ACUTE KIDNEY INJURY AMONG TRAUMA PATIENTS: CLINICAL PREDICTORS, GENOMICS AND OUTCOMES

By

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A THESIS PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
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To my father Jusuf Bihorac: my hero, the one to always rely on in the moments of great difficulties, the voice of reason, adviser, moj Tatica.

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Our objective was to determine clinical and genomic characteristics and in-hospital mortality risk associated with acute kidney injury (AKI) in a multicenter prospective cohort of patients with blunt trauma. Less severe stages of AKI characterized by small changes in serum creatinine (sCr) are inadequately studied among trauma patients. We performed a secondary analysis of subjects enrolled in the Inflammation and the Host Response to Injury (Glue Grant) database who were adult blunt trauma patients without history of kidney disease. AKI was defined by the RIFLE (Risk, Injury, Failure, Loss, and End-stage Kidney) classification, which requires a 50% increase in sCr and stratifies patients into three severity stages: risk, injury, and failure. Association between all stages of AKI and in-hospital mortality was analyzed using a multivariable logistic regression analysis. Genome-wide expression analysis was performed on whole blood leukocytes obtained within 12 hours of trauma.

Our results showed that AKI occurred in 26% of 982 patients. The adjusted risk for hospital death was three times higher for patients with AKI compared to patients without AKI (odds ratio [OR] 3.05 (95% confidence interval [CI], (1.73, TO 5.40). This risk was proportional to the severity of AKI and even patients with mild AKI had OR for dying of

2.57 (95% CI, 1.19 to 5.50) compared to patients without AKI. Genome-wide expression analysis failed to show a significant number of genes whose expression could discriminate among patients with and without AKI. We concluded that, in a multi-center prospective cohort of blunt trauma patients, AKI characterized by small changes in sCr was associated with an independent risk of in-hospital death. Early genomic changes of the blood leukocyte transcriptome are not helpful in identifying trauma patients at increased risk of AKI.

CHAPTER 1
INTRODUCTION

Although acute kidney injury (AKI) is independently associated with adverse outcomes among critically ill patients, only a few studies have studied AKI among trauma patients.[1,2] The majority of these studies have been retrospective, single center reports focusing on severe AKI defined by the need for renal replacement therapy (RRT) or by an increase in serum creatinine (sCr) above a predefined, usually very high cut-off point.[3-6] Although a few recent studies have reported the incidence for less severe AKI as high as 31%,[7,8] severe AKI defined by the need for RRT had a low incidence (between 0.1% and 8.4%) and high mortality (40% to 70%).[3-5] Hence, the clinical importance of AKI with small changes in kidney function after trauma has not been adequately studied or appreciated in clinical practice.

With the recent introduction of the RIFLE (Risk, Injury, Failure, Loss, and End-stage Kidney) classification system for AKI, the adverse effects of small changes in sCr level have begun to be recognized and the term "AKI" has been proposed to encompass the entire spectrum of the syndrome, from minor changes in renal function to the requirement for RRT, replacing the old term of "acute renal failure (ARF)."[9,10] The RIFLE classification defines three grades of AKI severity (R-Risk, I-Injury, F-Failure) based on changes in sCr level relative to the baseline (Tables 1-1 and 1-2).[11] Since the classification's publication in 2004, numerous original investigations using RIFLE have been published and are summarized in recent systematic review of 24 of these studies [12]. The majority of the studies included critically ill patients in general or cardiac intensive care unit (ICU) settings[12] although one study made a population-based estimate of AKI incidence in Scotland.[13] In the analysis of pooled data, increasing AKI

severity was associated with the stepwise increase in relative risk for in-hospital mortality (Risk, 2.40; Injury, 4.15; Failure, 6.37, with respect to non-AKI patients) (Figure 1-1).[12] A recent large retrospective study of 120,000 patients evaluated on the first ICU day confirmed the findings of the systematic review.[14] In addition, worsening RIFLE-AKI was associated with longer ICU and hospital stays and a lower rate of renal recovery.[14-16] We have recently demonstrated that not only worse short-term outcomes but also worse long-term survival is associated with AKI and is proportional to its severity.[17] No study to date has assessed AKI defined by RIFLE criteria among trauma patients.

The Inflammation and the Host Response to Injury is a large-scale interdisciplinary research program funded by a Glue Grant award from the National Institute of General Medical Sciences to uncover the biological reasons for different clinical outcomes after traumatic injury. The Trauma-Related Database (TRDB), a large multicenter database containing de-identified, prospectively collected clinical and gene expression data from patients with severe blunt trauma, was developed as a part of this program and has greatly facilitated research of clinical outcomes after trauma.

The goal of this study was to assess the incidence, clinical predictors, early genomic response of blood leukocytes, and the short-term mortality risk associated with RIFLE-defined AKI among patients with severe blunt trauma enrolled in the Inflammation and the Host Response to Injury study.

Table 1-1. Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) classification

Class	GFR criteria	Urine output criteria
Risk	Serum creatinine × 1.5	< 0.5 ml/kg/hour × 6 hours
Injury	Serum creatinine × 2	< 0.5 ml/kg/hour × 12 hours
Failure	Serum creatinine × 3, or serum creatinine ≥ 4 mg/dl with an acute rise > 0.5 mg/dl	< 0.3 ml/kg/hour × 24 hours, or anuria × 12 hours
Loss	Complete loss of kidney function > 4 weeks	
End-stage kidney disease	Complete loss of kidney function > 3 months	
Renal recovery		
Complete recovery	Patient returns to baseline classification within RIFLE criteria	
Partial recovery	Persistent change in RIFLE classification but not persistent need for Renal Replacement Therapy	

Multiply by 88.4 to convert creatinine to µmol/l. Glomerular filtration rate (GFR) criteria are calculated as an increase of serum creatinine above the baseline serum creatinine level. In patients without a history of chronic kidney disease and unknown baseline serum creatinine, it is recommended calculating a baseline serum creatinine using the Modification of Diet in Renal Disease equation, assuming a GFR of 75 ml/min/1.73 m^2. AKI should be both abrupt (within 1–7 days) and sustained (more than 24 hours).[11]

Table 1-2. Values for estimated baseline creatinine using “Modification of diet in renal disease” equation (CrMDRD)

Age (years)	Black males (mg/dl)	Other males (mg/dl)	Black females (mg/dl)	Other females (mg/dl)
20–24	1.5	1.3	1.2	1.0
25–29	1.5	1.2	1.1	1.0
30–39	1.4	1.2	1.1	0.9
40–54	1.3	1.1	1.0	0.9
55–65	1.3	1.1	1.0	0.8
>65	1.2	1.0	0.9	0.8

Cr_{MDRD} is calculated by solving the abbreviated “Modification of diet in renal disease” (MDRD) equation for sCr assuming a glomerular filtration rate (GFR) of 75 ml/minute/1.73 m^2.Estimated glomerular filtration rate = 75 (ml/min per 1.73 m^2) = 186 × (serum creatinine [S_{Cr}])- 1.154 × (age) - 0.203 × (0.742 if female) × (1.210 if black) = exp(5.228 - 1.154 × ln [S_{Cr}]) – 0.203 × ln(age) - (0.299 if female) + (0.192 if black).[11]

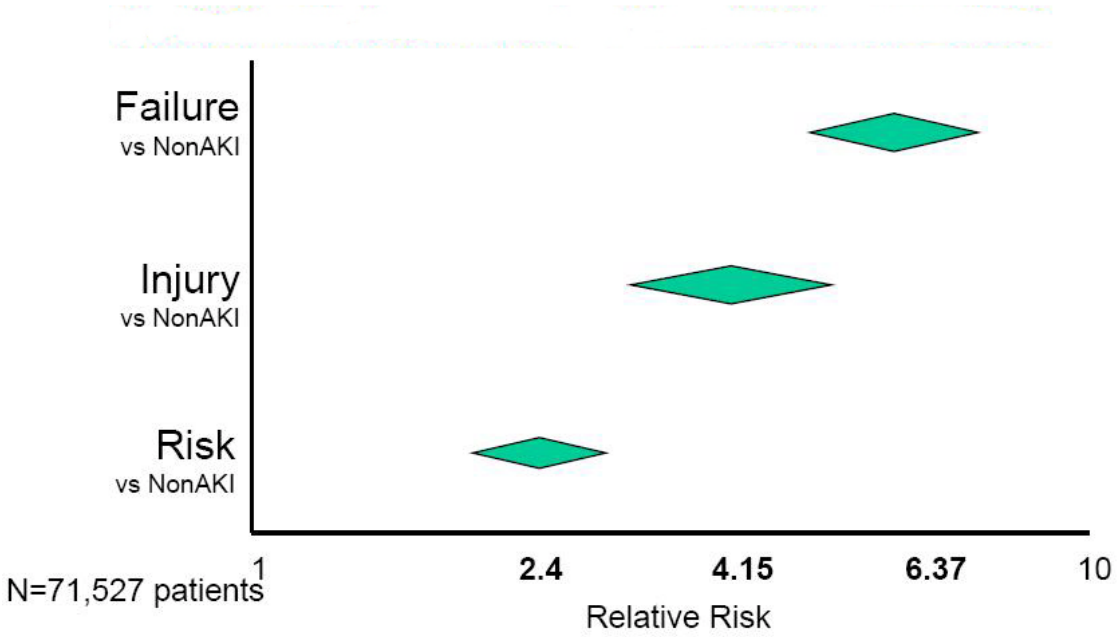

Figure 1-1. Stages of AKI defined by RIFLE criteria and associated mortality risk in the pooled analysis of 71 527 patients.[12]

CHAPTER 2
METHODS

This study is a secondary analysis of the TRDB and comprises a multicenter prospective cohort of adult severe blunt trauma patients with no previous history of kidney disease. The Steering Committee of the Inflammation and the Host Response *to Injury* research program and the Institutional Review Board of the University of Florida approved our use of the database, in accordance with the federal requirements for access to protected patient information.

