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Title: Outcome of Critically ill Patients with Acute Kidney Injury using the AKIN Criteria

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Abstract: Objective: Acute kidney injury (AKI) affects 5-7% of all hospitalized patients with a much higher incidence in the critically ill. The Acute Kidney Injury Network proposed a definition in which serum creatinine rises (>0.3mg/dl) and/or oliguria (<0.5/ml/kg/h) for a period of 6 hours are used to detect AKI. Accurate urine output measurements as well as serum creatinine values from our database were used to detect patients with AKI and calculate their corresponding mortality risk and length of stay.

Design: Retrospective cohort study

Setting: 7 intensive care units at, a large, academic, tertiary medical center .

Patients: Adult patients without evidence of end stage renal disease, with more than 2 creatinine measurements and at least a 6 hours urine output recording , who were admitted to the ICU between 2001 and 2007.

Interventions: Medical records of all the patients were reviewed. Demographic information, lab results, charted data, discharge diagnoses, physiological data and patient outcomes were extracted from the MIMIC-II database using a SQL query.

Measurements and main results: From 19,677 patient records, 14,524 patients met the inclusion criteria. 57% developed AKI during their ICU stay. In-hospital mortality rates were: 13.9%, 16.4%, 33.8% for AKI 1, 2 and 3 respectively compared to only 6.2% in patients without AKI ($p<0.0001$). After adjusting for multiple covariates AKI was associated with increased hospital mortality (OR 1.4 and 1.3 for AKI1 and AKI2 and 2.5 for AKI3; $p<0.0001$). Using multivariate logistic regression, we found that in patients who developed AKI, urine output alone was a better mortality predictor than creatinine alone or the combination of both.

Conclusions: More than 50% of our critically ill patients developed some stage of AKI resulting in stage-wise increased mortality risk. However, the mortality risk associated with AKI stages 1 and 2 does not differ significantly. In light of these findings reevaluation of the AKIN staging criteria should be considered.

Response to Reviewers: Reviewer #1: Thanks to the editors for the opportunity to review this very well written and informative manuscript that enhances the existing credible evidence in the ongoing evaluation of the AKIN's proposed scoring system. I support the publication of this manuscript based on, and in consideration of, the following comments:
This manuscript references similar work by the Riyadh ICU users group. They represent large datasets of ICU patients evaluating epidemiology of AKI and the correlation between AKI classification and mortality. The Riyadh group is a non-US population of patients from the decade 1989-1999 and the current authors report from US-only intensive care units between the years 2001-2007. It is fascinating to speculate on the reasons for differences between AKI incidence (52.5 % in the US group and 35.4% in the Riyadh group) and the mortality rates for each increment as almost double for the Riyadh group. This is not the point of the manuscript however, one important contribution of the current manuscript, besides its more contemporary cohort of patients, is its use of a more accurate form of measurement of urine output. Did the improved accuracy of urine output measurements contribute to the shift the diagnostic threshold?

Answer:
We would like to thank the reviewer for his/her constructive comments and suggestions. We did not aim to validate the AKIN definition in this study. However, we fully acknowledge the importance of such work and we are already conducting a separate study to examine this question.

The authors are applauded for using a more accurate method for urine output measurement. As is frequently reported, acute kidney injury is associated with significant increases in ICU morbidity and mortality. Establishing a consensus definition/diagnostic criteria provides a forum for assessing risk for AKI and as a test for risk assessment high sensitivity is preferred so as to not miss an opportunity for prevention or to direct an intervention.
The authors report that the mortality predictive power of urine output was superior to that of creatinine. While they do not reflect mechanism of renal injury, they are markers of organ function. In a generalized ICU population, acute illness may be associated with tubular function alterations as measured by urine output than by situations that alter GFR and is measured by creatinine. It would be interesting to evaluate the predictive power of either component in ICU subset populations with high risk for death such as sepsis and pulmonary disease.
While the stages AKI I and AKI II did not show a stage-wise increased mortality risk, they may be important in guiding therapy and in determining response to therapy or identifying those who are most likely to respond to therapy. These important components are yet to be determined using AKI criteria.
The paragraph on page 10 should be reworded with respect to the concept of "tackling AKI." I suggest the following, ..."it would seem logical to assume that early identification of AKI would create a beneficial effect for these patients. However, this approach while useful to prognosticate, remains unproven when used to direct therapy".
The conclusion is an accurate summary of the manuscript.

Answer:
The suggestion of the reviewer was accepted and we added the phrase suggested by the reviewer to the manuscript in the related paragraph.

Reviewer #2: This is a large single center cohort study which in retrospect and based on computerized patient charts aims at correlating the 3 stages of AKI (as defined by the AKIN criteria) to 28-day in hospital mortality.
The study is carefully conducted, the data are important to the scientific community, and the manuscript is very nicely written.
COMMENTS:
A) Urine Measurements
The main novelty of the study is inclusion of urine output data, which are available in the majority (14,525 out of 17,294), but, however, not in all of study patients. Accurate urine output measurements are difficult to perform in everyday clinical practice, and the goal of hourly recording is almost impossible to achieve. To me it seems that the authors defined that urine output measurements were "sufficient" if during a 6 hours interval at least 3 measurements had been done. Is this true? However, I wonder why the authors haven't chosen to investigate solely those 14,252 patients with "sufficient" data on urine output.
-> The authors should check if using only those patients with "sufficient" urine output data would alter the study's results.

