7=186* (Cr7)**-1.154 * age**-0.203 * 0.742 * 1.212. EXECUTE.
IF  (male = 1 & white = 0) bgfr=186* (MinPreopCr)**-1.154 * age**-0.203 * 1.212. EXECUTE.
IF  (male = 1 & white = 0) gfr0=186* (Cr0)**-1.154 * age**-0.203 * 1.212. EXECUTE.
IF  (male = 1 & white = 0) gfr1=186* (Cr1)**-1.154 * age**-0.203 * 1.212. EXECUTE.
IF  (male = 1 & white = 0) gfr2=186* (Cr2)**-1.154 * age**-0.203 * 1.212. EXECUTE.
IF  (male = 1 & white = 0) gfr3=186* (Cr3)**-1.154 * age**-0.203 * 1.212. EXECUTE.
IF  (male = 1 & white = 0) gfr4=186* (Cr4)**-1.154 * age**-0.203 * 1.212. EXECUTE.
IF  (male = 1 & white = 0) gfr5=186* (Cr5)**-1.154 * age**-0.203 * 1.212. EXECUTE.
IF  (male = 1 & white = 0) gfr6=186* (Cr6)**-1.154 * age**-0.203 * 1.212. EXECUTE.
IF  (male = 1 & white = 0) gfr7=186* (Cr7)**-1.154 * age**-0.203 * 1.212. EXECUTE.
```

Coding RIFLE by GFR:

```
COMPUTE gfrRIFLE=0. EXECUTE.
IF (MinGFR0_7  <  (bgfr - 0.25 * bgfr)) gfrRIFLE=1. EXECUTE.
IF (MinGFR0_7  <  (bgfr - 0.5 * bgfr)) gfrRIFLE=2. EXECUTE.
IF (MinGFR0_7  <  (bgfr - 0.75 * bgfr)) gfrRIFLE=3. EXECUTE.
```

Coding RIFLE by worst of GFR or creatinine:

```
COMPUTE wRIFLE=0. EXECUTE.
IF (crRIFLE = 1 | gfrRIFLE = 1) wRIFLE=1. EXECUTE.
IF (crRIFLE = 2 | gfrRIFLE = 2) wRIFLE=2. EXECUTE.
IF (crRIFLE = 3 | gfrRIFLE = 3) wRIFLE=3. EXECUTE.
```

```
COMPUTE MaxCr0_2=MAX(cr0,cr1,cr2). EXECUTE.
COMPUTE MaxCr1_3=MAX(cr1,cr2,cr3). EXECUTE.
COMPUTE MaxCr2_4=MAX(cr2,cr3,cr4). EXECUTE.
COMPUTE MaxCr3_5=MAX(cr3,cr4,cr5). EXECUTE.
COMPUTE MaxCr4_6=MAX(cr4,cr5,cr6). EXECUTE.
COMPUTE MaxCr5_7=MAX(cr5,cr6,cr7). EXECUTE.
COMPUTE MaxCr6_7=MAX(cr6,cr7). EXECUTE.
```

Coding AKIN:

```
COMPUTE AKIN0_2=0. EXECUTE.
IF ((MAX(cr0,cr1,cr2) - MinPreopCr >= 0.3) | (MAX(cr0,cr1,cr2) >= 1.5 * MinPreopCr))
AKIN0_2=1. EXECUTE.
IF ((MAX(cr0,cr1,cr2) >= 2 * MinPreopCr)) AKIN0_2=2. EXECUTE.
IF ((MAX(cr0,cr1,cr2) >= 3 * MinPreopCr) | (MAX(cr0,cr1,cr2) >= 4 & (MAX(cr0,cr1,cr2) -
MinPreopCr >= 0.5)) ) AKIN0_2=3. EXECUTE.

COMPUTE AKIN3=0. EXECUTE.
IF ((cr3 - cr2 >= 0.3) | (cr3 - cr1 >= 0.3) | (cr3 >= 1.5 * MinPreopCr) & AKIN0_2 = 0) AKIN3=1.
EXECUTE.
IF ((cr3 >= 2 * MinPreopCr) & AKIN0_2 = 0) AKIN3=2. EXECUTE.
IF ((cr3 >= 3 * MinPreopCr) | (cr3 >= 4 & (cr3 - MinPreopCr >= 0.5)) & AKIN0_2 = 0)
AKIN3=3. EXECUTE.