Subjects and Data Collection

Beginning November 2003, the Inflammation and the Host Response to Injury research program enrolled patients with severe blunt trauma in eight participating Level I trauma centers (Table 2-1). We analyzed completed clinical data for patients older than 18 years (age range 18-90 years) who lived longer than 24 hours following injury and were enrolled between November 2003 and March 2008 (85 patients who died in the first 24 hours after injury were excluded). The analysis of infectious complications and AKI was performed in November 2010 and at that time the TRDB had accrued 1952 patients. Although patients with a history of renal disease and sCr >2 mg/dl were excluded from enrollment, we also excluded an additional nine patients who had sCr >1.5 mg/dl and reported history of chronic kidney disease, as documented in the TRDB. The cohort that was selected for genomic analysis included a subset of these patients whose age was limited to < 55 years and who lived longer then initial 24 hours after trauma.

The steering committee of the collaborative research program developed standard operating procedures for clinical management of the patients to minimize

variation across centers involved in the data collection.[18] As implemented, they were considered the standard of care for patient management and were mandated for all enrolled patients as well as for uniform routine care at each of the participating trauma centers. Trained nurse abstractors prospectively collected clinical data into TRDB, a web-based data collection platform adapted for this program.[19]

Outcomes and Covariate Definition

The Injury Severity Score (ISS) was used as a measure of anatomic injury severity. The ISS is an anatomical scoring system that provides an overall score for patients with multiple injuries. Each injury is assigned an Abbreviated Injury Scale (AIS) score and is allocated to one of six body regions (head, face, chest, abdomen, extremities (including pelvis), external). The Abbreviated Injury Scale (AIS) is an anatomical scoring system that ranks severity of injuries on a scale of 1 to 6, with 1 being minor, 5 severe and 6 an survivable injury. Only the highest AIS score in each body region is used. The three most severely injured body regions have their score squared and added together to produce the ISS score.[20] Clinical outcomes occurring within 28 days of injury were recorded. We used definitions of nosocomial infections and surgical site infections recommended by the Centers for Disease Control.[21] The Marshall multiple organ dysfunction (MOD) score ≥ 3 was used as a cut-off point for an organ failure (Table 2-2).[22] For each patient an Acute Physiology and Chronic Health Evaluation (APACHE II) score was calculated for the first 24 hours of injury.[23] In addition, whenever analyzing effect of AKI we modified APACHE II and MOD scores to exclude renal data (APACHE $II_{non\text{-}renal}$ and $MOD_{max\text{-}nonrenal}$) scores by subtracting renal components from the total scores.

Assessment of Acute Kidney Injury

AKI was defined by the RIFLE classification using the change in sCr during the first 28 days of hospitalization compared to baseline sCr (Tables 1-1 and 1-2).[11] For the baseline sCr we used the lower of two values: the lowest measured sCr in the first 24 hours after trauma (85%, 832/982 patients) or the estimated sCr (Cr_{MDRD}) (15%, 150/982 patients). Cr_{MDRD} was calculated by solving the abbreviated "Modification of diet in renal disease" (MDRD) equation for sCr assuming a glomerular filtration rate (GFR) of 75 ml/minute/1.73 m^2.[11]

Patients with AKI were stratified according to the severity determined by comparing the highest sCr with the baseline sCr. RIFLE-R corresponds to a 50% increase in sCr, RIFLE-I to a two-fold increase in sCr, and RIFLE-F to a three-fold increase in sCr. Renal outcome was evaluated by comparing the last recorded sCr to the baseline sCr. Complete renal recovery existed if the sCr returned to a level less than 50% above baseline sCr. Partial renal recovery existed for a persistent increase more than 50% above baseline sCr but no need for RRT. No renal recovery implied a need for RRT at the time of hospital discharge or death (Table 1-1).

Genomics Data Analysis

Microarray data from whole blood leukocytes for the initial 12 hours of injury were evaluated in a subset of the total trauma population. This subset differed from the total population in that the age distribution was 16 – 55 years. Microarray data from these patients were normalized using DNA Chip Analyzer 2007 (developed and maintained by Cheng Li Lab, Harvard School of Public Health). Only patients with complete data for the RIFLE classification and DNA quality score greater than or equal to 2 were included. Unsupervised analyses were conducted by filtering for probe sets with greater than 50%

coefficient of variation followed by hierarchical cluster analysis. BRB-ArrayTools (developed by Dr. Richard Simon and BRB-ArrayTools Development Team) was used to perform significance analysis of microarray (SAM^{TM}) comparisons between injured and healthy subjects and AKI vs. no AKI patients. Class prediction models were used defining an F test ($p<0.001$) to identify significant probe sets followed by Leave One Out Cross Validation (LOOCV) analysis using diagonal linear discriminate analysis, K nearest neighbors (for K=1 and 3), and nearest centroid prediction methods. All class comparisons and prediction models were carried out using 1000 permutations of the data set. Significance for SAM^{TM} analysis was set using a false discovery rate (FDR) of <0.001.

Statistical Analyses

Multivariate logistic models were used to assess factors associated with AKI and mortality during the hospitalization. Multiple risk factors (patient characteristics, anatomic and physiologic injury indicators) identified on the basis of prior studies of outcomes in the trauma and potential clinical and physiological significance (as determined by the practicing trauma surgeons and intensivists) were evaluated for univariate association with the primary outcome (two-tailed $P\leq0.20$) and then entered stepwise into multivariable logistic models, with assessment of the association between AKI groups and outcome in the presence of the significant covariates. Each variable with a significant association ($P<0.05$) and additional variables that were not significant but had potential clinical importance were included in the final full model. The goodness of fit of the logistic-regression model was assessed with the Hosmer–Lemeshow test and concordance indices reported as a measure of discriminatory capability of the models. Probit models were used to assess the estimated probability of any in-hospital

AKI with specific parameters of interest occurring within 24 hours of hospitalization. Missing parameters were considered missing at random (there were <10% missing values for the worst lactate levels in the first 24 hours while all other variables had < 1% missing values) and were categorized as a separate level for the purposes of the analytic models. Sensitivity analyses confirmed that the primary study results were consistent with and without inclusion of these cases. All statistical tests for group comparisons were two-tailed. We used correspondence analysis, an exploratory data analytic technique, to analyze multi-way tables and provide measure of correspondence between the rows and columns when appropriate. Statistical analyses were performed with SAS (version 9.2, Cary, N.C.).

Table 2-1. Glue Grant inclusion and exclusion criteria for Inflammation and the Host Response to Injury

Criteria	Description
Inclusion Criteria	
1.	Patient with blunt trauma without isolated head injury.
2.	Emergency department arrival <= 6 hours from time of injury.
3.	Blood transfusion within 12 hrs of injury.
4.	Base deficit >= 6 OR systolic blood pressure < 90 mmHg within 60 minutes of emergency department arrival.
5.	Fully or partially intact cervical spinal cord.
6.	AIS (Abbreviated Injury Scale) head (brain or cranium) $\leq$ 3 OR no AIS head.
Exclusion Criteria	
1.	Age < 16 OR age > 55 years.(the upper age limit was applicable for the genomic analysis only)
2.	Anticipated survival < 24 hours from injury.
3.	Anticipated survival < 28 days due to pre-existing medical condition.
4.	Inability to obtain first blood draw within first 12 hours after injury.
5.	Traumatic brain injury, i.e. GCS (Glasgow Coma Scale) less than or equal to 8 after ICU admission AND brain computerized tomography scan abnormality within first 12 hours after injury.
6.	Inability to obtain informed consent.
7.	Pre-existing, ongoing immunosuppression, - e.g. Transplant recipient.
8.	Pre-existing, ongoing immunosuppression - e.g. Chronic high dose corticosteroids (>20 mg/prednisone-equivalents/day).
9.	Pre-existing, ongoing immunosuppression - Oncolytic drug(s) therapy within the past 14 days.
10.	Pre-existing, ongoing immunosuppression - HIV positive AND CD4 count <200 cells/mm^3.
11.	Possible requirement for early immunosuppression - e.g. significant likelihood of requiring high dose corticosteroids (e.g. spinal cord injury).
12.	Significant pre-existing organ dysfunction - Lung: currently receiving home oxygen therapy, as documented in medical records.
13.	Significant pre-existing organ dysfunction - Heart: congestive heart failure, as documented in medical records.
14.	Significant pre-existing organ dysfunction - Renal: chronic renal failure (creatinine > 2 mg/dl).
15.	Significant pre-existing organ dysfunction - Liver: cirrhosis with portal hypertension or encephalopathy.

Table 2-2. Marshall score from the Inflammation and Host Response to Injury Glue Grant

Component	Measurement	Score				
		0	1	2	3	4
Repiratory	PaO2/FiO2	> 300	(225, 300)	(150, 225)	(75, 150)	≤ 75
Renal	Creatinine	< 1.2	(1.2 , 2.4)	(2.4, 4.0)	(4.0, 5.7)	≥ 5.7
Hepatic	Bilirubin	< 1.2	(1.2, 3.6)	(3.6, 7.2)	(7.2. 14.2)	≥ 14.2
Cardiovascular	PAR[†]	≤ 10	(10, 15)	(15, 20)	(20, 30)	> 30
Hematologic	Platelet count	> 120	(80, 120)	(50, 80)	(20, 50)	≤ 20
Neurologic	Glasgow Coma Score	15	13-14	10-12	7-9	≤6

[†] PAR (Pressure adjusted heart rate is computed as

$$PAR = heart\ rate\ x \left(\frac{CVP}{\frac{1}{3}\ sbp + \frac{2}{3}\ dbp} \right)$$

The classic Marshall score is the sum of the 6 component scores shown below. For the Inflammation and Host Response to Injury Glue Grant data analysis, the Marshall score is defined as the sum of 5 component scores with the neurologic component excluded. For the analysis of the data from the initial five years of the study, linearly interpolated component scores were computed. This resulted in a slight over-estimate for the renal, hepatic and cardiovascular scores and a slight under-estimate for the respiratory and hematologic scores.