Answer:
We would like to thank the reviewer for his/her constructive comments and suggestions. In order to emphasize the difference between our study and previous studies (i.e. Riyadh group study), we decided to include only the patient who had sufficient accurate urine output measurements (at least one six hours period of urine output collection). The results did not differ much from the original results except for the increased relative number of patients with AKI (most probably due to the fact that patient with less critical conditions did not have accurate surveillance of their urine output). We re-computed all the statistics and logistic regression models according to the new population and updated Tables 2-5 and corresponding text with new results.

B) AKI Patients Falsely Excluded from the Study
The data base used in this study has a number of limitations:
- Urine output and serum creatinine data were only available during the ICU period
- The diagnose of AKI was not documented. Instead, the authors had to retrospectively rule out those patients with pre-existing ESRD.
It is important to recognize what kind of in-hospital patients were excluded from this study, although they've had AKI:
- patients which had developed AKI prior to admission to the ICU
- patients which had developed AKI during the first day of their stay on the ICU
- patients with KDOQI stages III and IV of chronic renal disease, which had experienced acute on chronic renal failure leading to a serum creatinine above 4 mg/dl on the day of admission to the ICU
Thus, seemingly, the present study included only those patients which were ill enough to require intensive care therapy, and developed AKI after day 2 of their stay in the ICU.
-> Is this true? If yes, the authors should mention this.

Answer:
Yes, the MIMIC-II database was collected from ICUs and as a result this study focused solely on ICU patients. Patients that had dialysis on day 2 and afterwards, were classified as AKI3 (according to the proposed AKIN criteria- paragraph "Definition of Acute Kidney Injury" in the manuscript).

C) Important Results:
Nevertheless, the authors provide new and important data on this particular subset of AKI patients: Of 17,294 ICU patients 52.5% developed AKI. In-hospital mortality rates were: 7.6%, 9.7%, 24.7% for AKI

1, 2 and 3 respectively compared to only 3% in patients without AKI ($p<0.0001$). The univariate in-hospital mortality odds ratios were 2.5, 3.2, and 8.1 for AKI 1, AKI 2, and AKI 3 patients, respectively, compared to patients with no AKI ($p<0.0001$). In light of these data it seems that, indeed, AKI of stages 1 to 3 associates with increasingly poor survival. The authors further show that in comparison with serum creatinine, the AKIN criteria of urine output better correlate with survival.
D) Problematic Conclusions, Unreported Co-morbidities
However, AKI 1 and AKI 2 had similar odds ratio for mortality in the multivariate logistic regression model using age, sex, SOFA score (non-renal) and co-morbidities.
However, the list of relevant co-morbidities is largely incomplete. For example, conditions relevant to outcome, but not considered in the study are: coronary artery disease, heart failure, diabetes, peripheral arterial disease. Some co-morbidities considered in the study (pulmonary disease and gastrointestinal disease) need to be defined. The fact that "gastrointestinal disease" had an OR for mortality of 0.8 is difficult to understand. In my view gastrointestinal bleeding or liver cirrhosis would aggravate AKI. The fact that female gender had an OR for mortality of 1.25 is also counter-intuitive.
-> The authors should comment on this. In case that data on neither CAD nor diabetes are available, multivariate logistic regression is very problematic.

Answer:
We included more covariates to the multivariate logistic regression such as CAD, PVD, and sepsis in the revised manuscript. All the covariates are mentioned on page 5. Also, Table 3 was updated according to the new logistic regression model.

-> Can the authors provide any data on contrast media exposure during the ICU stay? Perhaps they can define a subgroup of patients which developed AKI after x-ray CM, and analyze their outcome with respect to AKI patients with no CM exposure.

Answer:
Unfortunately, the database in the version that was used to extract the data for this study did not contain accurate data on the use of CM and therefore we did not perform a sub-analysis of patients who received CMs.

Reviewer #4: The authors have performed a retrospective evaluation of AKIN (Acute Kidney Injury network) criteria as a predictor of outcome in a large patient population with critical illness. AKI was found to be an independent predictor of in-hospital mortality with increased risk arising from progression from stage 2 to 3, but not from stage 1 to 2. AKIN criteria by accurate measurements of urine output, alone, was more predictive than by creatinine, alone, or a combination of the two variables.
The paper is presented clearly. It is also of interest given the context of other studies using less accurate measurements of urine output that conflict with the detail of the original AKIN criteria. There are, however, a number of concerns, which follow.
I would question the validity of using 2 different populations to test AKIN staging by urine output, alone, and serum creatinine, alone. Might there not be bias introduced by this? One could speculate that those who required significant periods away from the ICU (and so would have had less complete urine output recording) might have represented a very different patient group to those who did not. The findings might have been more robust if the study population was confined to those who could be staged by both measures. On a slightly separate note, it would have been useful to know of case mix within the population.

Answer:
We would like to thank the reviewer for his/her constructive comments and suggestions. As mentioned above we decided to include only the patients who had "sufficient" UO measurements in order to prevent the mixing of two separate populations (patients that were classified by UO and

creatinine and patients that were classified solely by creatinine).We re-computed all the statistics and logistic regression models according to the new population and updated Tables 2-5 and corresponding text with new results. Unfortunately, MIMIC-II doesn't have case mix information. Hence, we are unable to provide these statistics.

It does not seem that the authors were able to account for those who required renal support after day 1 of the admission. The institution of therapy would have had an impact on AKI staging by serum creatinine, alone, but not by urine output so should have been known. I feel this is a significant drawback of the study.