COMPUTE AKIN4=0. EXECUTE.
IF ((cr4 - cr2 >= 0.3) | (cr4 - cr3 >= 0.3) | (cr4 >= 1.5 * MinPreopCr) & (AKIN0_2 = 0 & (AKIN3
= 0))) AKIN4=1. EXECUTE.
IF ((cr4 >= 2 * MinPreopCr) & (AKIN0_2 = 0 & (AKIN3 = 0))) AKIN4=2. EXECUTE.
IF ((cr4 >= 3 * MinPreopCr) | (cr4 >= 4 & (cr4 - MinPreopCr >= 0.5)) & (AKIN0_2 = 0 &
(AKIN3 = 0))) AKIN4=3. EXECUTE.

COMPUTE AKIN5=0. EXECUTE.
IF (((cr5 - cr4 >= 0.3) | (cr5 - cr3 >= 0.3) | (cr5 >= 1.5 * MinPreopCr)) & (AKIN0_2 = 0 &
AKIN3 = 0 & AKIN4 = 0)) AKIN5=1. EXECUTE.
```

```
IF ((cr5 >= 2 * MinPreopCr) & (AKIN0_2 = 0 & AKIN3 = 0 & AKIN4 = 0)) AKIN5=2.
EXECUTE.
IF ((cr5 >= 3 * MinPreopCr) | (cr5 >= 4 & (cr5 - MinPreopCr >= 0.5)) & (AKIN0_2 = 0 &
AKIN3 = 0 & AKIN4 = 0)) AKIN5=3. EXECUTE.

COMPUTE AKIN6=0. EXECUTE.
IF (((cr6 - cr4 >= 0.3) | (cr6 - cr5 >= 0.3) | (cr6 >= 1.5 * MinPreopCr)) & (AKIN0_2 = 0 &
AKIN3 = 0 & AKIN4 = 0 & AKIN5 = 0)) AKIN6=1. EXECUTE.
IF ((cr6 >= 2 * MinPreopCr) & (AKIN0_2 = 0 & AKIN3 = 0 & AKIN4 = 0 & AKIN5 = 0))
AKIN6=2. EXECUTE.
IF ((cr6 >= 3 * MinPreopCr) | (cr6 >= 4 & (cr6 - MinPreopCr >= 0.5)) & (AKIN0_2 = 0 &
AKIN3 = 0 & AKIN4 = 0 & AKIN5 = 0)) AKIN6=3. EXECUTE.

COMPUTE AKIN7=0. EXECUTE.
IF (((cr7 - cr6 >= 0.3) | (cr7 - cr5 >= 0.3) | cr7 >= 1.5 * MinPreopCr) & (AKIN0_2 = 0 & AKIN3
= 0 & AKIN4 = 0 & AKIN5 = 0 & AKIN6 = 0)) AKIN7=1. EXECUTE.
IF ((cr7 >= 2 * MinPreopCr) & (AKIN0_2 = 0 & AKIN3 = 0 & AKIN4 = 0 & AKIN5 = 0 &
AKIN6 = 0)) AKIN7=2. EXECUTE.
IF ((cr7 >= 3 * MinPreopCr) | (cr7 >= 4 & (cr7 - MinPreopCr >= 0.5)) & (AKIN0_2 = 0 &
AKIN3 = 0 & AKIN4 = 0 & AKIN5 = 0 & AKIN6 =  0)) AKIN7=3. EXECUTE.

COMPUTE AKIN=0. EXECUTE.
IF (AKIN0_2 = 1 | AKIN3 = 1 | AKIN4 = 1 | AKIN5 = 1 | AKIN6 = 1 | AKIN7 = 1) AKIN=1.
EXECUTE.
IF (AKIN0_2 = 2 | AKIN3 = 2 | AKIN4 = 2 | AKIN5 = 2 | AKIN6 = 2 | AKIN7 = 2) AKIN=2.
EXECUTE.
IF (AKIN0_2 = 3 | AKIN3 = 3 | AKIN4 = 3 | AKIN5 = 3 | AKIN6 = 3 | AKIN7 = 3) AKIN=3.
EXECUTE.
```

Coding Waikar:

```
COMPUTE w0_1=0. EXECUTE.
IF (MAX(cr0,cr1) - MinPreopCr >= 0.3) w0_1=1. EXECUTE.
IF (MAX(cr0,cr1) - MinPreopCr >= 0.5) w0_1=2. EXECUTE.
IF (MAX(cr0,cr1) - MinPreopCr >= 1) w0_1=3. EXECUTE.