CHAPTER 3
RESULTS

Incidence and Progression of Acute Kidney Injury

We analyzed data for 982 adult patients with severe blunt trauma and no previous history of kidney disease who lived longer than 24 hours following injury (85 patients who died in the first 24 hours after injury were excluded) (Tables 3-1, 3-2, and 3-3). This cohort included severely injured patients as defined by inclusion criteria (82% of patients had ISS score >=25, 80% had an episode of hypotension and 60% required > six units of blood transfusion in the first 24 hours of injury) (Table 3-1, 3-2 and 3-3). Over one-fourth of these patients developed AKI in the first 28 days after trauma (26%, 253/982) and two-thirds had only mild to moderately severe AKI (RIFLE-R and RIFLE-I) (Tables 3-1 and 3-2). The majority of the patients had the onset of AKI within the first two days of hospital admission (68%) and close to half of the patients progressed from RIFLE class R to RIFLE class I or class F (42%, 77/183). The time to progress from class R to class I was 2 days (interquartile range 2- 5 days) while time to progress to class F was 6 days (interquartile range 3- 10 days). Only 11% of AKI patients required RRT. Almost half of the patients with AKI failed to completely recover their kidney function in the first 28 days after trauma. Increasing severity of AKI was associated with less likelihood of renal recovery (Table 3-4).

Clinical Characteristics of Patients with Acute Kidney Injury

Neither the baseline host factors nor anatomic injury severity score were associated with the risk for AKI in a multiple logistic regression model that included a number of clinical parameters obtained during the first 24 hours of trauma (Table 3-5). In contrast, several indicators of physiologic injury severity including the lowest body

temperature, the highest lactate level, and the need for packed red blood cells (PRBC) and cryoprecipitate transfusion were independently associated with a higher risk for developing AKI (Table 3-5 and Figure 3-1). Interestingly, an absolute value of first measured sCr was not independently associated with the risk for AKI but rather the ratio between first measured sCr and estimated Cr_{MDRD} based on patient's age, gender and race was independently associated with the risk for developing AKI. Every 10% increase in the ratio between measured sCr on admission and estimated Cr_{MDRD} increased risk for developing AKI by 8%.

Acute Kidney Injury and Clinical Outcomes after Trauma

Patients with AKI were more severely ill as reflected in the higher MOD scores (Table 3-4). Organ dysfunction as defined by MOD score ≥ 3 was more likely to occur among AKI patients and the occurrence of organ dysfunction was proportional to the severity of kidney injury. Notably, none of the patients with RIFLE-R and RIFLE-I and only half of the patients with RIFLE-F had kidney dysfunction on the basis of the MOD score. Similarly, only 15% of all AKI patients would be classified as having posttraumatic acute renal failure using the American College of Surgeons Committee on Trauma definition (sCr above 3.5 mg/dl) and all of them were in the Rifle-F class. Even the American College of Surgeons National Surgical Quality Improvement project's (NSQIP) definition of acute renal dysfunction as sCr above 2 mg/dl does not identify 85% of patients with RIFLE-defined AKI (Table 3-4). Patients with AKI were more likely to develop both infectious and non-infectious complications. They required a longer ICU and hospital stay. The in-hospital mortality for patients with AKI was 30% in contrast to 5% for those with no AKI.

AKI was associated with a three-fold increase in the risk for hospital mortality in the multivariate logistic model. This model also included host factors, anatomic and physiologic injury indicators in the first 24 hours after trauma and severity scores. This increase in the risk for hospital mortality was proportional to the severity of AKI (Table 3-6). The least severe yet the most frequent AKI (RIFLE-R) was associated with a 2.5-fold increase in the risk for mortality even after adjustment for the host characteristics, anatomic and physiologic injury indicators, and severity scores (Table 3-6). The most severe AKI (RIFLE-F) was associated with a five-fold risk for dying in hospital. In addition to AKI, ISS and APACHE II scores on admission, use of vasopressors in the first 24 hours, and the highest MOD score in the first 28 days were independently associated with in-hospital mortality.

Acute Kidney Injury and Infectious Complications after Trauma

The analysis for infectious complications was performed in January 2011; at that time TRDB database had 1952 completed clinical cases. After excluding 213 patients who did not have sCr data beyond day 0, remaining cohort of 1793 patients was analyzed for the association between RIFLE-AKI and infectious complications. The prevalence of nosocomial infections (NCI) after trauma was 49%. The prevalence of nosocomial pneumonia, bloodstream infections (BSI) and central line-related bloodstream infections (CLBSI) was significantly higher among patients with AKI in proportion to AKI severity stages (Figure 3-2). Patients with AKI had 1.6 times the odds of having NCI compared to patients without AKI (Table 3-7). This relationship was proportional to the severity of AKI and ranged from 1.3 times the odds for least severe RIFLE-R to 2.7 times the odds for most severe RIFLE-F when compared to patients without AKI. Among NCI, the odds for pneumonia (1.55), bloodstream infections (2.06)

and intravenous catheter-related infections (1.96) were higher for AKI patients. On average, the onset of AKI preceded the onset of pneumonia and bloodstream infections by 5 and 6 days, respectively (Table 3-8). Interestingly, simple correspondence analysis map revealed a number of clusters: Patients with RIFLE-R were associated with isolated pneumonia episodes while patients with RIFLE-I and RIFLE-F were clustered with BSI and combined episodes of pneumonia and BSI. Since Dimension 1 accounted for 93.77% of the inertia of the map, the severity stage of AKI (RIFLE-I and RIFLE-F) were the most important determinants of this association (Figure 3-3).

In regard to causative pathogens for nosocomial pneumonias, *Staphylococcus aureus* was more common gram-positive pathogen among patients with AKI (Table 3-8). The most significant association, however, was for gram-negative bacteria and especially *Acinetobacter baumannii*: the prevalence of *Acinetobacter* pneumonia was three fold higher among patients with RIFLE-F as compared to patients with no AKI. The simple correspondence analysis map of this matrix revealed a number of clusters: Patients with RIFLE-R were associated with isolated *Staphylococcus aureus* pneumonia episodes while patients with RIFLE-I and RIFLE-F were clustered with *Acinetobacter* pneumonias or combined *Staphylococcus aureus* and *Acinetobacter* infections. Dimension 1 accounted for 64.45% of the inertia of the map and RIFLE-F (far right quadrant) was the most important determinant of the association. Dimension 2 accounted for 31.68% of the inertia of the map and combined *Staphylococcus aureus* and *Acinetobacter* pneumonias as well as isolated *Acinetobacter* pneumonias (Top quadrants) were the most important determinants of the association (Figure 3-4).

The gram-negative bloodstream infections with *Acinetobacter*, *Escherichia coli* and *Serratia marcescens* and also with *Candida* species were more likely to occur among AKI patients (Table 3-8). The simple correspondence analysis map of this matrix revealed a few interesting clusters: Patients with RIFLE-R were associated with coagulase-negative *Staphylococcus* BSI while patients with RIFLE-F were clustered with *Acinetobacter*, *Candida* and *Escherichia coli* BSIs. *Serratia* and *Klebsiella* BSIs clustered with RIFLE-I. Dimension 1 accounted for 65.79% of the inertia of the map and all three AKI stages were contributing to the association. Dimension 2 accounted for 22.21% of the inertia of the map with *Serratia*, *Klebsiella*, *Acinetobacter* and *Candida* pathogens being the most important determinants of the association (Figure 3-4).

Genomics Analysis

The TRDB contained microarray data for 173 patients sampled within 12 hours of traumatic injury along with data obtained from 24 healthy uninjured subjects. Of the 173 trauma patients, 158 met inclusion criteria with 125 subjects having no AKI and 33 with AKI (13 RIFLE-R, 9 RIFLE-I and 11 RIFLE-F). After microarray normalization and model based expression, a supervised analysis between the 173 trauma patients and 24 uninjured subjects incorporating a two-class comparison (Student's t-test, $P<0.001$) and Leave One Out Cross Validation^{TM} (LOOCV) identified 30,956 probe sets that were able to correctly classify the healthy subjects from the injured patients in greater than 98% of cases (Table 3-9). The results were verified using the SAM^{TM} algorithm (FDR<0.001), which identified 31,165 probe sets that distinguished the healthy subjects from the injured patients (Figure 3-5). The 31,165 probe sets identified by SAMTM analysis were then incorporated into the PAMTM algorithm, which correctly classified the healthy controls and the injured patients 100% of the time (data not shown). These results

indicate that a robust genomic signature is generated from whole blood leukocytes, which can readily discriminate the trauma population early after initial injury from healthy control subjects. Class comparison and prediction between the 125 patients with no AKI and all 33 patients with AKI, identified 230 probe sets with a 68% to 77% correct classification rate (Table 3-10). Similarly, a multiclass comparison and prediction between injured patients without AKI and those with RIFLE classes R, I, and F, identified 151 probe sets with a 51% to 77% correct classification rate (Table 3-11). When the 125 patients with no AKI were compared to the 11 patients in class RIFLE-F, 95 probe sets were identified that correctly classified the patients 85% to 91% of the time; however the positive predictive value for patients with RIFLE-F was only 0.20 while patients with no AKI carried a positive predictive value of 0.93 (Table 3-12). SAM™ analysis was used to verify the class comparison and prediction findings. However, analysis of patients with and without AKI, multiclass analysis between AKI and RIFLE classes, and injured patients with no AKI compared with RIFLE-F yielded no significant probe set differences. These findings suggest that although trauma patients with and without AKI may have different patterns of leukocyte gene expression, the genomic changes are modest and lack strong predictive properties. Such findings suggest that there do not appear to be strong genomic signatures associated with AKI in a severely injured cohort in which marked genomic changes are occurring after the injury.