Answer:
The institution of RRT after day 2 resulted in the classification of the patient as having AKI 3 (according to the AKIN criteria). This classification was independent of both creatinine and urine output measurements. Hence, there was no discrepancy between creatinine and urine output classifications.

The assumption of the lowest serum creatinine over the course of the admission as being equivalent to the baseline reading is another significant drawback. The validity of this approach is questionable in the setting of AKI. Although the authors have attempted to address concerns about suspect urine output calculations in historical work, they have now introduced uncertainty with their delta creatinine methodology. The impact of renal support on the 'lowest serum creatinine' has not been acknowledged. Back-calculation of an assumed baseline creatinine using gender, ethnicity and the MDRD formula is an approach that has been used by some where the actual value has not been known. It's increasingly apparent that errors are introduced by this approach but the authors could have commented on this.

Answer:
As mentioned by the reviewer because of the inaccuracy of the MDRD formula use for the calculation of baseline creatinine level and for the fact that unfortunately our database did not have sufficient data at the time of extraction on ethnicity (preventing the use of MDRD formula for a large number of our patients), we decided to use the lowest Cr level of a patient during his hospital stay (also outside of the ICU) for a referral Cr level. We added this fact in the limitation section as well.

AKI1 was not found to be different from AKI2 in terms of prediction of mortality. It would have been useful to see similar analysis but with the predictive value of staging when calculated by urine output, alone, and by serum creatinine, alone.
Such separate predictions based on creatinine and urine output were already performed and reported in the last paragraph of Results and Table 6.
In the last paragraph of the results section, the superiority of urine output in predicting mortality is reported but only for those defined as actually having AKI. For those without AKI, a change in urine output (which I don't believe has been described) is an inferior predictor to a change in serum creatinine (again, not described). This raises the possibility that urine output is actually somewhat less diagnostically specific for AKI (i.e. also reflective of reversible pre-renal azotaemia) - perhaps the authors could comment on this.

Answer:
We would like to clarify that we did not use actual urine output or creatinine values in our mortality prediction models. The actual values were only used to determine AKI classification, and this AKI classification along with other covariates were the inputs to the prediction models. In other words,changes in urine output or creatinine were never explicitly used in this study. Also, we already state in the first sentence of the last paragraph of Results that creatinine is superior
to urine output for non-AKI patients in mortality prediction. Both urine output and serum creatinine are valid parameters for mortality predication (area under

ROC curve is greater than 0.7). Although UO is superior to creatinine for prediction in non-AKI patients the difference in AUC is minor and therefore we cannot conclude that one is superior in terms of specificity or sensitivity to the other.

The quality assurance assessment for ESRD looked at 100 patients from the excluded group. A similar QA would have been useful in included study patients.
For a patient with ESRD to be incorrectly included in this study, the text notes corresponding to the patient must include a keyword that we did not consider or a misspelled keyword. A match to any keyword would exclude a given patient; this implies that all the keywords would need to be misspelled or none of the keywords is mentioned. We feel that this is highly unlikely to occur and hence the number of such patients would be insignificant.
In their description of urine output methodology, could the authors clarify that a 'blank' (uncompleted) hourly record was assumed to represent a missed recording or absent patient and that a '0' was the standard practice for documenting anuria?

Answer:
In MIMIC-II, a urine output measurement of '0' means no urine production for that hour, whereas a non-existent measurement means that no measurement was taken for that hour.

Outcome of Critically ill Patients with Acute Kidney Injury using the AKIN Criteria

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Acute kidney injury (AKI) affects 5-7% of all hospitalized patients [1], with a much higher incidence in the critically ill. Although AKI carries considerable morbidity and mortality [1-2] more than 35 definitions of AKI have been used in the literature. This results in confusion as well as an ill defined association between acute renal dysfunction and morbidity and mortality [2-3]. Hence, in 2002 the Acute Dialysis Quality Initiative (ADQI) defined universal AKI criteria for the first time [4]. This definition was the first consensus classification to integrate both urine output and creatinine measurements. The ADQI definition resulted in extensive debate about its prediction of outcomes [5-8] and did not include a complete definition for Renal Replacement Therapy (RRT). Therefore, in 2005 it was revised by the Acute Kidney Injury Network (AKIN), using a more updated serum creatinine and urine output criteria and including information regarding RRT. Furthermore, the definition of time to occurrence of kidney injury was narrowed from 7 days to 48 hours, emphasizing the acute nature of this disorder [9].
In recent years, two large multicenter studies have been preformed to validate this relatively new classification: The SAPS3 Hospital Outcome Cohort having data from 303 intensive care units [10]and the Riyadh Intensive Care Program database with data from 22 intensive care units [11]. Both of these studies demonstrated an increased morbidity and mortality associated with the development of AKI. However, both used modified AKIN criteria and neither employed accurate urine output measurement for the detection of AKI.

Recently an American Thoracic Society statement aimed to prevent the development of AKI[12] by emphasizing the significance of the urine output measurement in the continuous evaluation of critically ill patients to facilitate early detection of AKI. The Multi-parameter Intelligent Monitoring for Intensive Care (MIMIC)-II database [13] , unlike the 2 databases used in the above studies, has high resolution urine measurements and can therefore more accurately detect the development of the various stages of AKI.