COMPUTE w2=0. EXECUTE.
IF (((cr2 - cr1 >= 0.3) | (cr2 - cr0 >= 0.5)) & w0_1 = 0) w2=1. EXECUTE.
IF (((cr2 - cr1 >= 0.5) | (cr2 - cr0 >= 1)) & w0_1 = 0) w2=2. EXECUTE.
IF (((cr2 - cr1 >= 1) | (cr2 - cr0 >= 1.5)) & w0_1 = 0) w2=3. EXECUTE.

COMPUTE w3=0. EXECUTE.
IF (((cr3 - cr2 >= 0.3) | (cr3 - cr1 >= 0.5)) & (w0_1 = 0 & w2 = 0)) w3=1. EXECUTE.
IF (((cr3 - cr2 >= 0.5) | (cr3 - cr1 >= 1)) & (w0_1 = 0 & w2 = 0)) w3=2. EXECUTE.
IF (((cr3 - cr2 >= 1) | (cr3 - cr1 >= 1.5)) & (w0_1 = 0 & w2 = 0)) w3=3. EXECUTE.

COMPUTE w4=0. EXECUTE.
IF (((cr4 - cr3 >= 0.3) | (cr4 - cr2 >= 0.5)) & (w0_1 = 0 & w2 = 0 & w3 = 0)) w4=1. EXECUTE.
IF (((cr4 - cr3 >= 0.5) | (cr4 - cr2 >= 1)) & (w0_1 = 0 & w2 = 0 & w3 = 0)) w4=2. EXECUTE.
IF (((cr4 - cr3 >= 1) | (cr4 - cr2 >= 1.5)) & (w0_1 = 0 & w2 = 0 & w3 = 0)) w4=3. EXECUTE.
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COMPUTE w5=0. EXECUTE.
IF (((cr5 - cr4 >= 0.3) | (cr5 - cr3 >= 0.5)) & (w0_1 = 0 & w2 = 0 & w3 = 0 & w4 = 0)) w5=1.
EXECUTE.
IF (((cr5 - cr4 >= 0.5) | (cr5 - cr3 >= 1)) & (w0_1 = 0 & w2 = 0 & w3 = 0 & w4 = 0)) w5=2.
EXECUTE.
IF (((cr5 - cr4 >= 1) | (cr5 - cr3 >= 1.5)) & (w0_1 = 0 & w2 = 0 & w3 = 0 & w4 = 0)) w5=3.

COMPUTE w6=0. EXECUTE.
IF (((cr6 - cr5 >= 0.3) | (cr6 - cr4 >= 0.5)) & (w0_1 = 0 & w2 = 0 & w3 = 0 & w4 = 0 & w5 = 0))
w6=1. EXECUTE.
IF (((cr6 - cr5 >= 0.5) | (cr6 - cr4 >= 1)) & (w0_1 = 0 & w2 = 0 & w3 = 0 & w4 = 0 & w5 = 0))
w6=2. EXECUTE.
IF (((cr6 - cr5 >= 1) | (cr6 - cr4 >= 1.5)) & (w0_1 = 0 & w2 = 0 & w3 = 0 & w4 = 0 & w5 = 0))
w6=3. EXECUTE.

COMPUTE w7=0. EXECUTE.
IF (((cr7 - cr6 >= 0.3) | (cr7 - cr5 >= 0.5)) & (w0_1 = 0 & w2 = 0 & w3 = 0 & w4 = 0 & w5 = 0 &
w6 = 0)) w7=1. EXECUTE.
IF (((cr7 - cr6 >= 0.5) | (cr7 - cr5 >= 1)) & (w0_1 = 0 & w2 = 0 & w3 = 0 & w4 = 0 & w5 = 0 &
w6 = 0)) w7=2. EXECUTE.
IF (((cr7 - cr6 >= 1) | (cr7 - cr5 >= 1.5)) & (w0_1 = 0 & w2 = 0 & w3 = 0 & w4 = 0 & w5 = 0 &
w6 = 0)) w7=3. EXECUTE.

COMPUTE Waikar=0. EXECUTE.
IF (w0_1 = 1 | w2 = 1 | w3 = 1 | w4 = 1 | w5 = 1 | w6 = 1 | w7 = 1) Waikar=1. EXECUTE.
IF (w0_1 = 2 | w2 = 2 | w3 = 2 | w4 = 2 | w5 = 2 | w6 = 2 | w7 = 2) Waikar=2. EXECUTE.
IF (w0_1 = 3 | w2 = 3 | w3 = 3 | w4 = 3 | w5 = 3 | w6 = 3 | w7 = 3) Waikar=3. EXECUTE.
```