Table 3-1. Comparison between epidemiological cohort (n=982) and genomic cohort (n=158)

	Epidemiological cohort	Range†	Genomic cohort	Range†	P Value††
Baseline host characteristics					
Age (years)(mean, 95% CI)	41 (41-44)	18-90	35 (33-37)	18-55	<0.001
Male, No. (%)	632 (64)		106 (67)		0.45
African-American ethnicity, No. (%)	72 (7)		10 (6)		0.63
BMI (kg/m^2,) (mean, 95% CI)	28.3 (27.8-28.7)	14.1-67.9	28.6 (27.6-29.7)	17.6-67.9	0.49
Anatomic injury indicators 0 to 24 hours					
Injury Severity Score, No. (%)					0.58
Mild injury (<16)	26 (3)		5 (3)		
Moderate injury (16-24)	145 (15)		25 (16)		
Severe injury (25-40)	565 (57)		91 (58)		
Massive injury (>40)	246 (25)		37 (23)		
Physiologic injury indicators 0 to 24 hours					
MAP<65 mmHg, No. (%)	787 (80)		123 (78)		0.55
Temperature < 34.5º C, No. (%)	321 (33)		51 (32)		0.81
Lowest Hct (%)(mean, 95% CI)	23.3 (22.9-23.7)	5.0-45.9	23.6 (22.7-24.5)	10.0-37.3	0.54
Apache II (no renal data) (mean, 95% CI)	28 (27-28)	6-47	27 (26-28)	10-37	0.28
Lactate ≥ 5 (mmol/l), No. (%)	444 (45)		71 (45)		1.00
Missing, No. (%)	92 (9)		11 (7)		
Base deficit ≤ -10 , No. (%)	497 (51)		77 (49)		0.64
Missing, No. (%)	5 (0.6)		1 (0.5)		
PO_2/FiO_2 ratio<200, No. (%)	638 (65)		110 (69)		0.33
Missing, No. (%)	62 (6)		6 (4)		

Table 3-1. Continued.

	Epidemiological cohort	Range†	Genomic cohort	Range†	P Value††
pH < 7.2 , No. (%)	412 (42)		66 (42)		1.00
Missing, No. (%)	6 (0.6)		1 (0.5)		
Blood glucose > 200 mg/dl, No. (%)	423 (43)		58 (37)		0.16
RBC transfusion > 6 U , No. (%)	492 (60)		92 (58)		0.63
Platelets transfusion, No. (%)	409 (42)		66 (42)		1.00
FFP transfusion, No. (%)	645 (66)		118 (71)		0.22
Cryoprecipitate transfusion, No. (%)	266 (27)		46 (29)		0.60
Severity of illness (first 28 days)					
MOD_{max} score (mean, 95% CI)	5.7 (5.5-5.9)	1-16	5.5 (5.1-5.9)	0-16	0.41
$MOD_{max\text{-}nonrenal}$ score††† (mean, 95% CI)	4.7 (4.5-4.8)	0-14	4.5 (4.2-4.9)	0-12	0.38
Complications (first 28 days)					
Non-infectious complications, No. (%)	449 (46)		81 (51)		0.24
Surgical site infections, No. (%)	158 (16)		27 (17)		0.75
Nosocomial infections, No. (%)	481 (49)		84 (53)		0.35
Ventilator-associated pneumonia, No. (%)	295 (30)		47 (28)		0.61
Renal outcomes (first 28 days)					
All AKI, No. (%)	253 (26)		33 (21)		0.18
RIFLE-R, No. (%)	106 (11)		13 (8)		0.25
RIFLE-I, No. (%)	79 (8)		9 (6)		0.63
RIFLE-F, No. (%)	68 (7)		11 (7)		1.00
Highest sCr in the first 28 days (mg/dl) (mean, 95% CI)	1.38 (1.32-1.44)	0.51-9.2	1.37 (1.18-1.55)	0.6-9.0	0.91

Table 3-1. Continued.

	Epidemiological cohort	Range†	Genomic cohort	Range†	P Value††
AKI duration (days) (median, IQR)	5 (2, 13)	1-28	7 (2, 13)		0.69
Renal replacement therapy, No. (%)	29 (3)		5 (14)		0.004
Renal recovery, No. (%)					
Complete recovery	128 (51)		20 (61)		0.28
Partial recovery	104 (41)		9 (28)		0.15
No recovery	21 (8)		4 (11)		0.56
Outcomes for whole hospital stay					
ICU length of stay (days) (median, IQR)	10 (5, 19)	0-142	9.5 (5, 18)		0.58
Hospital length of stay (days) (median, IQR)	19 (11, 31)	2-355	20.5 (12, 31)		0.71
Hospital mortality, No. (%)	119 (12)		8 (5)		0.009
Discharge to Home, No. (%)	292 (30)		49 (31)		0.79
Discharge to inpatient rehabilitation, No. (%)	275 (28)		35 (22)		0.12
Discharge to skilled nursing facility, No. (%)	252 (30)		56 (35)		0.21

Abbreviations: IQR, interquartile range; 95% CI, 95% confidence interval for the mean; MOD, the Marshall multiple organ dysfunction score. †Included minimum-maximum values for continuous variables only. ††Comparing epidemiologic and genomic cohort. †††Calculated by subtracting renal component from the total MOD score.

Table 3-2. Baseline host characteristics, anatomic and physiologic injury severity indicators in the first 24 hours after trauma for patients stratified by RIFLEmax class.

	No AKI N=729	AKI	P†	P††			
		All AKI patients N=253	RIFLE-R N=106	RIFLE-I N=79	RIFLE-F N=68		
Baseline host characteristics							
Age (years) (mean, 95% CI)	41 (40-42)	47 (45-50)	48 (44-52)	46 (42-50)	47 (20)	<0.001	0.79
Male, No. (%)	455 (62)	177 (70)	72 (68)	55 (70)	50 (74)	0.003	0.73
African-American ethnicity, No. (%)	51 (7)	21 (8)	10 (9)	6 (8)	5 (7)	0.49	0.85
BMI (kg/m_2) (mean, 95% CI)	27 (27-28)	29 (28, 30)	28 (27-30)	30 (29-32)	30 (28-32)	0.001	0.14
Baseline sCr (mg/dl) (mean, 95% CI)	0.79 (0.77-0.81)	0.81 (0.78-0.84)	0.78 (0.73-0.82)	0.84 (0.78-0.89)	0.84 (0.78-0.89)	0.20	0.16
Cr_{MDRD} used for baseline, No. (%)	80 (11)	70 (28)	21 (20)	28 (35)	21 (31)	<0.001	<0.001
Ratio between measured sCr (first 24 hrs) and Cr_{MDRD} (mean, 95% CI)	0.99 (0.97-1.01)	1.25 (1.19-1.32)	1.12 (1.05-1.18)	1.30 (1.19-1.41)	1.41 (1.23-1.59)	<0.001	<0.001
Anatomic injury indicators 0 to 24 hours							
Injury Severity Score No. (%)							
Mild injury (<16)	21 (3)	5 (2)	4 (4)	1 (1)	0 (0)	0.13	0.23
Moderate injury (16-24)	114 (16)	31 (12)	16 (15)	11 (14)	4 (6)		
Severe injury (25-40)	424 (58)	141 (56)	53 (50)	46 (58)	42 (62)		
Massive injury (>40)	170 (23)	76 (30)	33 (31)	21 (27)	22 (32)		
Glasgow Coma Scale ≤ 8							
Prior to ED admission	213 (31)	84 (33)	38 (36)	29 (37)	17 (25)	0.31	0.68
ED	367 (50)	138 (55)	31 (46)	61 (57)	46 (58)	0.25	0.22
Physiologic injury indicators 0 to 24 hours							
MAP < 65 mm Hg, No. (%)	565 (78)	222 (88)	88 (83)	71 (90)	63 (93)	<0.001	0.09
Temperature < 34.5º C, No. (%)	200 (27)	131 (52)	43 (41)	42 (53)	36 (53)	<0.001	0.14

Table 3-2. Continued

		AKI	P†	P††			
	No AKI N=729	All AKI patients N=253	RIFLE-R N=106	RIFLE-I N=79	RIFLE-F N=68		
Lowest Hct (%)(mean, 95% CI)	24 (23-24)	22 (21-22)	23 (22-24)	21 (20-23)	20 (19-22)	<0.001	0.07
INR (mean, 95% CI)	1.4 (1.34-1.44)	1.5 (0.7)	1.4 (1.3-1.5)	1.5 (1.3-1.6)	1.8 (1.4-2.1)	0.05	0.05
Apache II (no renal data) (mean, 95% CI)	27 (26-27)	31 (30-32)	29 (28-31)	32 (31-33)	32 (30-33)	<0.001	0.005
Lactate ≥ 5 mmol/l, No. (%)	288 (39)	156 (62)	55 (52)	58 (73)	43 (63)	<0.001	0.09
Base deficit ≤ -10, No. (%)	327 (45)	170 (67)	66 (62)	50 (63)	54 (79)	<0.001	0.24
PO_2/FiO_2 ratio<200, No. (%)	444 (61)	194 (77)	69 (65)	63 (80)	62 (91)	<0.001	0.005
pH < 7.2, No. (%)	269 (37)	143 (57)	49 (46)	49 (62)	45 (66)	<0.001	0.15
Blood glucose > 200 mg/dl, No. (%)	276 (38)	147 (58)	60 (57)	43 (54)	44 (65)	<0.001	0.79
RBC transfusion (U) (median, IQR)	5 (3, 9)	10 (5, 17)	6 (4, 13)	11 (5, 21)	12 (7, 25)	<0.001	<0.001
RBC transfusion > 6 U, No. (%)	322 (44)	170 (67)	58 (55)	56 (71)	56 (82)	<0.001	<0.001
Platelet transfusion, No. (%)	271 (37)	138 (55)	48 (45)	50 (63)	40 (59)	<0.001	0.36
FFP transfusion, No. (%)	448 (62)	197 (78)	75 (71)	64 (81)	58 (85)	<0.001	0.06
FFP transfusion (U) (median, IQR)	2 (0, 7)	6 (2, 14)	5 (0, 10)`	7 (2, 15)	9 (4, 18)	<0.001	0.01
Cryoprecipitate transfusion, No. (%)	157 (22)	109 (43)	35 (33)	40 (51)	34 (50)	<0.001	0.27
Crystalloids (L) (median, IQR)	13 (10, 17)	16 (10, 23)	14 (10.22)	17 (9, 26)	17 (11, 22)	<0.001	0.2
Use of vasopressors, No. (%)	107 (15)	84 (33)	21 (20)	29 (37)	34 (50)	<0.001	0.002

Abbreviations: IQR, interquartile range; CI, 95% confidence interval for the mean; .BMI, body mass index; MAP, mean arterial pressure; Hct, hematocrit; INR, international normalized ratio; PRBC, packed red blood cells; FFP, fresh frozen plasma; U, units. No acute kidney injury (AKI) is those patients without any occurrence of RIFLE criteria. †Comparing patients with AKI and patients without AKI. ††Comparing patients within the three $RIFLE_{max}$ subgroups