We therefore designed a study aimed to estimate the risk for morbidity and mortality of patients who developed AKI solely using the large cohort of critically ill patients from the MIMIC - II database. Our study was designed to test the hypothesis that occurrence of AKI would predict mortality in critically ill patients and that varying stages of AKI (detected by applying the AKIN criteria) would yield different levels of attributable mortality. Such data are critical to the validation of the AKI definition criteria; for example, if the inclusion of oliguria did not improve

predictive value beyond creatinine rise, then one might argue to refine the definition based on creatinine alone.

Methods

The MIMIC-II database:

The MIMIC-II project was approved by the institutional review boards of the Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC) and granted a waiver of informed consent. The MIMIC-II database includes physiologic information from bedside monitors in seven adult ICUs of BIDMC a large, academic, tertiary medical center in Boston, Massachusetts. These data (heart rate, blood pressures, etc.) were validated by ICU nurses on an hourly basis. The database also contains records of all lab values, nursing progress notes, IV medications, fluid intake/output, and other clinical variables. Other clinical data were added to the database including pharmacy provider order entry (POE) records, admission and death records, discharge summaries, ICD-9 codes, imaging and ECG reports. The database also contains bedside monitor waveforms and their associated derived parameters which were not investigated in this research. The database includes patients admitted between 2001 and 2007 and is maintained by researchers at the Harvard-MIT Division of Health Sciences and Technology (details at http://mimic.http://mimic.mit.edu/physionet.org).

Inclusion and Exclusion criteria:

We included all adult patients, with ICU length of stay of more than 24 hours, who had at least 2 serum creatinine measurements and at least one 6 hours urine output observation period (see "Definition of Acute Kidney Injury").

Patients who underwent RRT on the day of or prior to their hospital admission, or who had a first serum creatinine level of >4 mg/dL were categorized as having end-stage renal disease (ESRD), and therefore were excluded. Patients were also excluded if they had an ICD-9 code for ESRD. Since the MIMIC-II database did not have a specific coding system for RRT, patients were considered to have undergone RRT if they had the words "end stage renal disease" or "dialysis" (or equivalent i.e. CVVH, CVVHD, RRT etc.) in text notes on the day of admission. In order to

validate this text search, sampling of 100 patients was performed. In 98% (95.3 - 100) of the sampled cases the patients indeed underwent RRT on the day of admission.

Definition of Acute Kidney Injury:

We classified our patients into 3 classes according to AKIN criteria [9](Table 1). The AKIN class was determined by using serum creatinine measurements from lab reports, and urine output (UO) measurements that were recorded, as a part of the nursing flow sheet. In general, urine output measurements are entered hourly and the AKI criteria require urine output over a six hour window. To account for absences from the ICU and mis-entered information, the total urine output over the window was determined in two steps. First take a six hour period following each urine output measurement having at least three additional measurements. Second, calculate the weight-normalized total urine output during this 6 hour period.

Since our database did not include the pre-admission serum creatinine level of the patients, we considered the lowest serum creatinine level of a patient to be equivalent to the patient's pre-hospital baseline serum creatinine level. The worst serum creatinine increase or urine outputs were examined in 48 hour periods. The most severe acute kidney injury stage (from urine outputs or creatinine measurements which ever was more severe) was recorded for every patient. Patients who received some kind of renal replacement therapy were classified as AKI3 (AKIN criteria).

Data collection:

All data were extracted from the MIMIC-II database. The extracted data included demographic information (e.g. age, sex) as well as clinical information from lab results (e.g., serum creatinine and arterial blood gases), nursing-charted data (e.g. urine output) and discharge diagnoses (ICD-9 codes). Physiological data were collected only during the ICU stay, unlike lab results which were available throughout the whole hospitalization.

Physiological data including heart rate, blood pressure, respiratory rate, length of mechanical ventilation, neurological status (GCS) as well as non-renal-Sequential Organ Failure Assessment (SOFA) scores [14](calculated SOFA score excluding the renal component) were computed and reported.

Recorded outcomes such as mortality and length of stay were also extracted from the same database.

Statistical analysis:

STATA 11.1 (StataCorp, Collage Station, TX) was used for all statistical analysis. All continuous variables were expressed either as mean ± standard error (SE) and 0.95 confidence interval (CI) or as median and inter-quartile (Q1-Q3).

For the univariate analysis, we used the Chi-square or Fisher exact probability test to compare multiple groups with nominal variables. The Kruskal-Wallis one-way analysis of variance was used to test differences between continuous variables. All tests were two-sided, and a p value of < 0.05 was considered significant.

For the multivariate analysis, we performed a logistic regression analysis with a dependent variable of in-hospital mortality. The following covariates included in the model were considered to be related to mortality and morbidity in critically ill patients: age, gender, SOFA scores, AKI stage and co-morbidity groups taken from ICD-9cm codes using the Elixhauser's co-morbidity index [15](groups were: Disease of the Respiratory, Gastrointestinal and Circulatory systems as well as infectious diseases, malignancy, diabetes mellitus, gastrointestinal bleeding, coronary artery disease (CAD), congestive heart failure (CHF), peripheral vasculare disease (PVD), cirrhosis and gastrointestinal bleeding) After controlling for co-linearity, we applied a stepwise (forward and backward) selection of the covariates, the covariate that were used in our logistic regression analysis were: Age, SOFA score on admission, diseases of the respiratory and gastro-intestinal systems, sepsis, cirrhosis, gastrointestinal bleeding, malignancy, CHF, DM, CAD, PVD . Finally, we assessed the model's discrimination using the area under the receiver operating characteristic curve (AUC), and model calibration using the Hosmer-Lemeshow test.