Table 3-3. Preexisting host factors and injury description for patients stratified by $RIFLE_{max}$ class

		AKI					
All cohort (N=982)	No AKI N=729	All AKI patients N=253	RIFLE-R N=106	RIFLE-I N=79	RIFLE-F N=68	P[†]	P[††]
Preexisting host factors[†††]							
Obesity (BMI>30)	203 (28)	94 (37)	30 (28)	37 (47)	27 (40)	0.001	0.03
Hypertension (n=154, 16%)	100 (14)	54 (21)	20 (19)	14 (18)	20 (29)	0.004	0.16
COPD (n=37, 4%)	22 (3)	15 (6)	4 (4)	6 (8)	5 (7)	0.06	0.46
PVD (n=13, 1%)	9 (1)	4 (2)	2 (2)	1 (1)	1 (1)	0.41	0.67
Heart disease (n=68, 7%)	42 (6)	26 (10)	12 (11)	5 (6)	9 (13)	0.02	0.34
Neurologic disease (n=77, 8%)	51 (7)	26 (10)	9 (8)	7 (9)	10 (15)	0.10	0.39
Diabetes mellitus (n=66, 7%)	39 (5)	27 (11)	11 (10)	4 (5)	12 (18)	0.005	0.05
Malignancy (n=38, 4%)	24 (3)	14 (5)	6 (6)	4 (5)	4 (6)	0.11	0.97
Liver disease (n=43, 4%)	22 (3)	21 (8)	4 (4)	8 (10)	9 (13)	0.004	0.07
Smoker (n=303, 31%)	241 (33)	62 (25)	28 (26)	18 (23)	16 (24)	0.01	0.83
Chronic alcohol abuse (n=146, 15%)	99 (14)	47 (19)	23 (22)	13 (16)	11 (16)	0.06	0.55
Admission medications							
Antiplatelet agents[††††] (n=81, 8%)	53 (7)	28 (11)	12 (11)	5 (6)	11 (16)	0.06	0.16
Coumadin (n=19, 2%)	11 (2)	8 (3)	3 (3)	4 (5)	1 (1)	0.10	0.45
Mechanism of injury							
Pedestrian vs Motor vehicle crash (n=132, 13%)	84 (12)	48 (19)	21 (20)	16 (20)	11 (17)	0.002	0.48
Time from injury to ED (hr) (median, IQR)	1.3 (0.8, 2.5)	1.1 (0.7, 2.1)	1.1 (0.7, 2.2)	1.1 (0.5, 1.8)	1.3 (0.7, 2.6)	0.06	0.39

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease;. IQR, interquartile range. Categorical variables are presented as number (percentages). No acute kidney injury (AKI) is those patients without any occurrence of RIFLE criteria. [†]Comparing patients with AKI and patients without AKI. [††]Comparing patients within the three $RIFLE_{max}$ subgroups. [†††]Heart disease (myocardial infarction, congestive heart

failure, atrial or ventricular tachyarrythmias); Neurologic disease (cerebrovascular disease, dementia, traumatic brain injury, Parkinsons's disease); Malignancy (history of malignancy or metastatic solid tumor); ††††Including NSAIDs, aspirin and all other antiplatelet agents.

Table 3-4. Severity of illness and clinical outcomes for patients stratified by RIFLEmax class.

		AKI					
	No AKIN=729	All AKI patients N=253	RIFLE-R N=106	RIFLE-I N=79	RIFLE-F N=68	P^1	P^2
Severity of illness (first 28 days)							
MOD_{max} score (mean, 95% CI)	4.9 (4.7-5.1)	8.1 (3.4)	6.0 (5.5-6.5)	8.6 (7.9-9.2)	10.7 (10.0-11.4)	<0.001	<0.001
$MOD_{max\text{-}nonrenal}$ score (mean, 95% CI) [3]	4. (3.9-4.2)	6.4 (2.9)	4.9 (4.4-5.4)	7.0 (6.4-7.7)	7.9 (7.3-8.6)	<0.001	<0.001
$MOD_{max\text{-}nonrenal}$ score ≥ 6, No. (%)	146 (20)	141 (56)	40 (38)	50 (63)	51 (75)	<0.001	<0.001
Day of MOD_{max} score	2 (0, 4)	3 (2, 8)	2 (0, 6)	3 (2, 8)	7 (3, 12)	<0.001	<0.001
Organ dysfunction/failure[4], No. (%)							
Respiratory	67 (9)	78 (31)	20 (19)	25 (32)	33 (49)	<0.001	<0.001
Cardiovascular	270 (37)	184 (73)	59 (56)	65 (82)	60 (88)	<0.001	<0.001
Hepatic	26 (4)	45 (18)	7 (7)	16 (20)	22 (32)	<0.001	<0.001
Hematology	5 (1)	18 (7)	0 (0)	7 (9)	11 (16)	<0.001	<0.001
Renal	0	33 (13)	0 (0)	0 (0)	33 (49)	<0.001	<0.001
ICU MV duration (days) (median, IQR)	6 (2,12)	14 (6, 23)	10 (3, 20)	15 (7, 25)	20 (7, 28)	<0.001	<0.001
Complications (first 28 days)							
Non-infectious complications, No. (%)	278 (38)	171 (68)	56 (53)	54 (68)	61 (90)	<0.001	<0.001
Surgical site infections, No. (%)	94 (13)	64 (25)	18 (17)	24 (30)	22 (32)	<0.001	0.03
Nosocomial infections, No. (%)	325 (45)	156 (62)	54 (51)	56 (71)	46 (68)	<0.001	0.01
Ventilator-associated pneumonia, No. (%)	189 (26)	106 (42)	35 (33)	39 (49)	32 (47)	<0.001	0.05
Renal outcomes (first 28 days)							
Highest sCr (mg/dl) (mean, 95% CI)	1.08 (1.06-1.10)	2.25 (2.00-2.43)	1.33 (1.25-1.42)	1.92 (1.79-2.00)	4.05 (3.61-4.49)	<0.001	<0.001

Table 3-4. Continued

		AKI					
	No AKI N=729	All AKI patients N=253	RIFLE-R N=106	RIFLE-I N=79	RIFLE-F N=68	P[1]	P[2]
NSQIP Definition Highest sCr > 2 mg/dl[5], No. (%)	0	115 (45)	19 (17)	35 (44)	61 (90)	<0.001	<0.001
ACSCT Definition Highest sCr > 3.5 mg/dl[6], No. (%)	0	39 (15)	0	0	39 (56)	<0.001	<0.001
AKI duration (days) (median, IQR)		5 (2, 13)	3 (2, 6)	6 (3, 11)	14 (6, 24)		<0.001
Renal replacement therapy, No. (%)		29 (11)	2 (2)	5 (6)	22 (32)		<0.001
Renal recovery, No. (%)							
Complete recovery		128 (51)	72 (68)	46 (58)	10 (15)		<0.001
Partial recovery		104 (41)	33 (31)	30 (38)	41 (60)		<0.001
No recovery		21 (8)	1 (1)	3 (4)	17 (25)		<0.001
Outcomes for whole hospital stay							
ICU LOS (days) (median, IQR)	9 (4, 16)	18 (7, 27)	15 (5, 23)	20 (9, 30)	22 (8, 37)	<0.001	0.003
Hospital LOS (days) (median, IQR)	18 (11, 28)	24 (10, 38)	23 (11, 31)	27 (14, 41)	24 (9, 50)	<0.001	0.14
ICU Mortality, No. (%)	37 (5)	71 (28)	16 (15)	23 (29)	32 (47)	<0.001	<0.001
Hospital mortality, No. (%)	39 (5)	80 (32)	20 (19)	25 (32)	35 (51)	<0.001	<0.001
Discharge to Home, No. (%)	255 (35)	37 (15)	24 (23)	12 (15)	1 (1)	<0.001	<0.001
Discharge to inpatient rehabilitation, No. (%)	219 (30)	57 (23)	23 (22)	16 (20)	18 (26)	<0.001	<0.001
Discharge to skilled nursing facility, No. (%)	182 (25)	69 (27)	34 (32)	22 (28)	13 (19)	<0.001	<0.001

Abbreviations: IQR, interquartile range; 95% CI, 95% confidence interval for the mean; MOD, the Marshall multiple organ dysfunction score; ICU, Intensive care unit; MV, mechanical ventilation; sCr, serum creatinine; LOS length of stay. [1] Comparing patients with AKI and patients without AKI. [2] Comparing patients within the three $RIFLE_{max}$ subgroups. [3] Calculated by subtracting renal component from the total MOD score. [4]MOD score ≥ 3 was used as a cut-off point for an organ dysfunction/failure. [5]The American College of Surgeons Committee on Trauma (ACSCT) defines acute renal failure

after trauma as sCr above 3.5 mg/dl. [6]The American College of Surgeons National Surgical Quality Improvement project (NSQIP) defines acute renal dysfunction in surgical patients as sCr above 2 mg/dl.

Table 3-5. Association between baseline host factors and indicators of anatomic and physiologic injury obtained in the first 24 hours after trauma with the occurrence of acute kidney injury.

Patient Characteristics	Occurrence of AKI (all severity levels)	
	OR (95% CI)	P
Host factors		
Obesity (per kg/m$^{2)}$)	1.02 (0.99, 1.05)	0.16
Hypertension (Reference none)	1.38 (0.80, 2.40)	0.25
Heart disease (Reference none)	1.07 (0.48, 2.37)	0.88
Diabetes mellitus (Reference none)	1.49 (0.69, 3.26)	0.29
Smoking (Reference none)	0.83 (0.56, 1.24)	0.36
Use of antiplatelets/anticoagulation drugs (Reference none)	1.00 (0.49, 2.07)	0.99
Anatomic injury indicators in the first 24 hours		
Injury severity Score (per unit change)	0.99 (0.98, 1.00)	0.29
Physiologic injury indicators in the first 24 hours		
Ratio between measured sCr (first 24 hours) and Cr_{MDRD} (per 1 unit change=100% increase)	2.24 (1.05, 4.78)	0.03
Lowest temperature (per degree of Celsius)	0.77 (0.66, 0.89)	<0.001
Highest lactate (per mmol/l)	1.08 (1.01, 1.15)	0.02
Lowest hematocrit (per percent change)	0.97 (0.93, 1.01)	0.10
RBC transfusion (per unit log transformed)	1.60 (1.12, 2.27)	0.01
Platelets transfusion (Reference none)	0.59 (0.36, 0.96)	0.03
Cryoprecipitate transfusion (Reference none)	1.80 (1.13, 2.86)	0.01
Highest heart rate (per beats/min)	1.00 (0.99, 1.01)	0.71
Lowest mean arterial pressure (per mmHg)	1.00 (0.99, 1.01)	0.87
Highest serum sodium (per mEq/l)	1.01 (0.99, 1.06)	0.42
INR (per unit)	0.94 (0.76, 1.15)	0.49
Worst base deficit (per mEq/l)	0.97 (0.92, 1.00)	0.24
PO_2/FiO_2 ratio<200 (per unit change)	1.00 (1.00, 1.01)	0.39
Highest blood glucose (per mg/dl)	1.00 (1.00, 1.01)	0.64
Use of insulin (Reference none)	0.95 (0.64, 1.40)	0.72
FFP transfusion (Reference none)	0.93 (0.55, 1.59)	0.92
Crystalloids infusion (per liter)	1.00 (1.00, 1.01)	0.07
Colloids use (Reference none)	1.19 (0.78, 1.79)	0.41
Use of inotrope (Reference none)	1.25 (0.59, 2.67)	0.72
Use of vasopressors (Reference none)	1.40 (0.89, 2.20)	0.12

Age, sex and race were excluded from the model as they are already included in the calculation of the ratio of the measured sCr in the first 24 hours and Cr_{MDRD}. Components of Apache II (no renal data) score were included in the model as the score itself was not an important predictor in the model. The odds ratios were calculated with logistic regression analysis (Methods). Abbreviations: CI - confidence interval; OR- Odds ratio; Cr_{MDRD}, estimated serum creatinine for patient age, gender and race (methods); RBC, red blood cells, INR, international normalized ratio; FFP, fresh frozen plasma.

Table 3-6. Association between acute kidney injury and hospital mortality.

Patient Characteristics	Hospital mortality C=0.89, P<0.001 OR (95% CI)	P	Hospital mortality C=0.89, P<0.001 OR (95% CI)	P
Acute kidney injury (Reference no AKI)	3.05 (1.73, 5.40)	<0.001		
RIFLE Risk (Reference no AKI)			2.57 (1.19, 5.50)	0.001
RIFLE Injury (Reference no AKI)			2.67 (1.23, 5.83)	
RIFLE Failure (Reference no AKI)			4.55 (2.00, 10.36)	
Host factors				
Obesity (per kg/m$^{2)}$)	0.97 (0.93, 1.01)	0.18	0.97 (0.93, 1.01)	0.18
Hypertension (Reference none)	1.22 (0.58, 2.55)	0.61	1.19 (0.57, 2.50)	0.65
Heart disease (Reference none)	1.46 (0.49, 4.36)	0.49	1.42 (0.48, 4.22)	0.53
Diabetes mellitus (Reference none)	0.62 (0.20, 1.89)	0.41	0.55 (0.18, 1.71)	0.29
Smoking (Reference none)	0.52 (0.27, 0.99)	0.05	0.51 (0.26, 0.99)	0.05
Use of antiplatelets/ anticoagulation drugs (Reference none)	1.48 (0.55, 3.97)	0.45	1.48 (0.55, 3.97)	0.43
Physiologic injury indicators in the first 24 hours				
Highest lactate (per mmol/l)	1.05 (0.96, 1.14)	0.29	1.05 (0.96, 1.14)	0.29
Worst base deficit (per mEq/l)	1.01 (0.95, 1.08)	0.78	1.01 (0.95, 1.08)	0.70
PO_2/FiO_2 ratio<200 (per unit change)	1.00 (1.00, 1.01)	0.45	1.00 (1.00, 1.01)	0.36
Highest blood glucose (per mg/dl)	1.00 (1.00, 1.01)	0.25	1.00 (1.00, 1.01)	0.27
RBC transfusion (per unit)	1.01 (0.98, 1.05)	0.46	1.01 (0.98, 1.05)	0.54
Platelets transfusion (Reference none)	0.55 (0.28, 1.08)	0.08	0.56 (0.28, 1.10)	0.09
Cryoprecipitate transfusion (Reference none)	1.21 (0.63, 2.33)	0.56	1.22 (0.64, 2.35)	0.55
FFP transfusion (per unit)	1.00 (1.00, 1.04)	0.97	1.00 (0.96, 1.04)	0.96
Crystalloids infusion (per liter)	1.00 (1.00, 1.00)	0.23	1.00 (1.00, 1.00)	0.29
Colloids use (Reference none)	0.90 (0.49, 1.66)	0.72	0.91 (0.50, 1.67)	0.76
Use of vasopressors (Reference none)	2.84 (1.60, 5.06)	<0.001	2.75 (1.54, 4.92)	<0.001
Severity Scores				
Injury severity score (admission) (per unit change)	1.02 (1.00, 1.05)	0.02	1.03 (1.01, 1.05)	0.02
APACHE II (without renal component, first 24 hours)(per unit)	1.06 (1.00, 1.12)	0.05	1.07 (1.01, 1.13)	0.03
Maximum MOD score (without renal component, first 28 days) (per unit)	1.50 (1.32, 1.71)	<0.01	1.48 (1.29, 1.69)	<0.001

Age, sex and race were excluded from the model as they are already included in the calculation of Cr_{MDRD} and RIFLE categories. Age is also included in the calculation of APACHE score. APACHE II and MOD scores were calculated without renal components to avoid correlation with AKI. The odds ratios were calculated with logistic regression analysis. Abbreviations: CI - confidence interval; OR- Odds ratio; RBC, red blood cells; FFP, fresh frozen plasma; MOD, multiple organ dysfunction.

Table 3-7. Prevalence of nosocomial infections stratified by the occurrence of RIFLE-AKI

	All patients[†] (n=1739)	AKI (n=712)	No AKI (n=1027)	P[††]	OR (95% CI)
Nosocomial infections (all), n (%)	840 (49)	156 (62)	325 (45)	<0.001	1.57 (1.29, 1.9)
Pneumonia, n (%)	553 (32)	267 (38)	286 (28)	<0.001	1.55 (1.27, 1.91)
Bloodstream infections, n (%)	236 (15)	133 (19)	103 (10)	<0.001	2.06 (1.56, 2.72)
Catheter-related infections, n (%)	49 (3)	28 (4)	21 (2)	0.02	1.96 (1.1, 3.48)
Urinary tract infection (UTI), n (%)	286 (17)	136 (19)	150 (15)	0.01	1.38 (1.07, 1.78)
Meningitis, n (%)	12 (1)	3 (0)	9 (1)	0.45	1.74 (0.41, 7.32)
Pseudomembranous colitis, n (%)	43 (2)	17 (2)	26 (3)	0.85	0.94 (0.51, 1.75)

[†]Comparing patients with AKI to patients without AKI.
[††]213 patients did not have data on daily sCr so AKI-Rifle was not calculated.
Abbreviations: CI - confidence interval; OR- Odds ratio

Table 3-8. Characteristics of nosocomial pneumonias and bloodstream infections for patients stratified by RIFLEmax class.

		RIFLE-AKI					
	No AKI N=286[1]	All AKI patients N=267	RIFLE-R N=106	RIFLE-I N=79	RIFLE-F N=68	P[†]	P[††]
Pneumonia onset (days since injury) (median, 25th- 75th)	6 (4, 9)	7 (4, 10)	6 (4, 11)	7 (4, 9)	7 (5, 10)	0.21	0.65
Pneumonia onset (days since AKI onset) (median, 25th- 75th)		5 (2, 8)	5 (3, 9)	4 (1, 7)	5 (2, 7)		0.25
Bloodstream infection onset (days since injury) (median, 25th- 75th)		7 (5, 13)	6 (4, 13)	8 (6, 10)	8 (5, 14)		0.32
Bloodstream infection onset (days since AKI onset) (median, 25th- 75th)	7 (4, 12)	6 (3, 11)	5 (2, 12)	6 (3, 8)	6 (3, 11)	0.16	0.43
Causative Microorganism for Pneumonia[††]							
Staphylococcus aureus, No. (%)	76 (27)	83 (31)	53 (35)	23 (40)	7 (12)	0.24	0.002
Pseudomonas aeruginosa, No. (%)	38 (13)	39 (15)	17 (11)	7 (12)	15 (26)	0.65	0.04
Acinetobacter baumannii, No. (%)	24 (8)	49 (18)	21 (14)	11 (19)	17 (30)	<0.001	<0.001
Escherichia coli, No. (%)	13 (5)	22 (8)	17 (11)	2 (4)	3 (5)	0.07	0.04
Serratia marcescens, No. (%)	16 (6)	8 (3)	2 (1)	1 (2)	5 (9)	0.13	0.04
Causative Microorganism for Pneumonia							
Staphylococcus aureus, No. (%)	24 (23)	23 (17)	12 (23)	7 (19)	4 (9)	0.25	0.26
Coagulase-negative *Staphylococcus*, No. (%)	21 (20)	22 (17)	12 (23)	4 (11)	6 (14)	0.45	0.41
Acinetobacter baumannii, No. (%)	8 (8)	25 (19)	9 (17)	6 (16)	10 (23)	0.01	0.07
Escherichia coli, No. (%)	1 (1)	11 (8)	5 (9)	2 (5)	4 (9)	0.01	0.06
Serratia marcescens, No. (%)	4 (4)	9 (7)	3 (6)	4 (11)	2 (5)	0.33	0.46
Gram-negative organisms (NOS), No. (%)	1 (1)	8 (6)	2 (4)	3 (8)	3 (7)	0.04	0.15
Candida, No. (%)	3 (3)	13 (10)	5 (9)	2 (5)	6 (14)	0.03	0.08

[†]All percentages are calculated as proportions of patients with pneumonia episodes only, not the all cohort. [††] Data shown only for microorganisms with different distribution by AKI-RIFLE groups.