Results

The MIMIC-II database contains the records of 26,510 patients of whom 19,677 were adults aged 15 or more at the time of admission. 630 patients were excluded because they were considered to have had ESRD prior to their ICU admission; of these patients, 327 were excluded

by the text search of the medical notes and 303 due to the presence of an ICD-9 code for ESRD. 1,755 patients were excluded because they did not have sufficient creatinine measurements or their length of stay was 1 day or less and 2,768 because they did not have sufficient urine output recordings (Figure 1).

The final analytic cohort, therefore, contained 14,524 patients, of which 6161 were females (42%). The median age on admission was 65.8 years (Q1-Q3 55.2-77.8). The median SOFA score (non-renal) on admission was 5 (Q1-Q3 2-8) (Table 2). 57% of the patients developed AKI during their ICU stay. AKI 1 was the most frequent (38%) followed by AKI 2 (14%) and AKI 3 (4%). The overall in-hospital and ICU mortality rates were 11.8% and 9% respectively. Hospital mortality rates were higher in patients with AKI (16% vs. 6.7%; $p<0.0001$) than in patients with no AKI. The same was found for ICU mortality rates (12.4% vs. 4.8%; $p<0.0001$). The univariate in-hospital mortality odds ratios were 2.41, 2.95, and 7.64 for AKI 1, AKI 2, and AKI 3 patients, respectively, compared to patients with no AKI ($p<0.0001$). The multivariate logistic regression model included Age, admission SOFA score (without renal component), diseases of the respiratory and gastrointestinal systems, sepsis, cirrhosis, gastrointestinal bleeding, malignancy, CHF, DM, CAD, PVD (Table 3). Patients with AKI 1 and AKI 2, compared to patients without AKI, had a 30% increase in the odds of death (AKI 1: OR 1.38, 95% CI 1.2-1.59, $p<0.0001$; AKI 2: OR 1.26, 95% CI 1.06-1.5, $p=0.01$), patients with AKI 3 were 2.5 times more likely to die (95% CI 1.98-3.12, $p<0.0001$) (Table 3). The 28-day Kaplan-Meier survival plot (Figure 2) clearly shows a diversion between the survival rates among the 3 different AKI stages {Logrank (Mantel-Cox) test $p<0.0001$}, because the survival probability of AKI 1 patients is again similar to that of AKI 2 patients, one could question the existence of 2 separate groups.

Analysis of ICU mortality rates was similar to in-hospital mortality rates. In univariate analysis, the odds ratios for ICU mortality were 2.35, 3.2 and 9.2 for AKI 1, 2 and 3, respectively, compared to patients with no AKI ($p<0.0001$). When we applied the same multivariate logistic regression model as for the in-hospital mortality, the odds ratios for ICU mortality were reduced to 1.27 for AKI 1 and AKI 2, and 3.7 for AKI 3, compared to patients with no AKI ($p<0.0001$) (Table 4).

Patients with AKI had a significant decrease in median 28 ICU-free days [16],from 26 for patients without AKI to 22, 17, and 6 days for patients with AKI 1, 2, and 3, respectively ($p<0.0001$) (Table 5). The length of ICU stay for patients who developed AKI was longer than

for those who did not develop AKI and increased gradually with the severity of AKI from a mean ICU stay of 2.3 days for patients without AKI to 5.6, 8.2 and 12.6 days for AKI 1, 2, 3 respectively ($p<0.0001$) (Table 5).

The classification of AKIN for the development of AKI is based on the combination of two components: urine output measurements (UO) and serum creatinine (CR) increases in a 48 hour window. We examined the ability of each component of the AKIN criteria (urine output or creatinine) to predict mortality independently. First we computed AUC for AKI categorized by urine output from 10-fold cross-validation using a logistic regression analysis (the same covariates were included as above). We then computed the AUC for AKI using CR. We then compared AUCs corresponding to UO and CR.

Regarding the subset of patients without AKI, we found that the mortality predictive ability of CR was superior to that of UO (AUC (CR) = 0.780 vs. AUC (UO) = 0.764; $p<0.0001$). However, for the subset of patients who developed AKI, divided according to severity stages, we found that the mortality predictive ability of UO was always superior to that of CR: AKI 1- AUC (UO) = 0.741 vs. AUC (CR) = 0.714; p=0.005.AKI 2- AUC (UO) = 0.722 vs. AUC (CR) = 0.655; p=0.001. AKI3- AUC (UO) = 0.763 vs. AUC (CR) = 0.660; p=0.001 (Table 6).

Discussion

Our analysis of a cohort of more than 14,000 patients, from a single, large, academic center, using the AKIN proposed acute kidney classification on data from the MIMIC-II database, showed a clear and significant increase in the risk for mortality in patients who developed acute kidney injury compared with patients who did not. The increased risk was found to be proportional to the stage of AKI although there is no clear risk difference between the patients with AKI 1 and AKI 2 compared to a large increase in mortality risk in patients with AKI 3. These results are consistent with previous studies, in which the authors hypothesized that an inaccurate use of the criteria, specifically data regarding urine output, which, by their nature, can be inaccurately collected, was the cause for this phenomenon[11]. In contrast with the aforementioned studies, the MIMIC-II database allowed us to follow urine output measurements in a higher resolution (6 hour windows), and therefore fully meet urine output criteria as designed in the AKIN classification. Nevertheless, we still did not see a significant difference between AKI 1 and 2, regarding the risk of mortality. This finding suggests that although these

patients are classified as two different groups according to the AKIN classification, this division should be reconsidered.