Table 3-9. Supervised genomic analysis between trauma patients and control group (uninjured subjects).

	Diagonal linear discriminant analysis	1-nearest neighbor	3-nearest neighbors	Nearest centroid
Mean percent of correct classification	98	100	99	98
Positive predictive value healthy control (n=24)	0.89	1.00	0.96	0.89
Positive predictive value trauma (n=158)	1.00	1.00	1.00	1.00

Analysis incorporated a two-class comparison (Student's t-test, $P<0.001$) and LOOCV (1000 permutations). 30,956 significant probe sets.

Table 3-10. Class comparison and prediction between patients with no AKI and patients with AKI. Identified were 230 probe sets with a 68% to 77% correct classification rate.

	Diagonal linear discriminant analysis	1-nearest neighbor	3-nearest neighbors	Nearest centroid
Mean percent of correct classification	72	71	77	68
Positive predictive value no AKI (n=125)	0.85	0.80	0.81	0.84
Positive predictive value AKI (n=33)	0.36	0.24	0.39	0.32

Table 3-11. Multi-class comparison and prediction between patients with no AKI vs. patients with AKI, all stages (RIFLE-R, I, and F)

	Diagonal linear discriminant analysis	1-nearest neighbor	3-nearest neighbors	Nearest centroid
Mean percent of correct classification	59	68	77	51
Positive predictive value no AKI (n=125)	0.83	0.82	0.78	0.84
Positive predictive value RIFLE-R (n=13)	0.05	0.15	0.00	0.05
Positive predictive value RIFLE-I (n=9)	0.00	0.00	0.00	0.00
Positive predictive value RIFLE-F (n=11)	0.15	0.07	0.00	0.06

F-test p<0.001. 158 significant probe sets. LOOCV, 1000 permutations

Table 3-12. Class comparison and prediction between patients with no AKI vs. patients with RIFLE-F AKI only

	Diagonal linear discriminant analysis	1-nearest neighbor	3-nearest neighbors	Nearest centroid
Mean percent of correct classification	85	91	91	81
Positive predictive value no AKI (n=125)	0.93	0.92	0.92	0.94
Positive predictive value RIFLE-F (n=11)	0.20	0.00	0.00	0.17

F-test p<0.001. 95 significant probe sets. LOOCV, 1000 permutations.

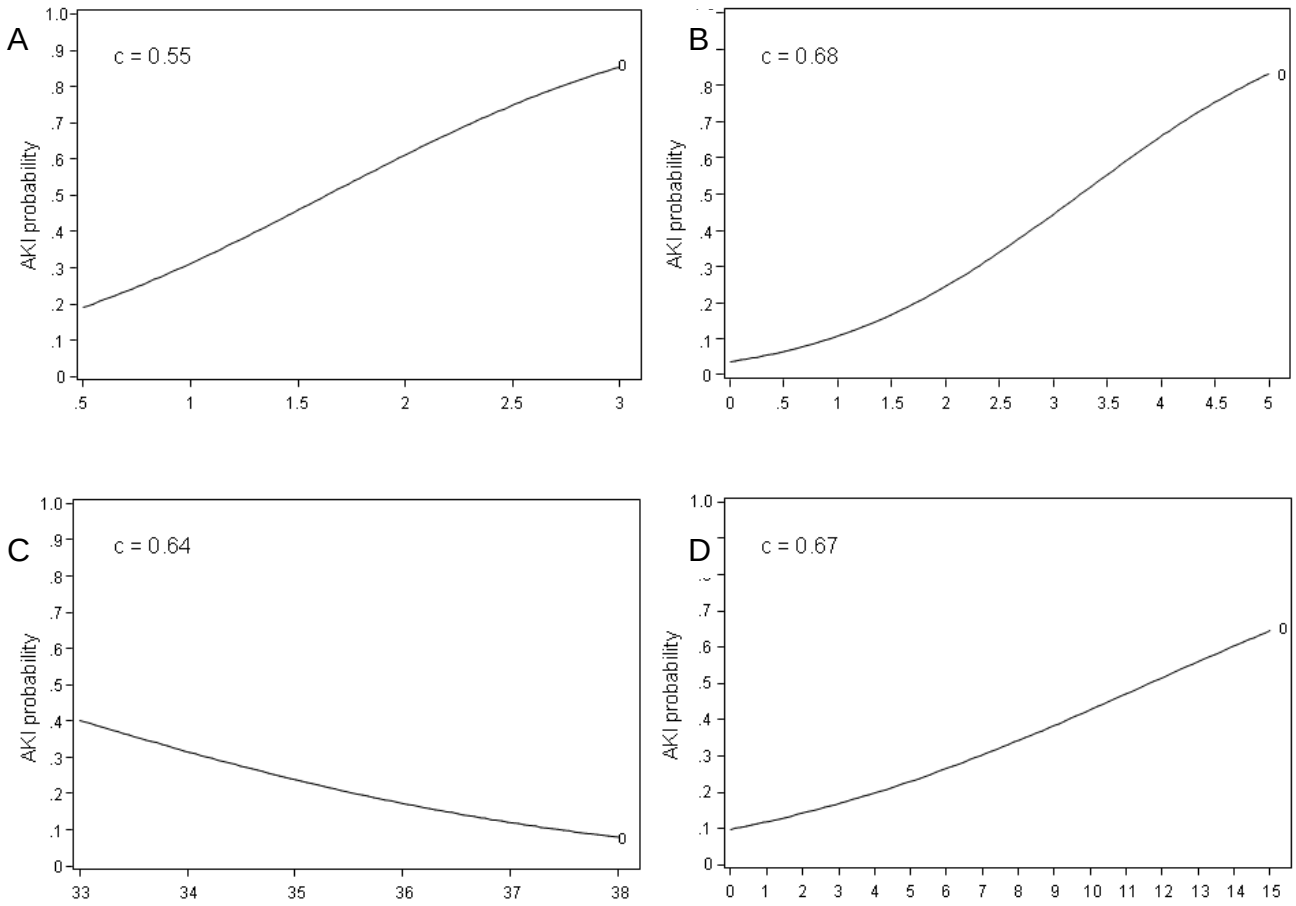

Figure 3-1. Probability curves for continuous variables associated with the occurrence of acute kidney injury (AKI). A) Ratio between measured serum creatinine in the first 24 hours and Crmord. B) Red blood cells transfusion in the first 24 hours (log transformation of number of units). C) Lowest temperature (in °C in the first 24 hours. D) Worst plasma lactate level (mmol/l) in the first 24 hours.

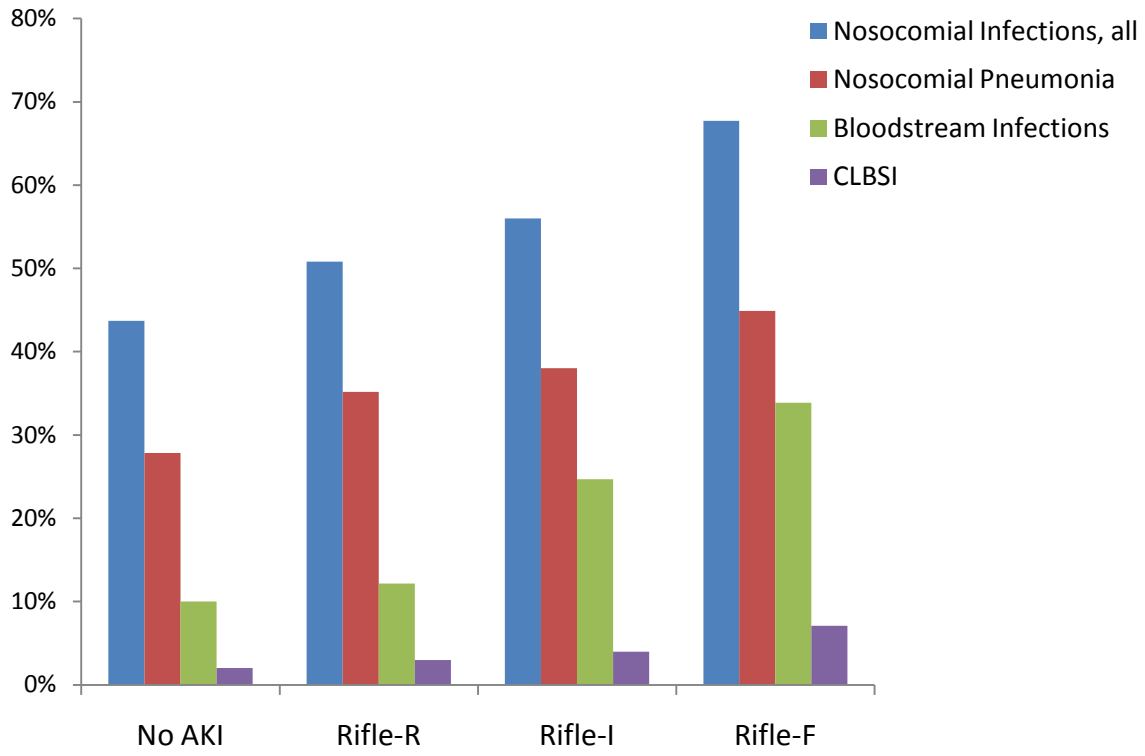

Figure 3-2. Most common nosocomial infections (NCI) stratified by severity stages of RIFLE-AKI. P <0.001 when comparing each group for all NCIs, nosocomial pneumonia and bloodstream infections. P=0.009 when comparing groups for central line-related bloodstream infections (CLBSI).