The increased mortality rate, especially in the less severe AKI groups (1 and 2), may be explained by an indirect rather than a direct mechanism. In the past there have been studies which demonstrated that kidney injury can influence morbidity and mortality directly by causing water and salt retention leading to hyperkalemia, acidosis [17-18]and fluid overload. However, AKI has been associated with increased insulin resistance and protein breakdown that can lead to immune system dysfunction. This can create an indirect influence on morbidity and mortality, particularly given that sepsis is the most common mechanism of death in AKI [16]. Kidney injury can also cause activation of the immune system that promotes the secretion of proinflammatory cytokines that can lead to an increased activity of pulmonary macrophages; this could result in increased pulmonary capillary permeability and cause respiratory compromise [19].

Accumulating data, including our results, show that although kidney injury is not always directly related to the cause of death, it is clearly a *marker* of worsening patient status, and may be a useful clinical marker of deterioration. We therefore suggest that it might be used as a risk assessment tool for clinicians.

In view of the above it would seem logical to assume that tackling AKI would create a beneficial effect for these patients. However, this approach while useful to prognosticate remains unproven when used to direct therapy [20-26]. We believe the reason to be the multi-factorial nature of AKI and the fact that it might be only a part of a systemic process rather than its cause.

There are a number of limitations to our study. First, our database did not have a specific and accurate coding system for RRT. In order to exclude patients that had ESRD we had to use a text search. We have tried to overcome this limitation by refining the search and by sampling of 100 patients (out of 630 excluded patients) in order to ensure that patients who were excluded indeed had ESRD. The results were that in 98% of these sampled cases, patients have had RRT on the day of admission and were appropriately excluded. Because the misclassification rate in the manual review was 2% (95% CI 0-4.7%), a Simulated 5% misclassification rate among patients coded as having ESRD resulted in the movement of only 32 patients from ESRD to the cohort. The mortality rate and calculated OR for various AKI stages did not differ from the original

cohort. Secondly, the database contains data from a period of 7 years (2001-2007), during which there were changes in management of the critically ill and therefore possibly in patients outcome. Because the MIMIC II database is completely de-identified, we were unable to divide the patients into groups that correspond to their different treatment periods. Finally, although our study included the data of more than 14,000 patients and had strong statistical power, it was still a retrospective analysis with its characteristic limitations.

The use of lowest creatinine during hospital stay as baseline creatinine level can be also considered a limitation. Although, a number of studies have demonstrated the inaccuracy of the currently used methods for the calculation of baseline serum creatinine level (i.e. MDRD formula) especially in patients with pre-AKI reduced GFR{Bagshaw, 2009 #336}{Rule, 2007 #437}. Therefore we decided to use the lowest serum creatinine level of a patient during his hospital stay as baseline creatinine level.

Conclusion

In view of AKI's tremendous effect on prognosis, we propose using the AKI classification as a risk assessment tool for clinicians. Larger prospective randomized controlled trials are needed in order to examine whether the application of treatment measurements targeting the AKI will improve patient prognosis.

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Legends to Figures

Figure 1- Patient distribution from the MIMIC-II database 14524 patients were classified using a combination of urine output and creatinine measurements.

Figure 2 – Kaplan-Meier survival plot for 28 day in-hospital mortality divided by AKI stages.

Table 1- Classification of Acute Kidney Injury proposed by the AKIN[9]**

Stage	Serum creatinine criteria	Urine output criteria
1	↑serum creatinine ≥ 0.3mg/dl (≥26.4µmol/l) or ↑ 150-200% (1.5 to 2-fold) from baseline	<0.5 ml/kg/h for more than 6h
2	↑ serum creatinine 200-300% (>2 to 3-fold) from baseline	<0.5 ml/kg/h for more than 12h
3	↑ serum creatinine >300% (>3-fold) from baseline or serum creatinine ≥ 4 mg/ml (≥ 354µmol/l) with an acute increase of at least 0.5 mg/ml (44µmol/l) Or need for RRT.	<0.3 ml/kg/h for more than 24h or Anuria for 12h

****The patients AKI stage depends on the worst stage definition from the urine output criteria or serum creatinine criteria [e.g. an anuric patient (urine criteria stage 3) with an increase of 1.5 in creatinine (serum creatinine criteria stage 1) will have an overall AKI stage 3]**

Table 2: Characteristics of patient cohort, grouped by degree of kidney injury

	Overall cohort	No AKI	AKI 1	AKI 2	AKI3
Total, n (%)	14,524	6252(43)	5595(38.5)	2046 (14.1)	631(4.3)
Age, years: Median (Q1-Q3)	65.8(55.2-77.8)	61.7(48.6-75.7)	68.8 (55.6-79.2)	68.8 (56.5-78.6)	65.2 (52-76.5)
Sex, n: Female (%)	6161(42.4)	2546 (40.7)	2321 (42.5)	1000 (48.9)	294 (46.6)
SOFA(non–renal): Median (Q1-Q3)	5(2-8)	3(1-7)	6(3-8)	7(4-9)	7(5-10)

Table 3- Impact of covariates on in-hospital AKI relates mortality (Multivariate logistic regression analysis)

Covariate		Odds ratio	95% confidence interval	*P* (Chi-Square)
Age		1.037	1.033-1.041	<0.0001
Sepsis		1.997	1.698-2.349	<0.0001
CHF		1.211	1.071-1.369	0.002
CAD		0.464	0.408-0.527	<0.0001
Respiratory		2.124	1.878-2.402	<0.0001
Gastrointestinal		0.686	0.598-0.787	<0.0001
Gastrointestinal bleeding		1.930	1.512-2.464	<0.0001
cirrhosis		3.073	2.448-3.858	<0.0001
Malignancy		1.709	1.489-1.960	<0.0001
DM		0.792	0.679-0.924	0.003
Admission SOFA score	(non renal)	1.163	1.143-1.183	<0.0001
AKI1		1.380	1.201-1.586	<0.0001
AKI2		1.259	1.058-1.499	0.01
AKI3		2.484	1.979-3.119	<0.0001

Table 4- In-hospital and ICU Mortality

	In-hospital Mortality*			ICU Mortality		
	rate (%)	Univariate odds ratio	Multivariate odds ratio*	rate (%)	Univariate odds ratio	Multivariate odds ratio
NO AKI	6.25			4.54		
AKI 1	13.87	2.41	1.38	10.06	2.35	1.27
AKI 2	16.42	2.95	1.26	13.15	3.18	1.26
AKI 3	33.76	7.64	2.48	30.48	9.21	3.71

*The goodness to fit of the regression model was tested by the Hosmer-Lemshow statistics: $p = 0.001$, area under ROC curve 0.799

Table 5 - Length of Stay (LOS) and 28 days ICU free days

	ICU LOS Median(Q1,Q3)	Hospital LOS Median(Q1,Q3)	ICU Free days Median(Q1,Q3)
NO AKI	1.5(1, 2.3)	5(3, 8)	26.1(23.8,26.9)
AKI 1	3(1.8, 5.55)	9(6, 15)	23(0.9, 25.8)
AKI 2	4.3(2.3, 9.7)	12(7, 20)	17.8(0, 24.9)
AKI3	7.1(3, 15.65)	16(9,28)	0(0, 20.95)

P<0.0001 for all

Table 6– Mortality predictive value of urine output vs. serum creatinine

	Urine Output median(Q1-Q3)	Creatinine median(Q1-Q3)	Overall median(Q1-Q3)	Urine output VS. Creatinine *p*-value[1]
No AKI	0.764 (0.759-0.768)	0.780(0.777-0.784)	0.789(0.762-0.794)	0.002
AKI 1	0.741(0.724-0.747)	0.714(0.698-0.716)	0.713(0.709-0.724)	0.005
AKI 2	0.722(0.702-0.729)	0.655(0.626-0.683)	0.694(0.678-0.713)	0.001
AKI 3	0.763(0.728-0.789)	0.66(0.629-0.672)	0.661(0.646-0.68)	0.001

[1] from Mann-Whitney U-test comparing urine output and creatinine

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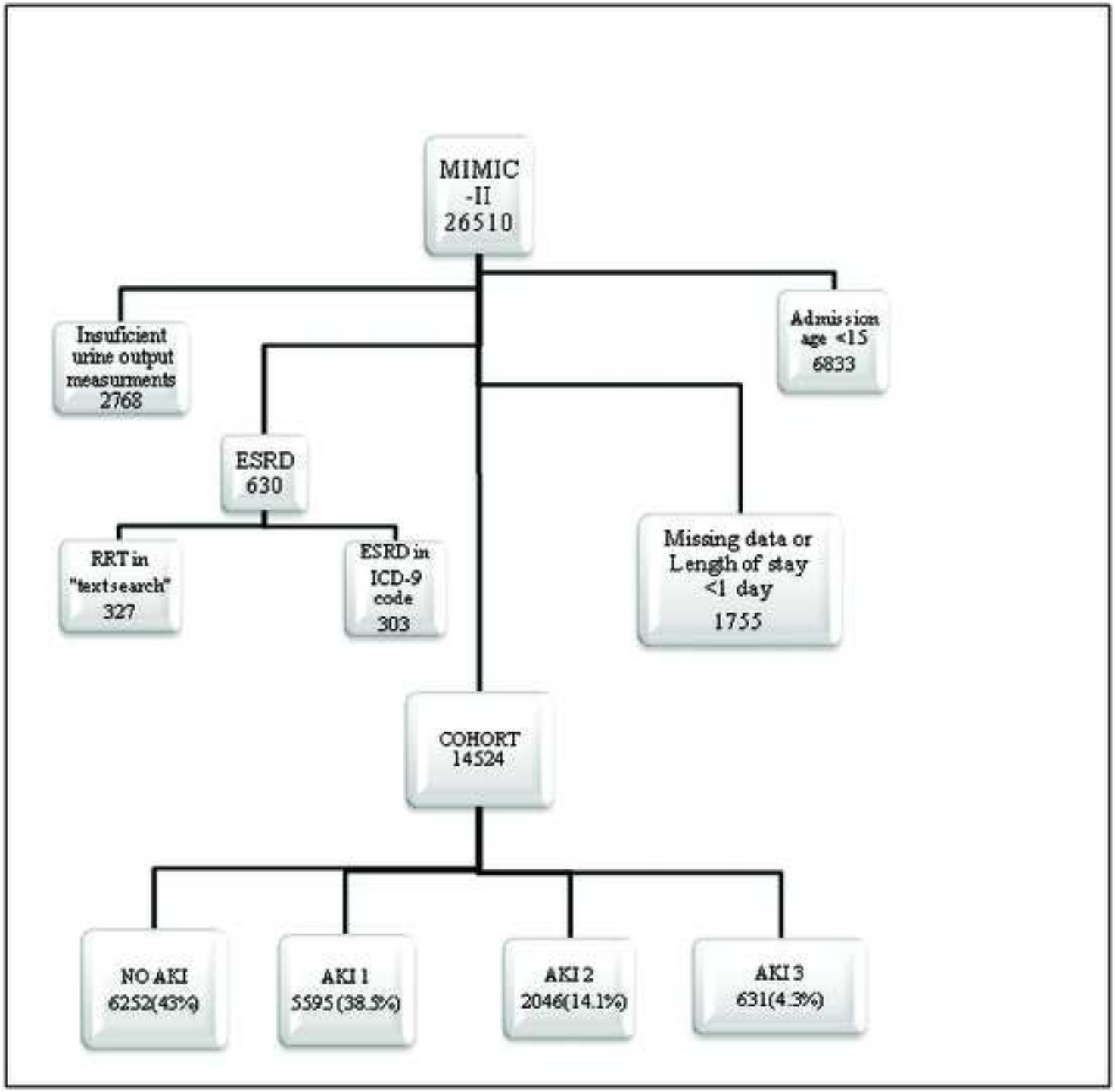

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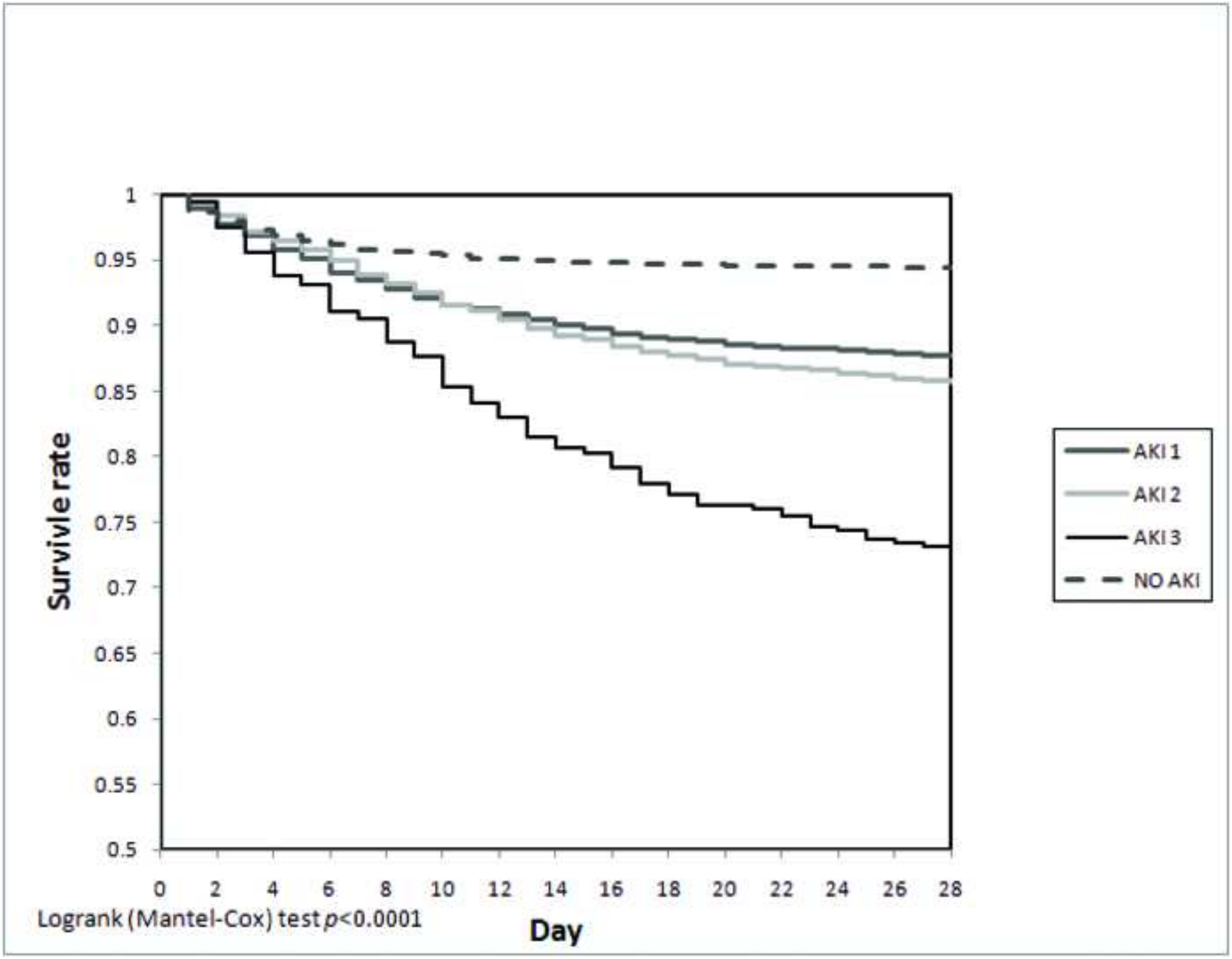

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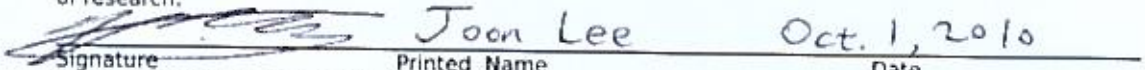

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