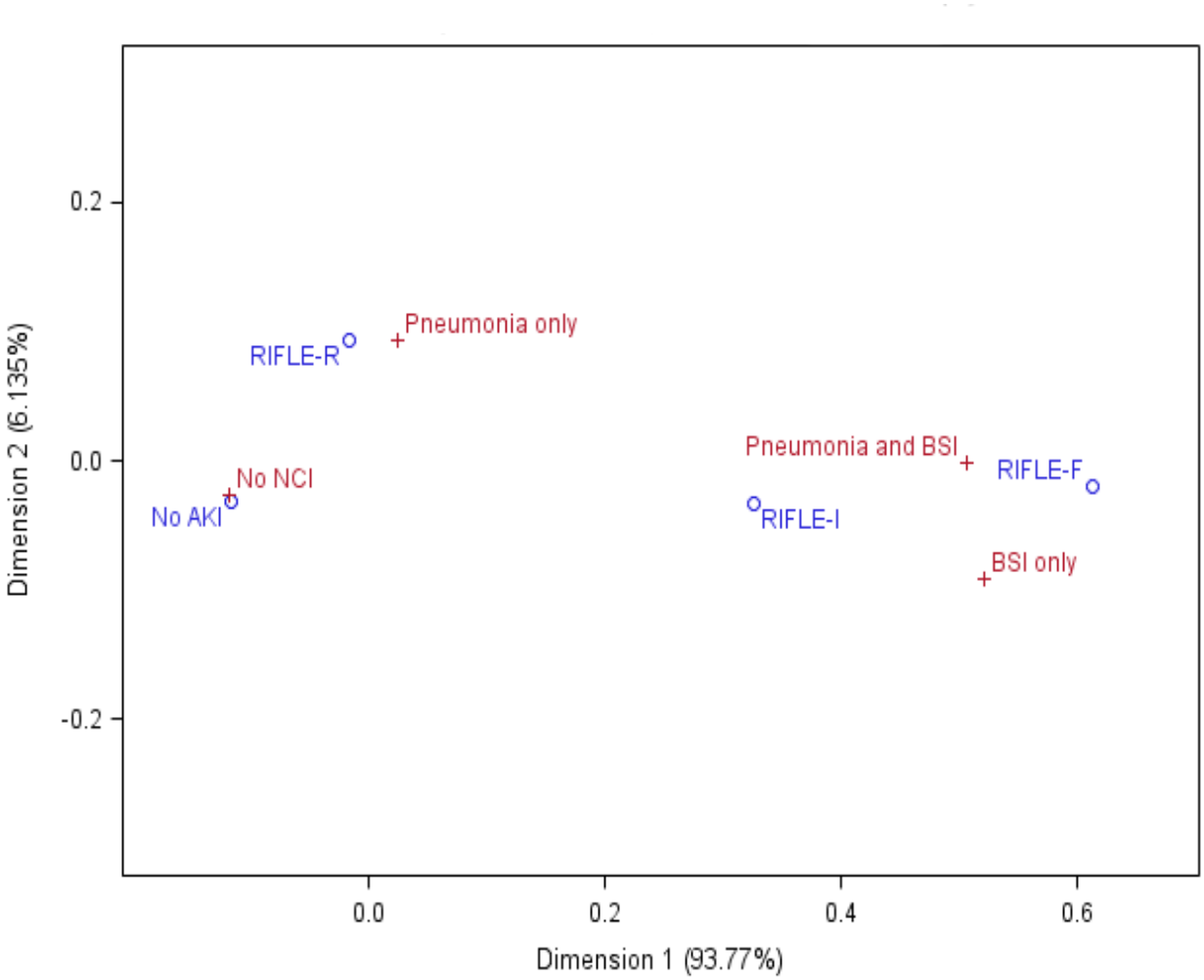

Figure 3-3. Correspondence analysis of Rifle-AKI stages and major types of nosocomial infections, nosocomial pneumonia and bloodstream infections. The columns represent AKI severity stages while the rows represent type of NCI.

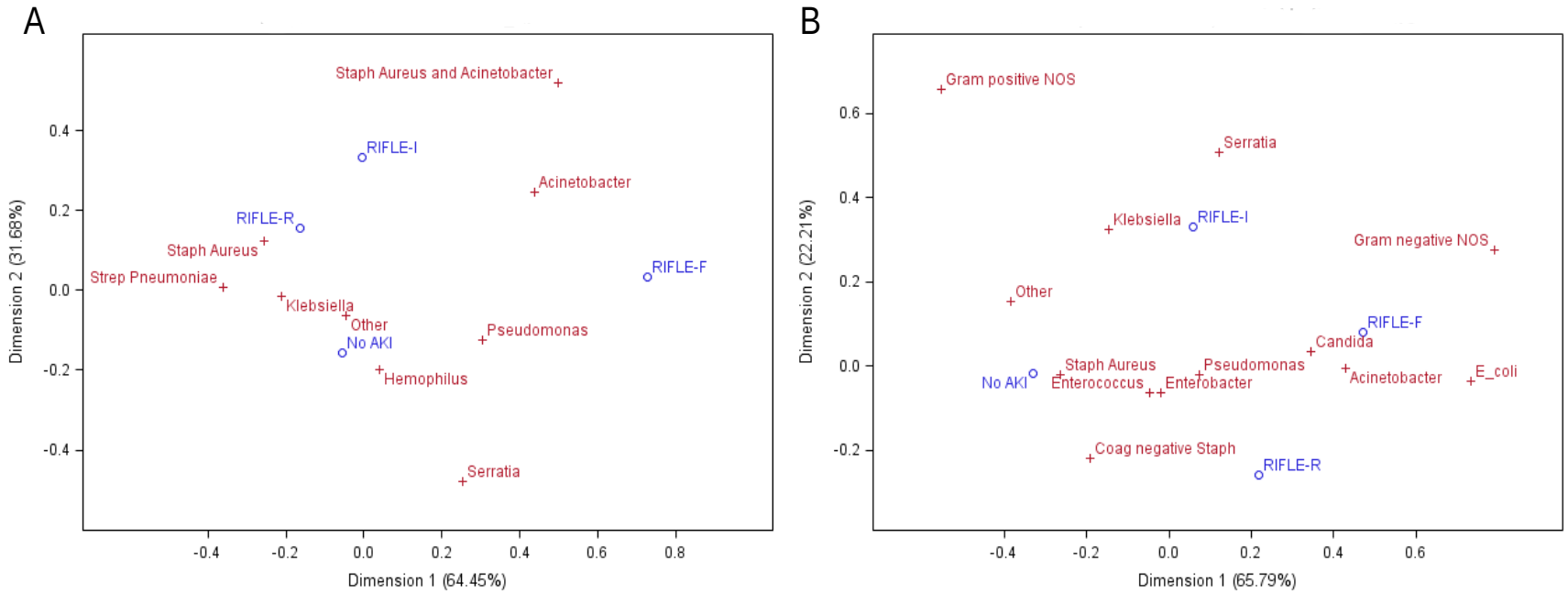

Figure 3-4. Correspondence analysis of Rifle-AKI stages and major pathogens for A) nosocomial pneumonia, and B) bloodstream infections. The columns represent AKI severity stages while the rows represent different types of pathogens.

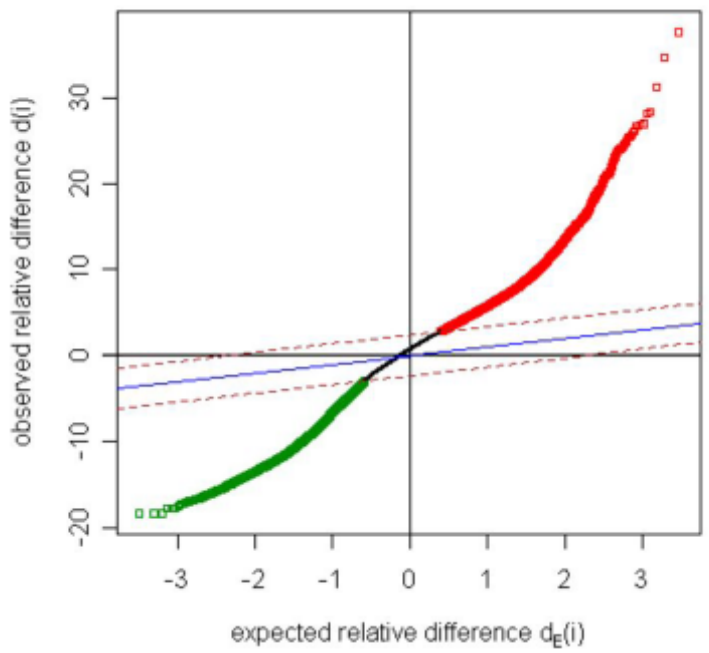

Figure 3-5. SAM plot showing 31,165 significant probe sets. Class comparison, SAM™, FDR>0.001, n-158 trauma vs. n=24 control microarrays.

CHAPTER 4
DISCUSSION

In a multi-center prospective cohort study of trauma patients with no previous kidney disease, AKI was a common complication associated with an independent risk of hospital death. Close to one fourth of all trauma patients developed AKI and two thirds of them had only mild to moderately severe AKI. Even patients with the least severe AKI had a 2.5-fold increase in adjusted risk for death compared to patients without AKI. This risk was independent of other indicators of anatomic and physiologic injury severity, and other organ dysfunction. Although the likelihood of developing AKI was associated with changes in several clinical parameters in the first 24 hours after trauma, no such association was observed with the initial genomic characteristics of patients with AKI.

Although the adverse effect of all stages of severity of AKI on in-hospital mortality is increasingly recognized,[9] few studies have examined the impact of less severe AKI among trauma patients.[3-5,7,8,24-26] The American College of Surgeons Committee on Trauma defines acute renal failure after trauma as sCr above 3.5 mg/dl, but only 15% of the AKI patients in our study had a sCr greater than 3 mg/dl. The average highest sCr among patients with mild AKI was 1.33 mg/dl, a value that often doesn't attract clinical attention in a population of younger trauma patients.[6] At the same time, none of the patients with mild and moderate AKI had a renal Marshall score greater or equal to 4, and consequently would not be classified as having kidney dysfunction by using this traditional scoring system.[22] Hence the importance of small changes in sCr early after trauma, indicative of less severe AKI, is likely to be under appreciated and adequate follow up for these patients may not occur in a timely manner. On the other hand, early diagnosis of AKI may help to identify high-risk patients who would benefit from

implementation of goal-directed resuscitation therapy, a strategy proven to work for patients with severe sepsis.[27]

Our findings reiterate the importance of relative changes in sCr rather than absolute sCr value in determining the risk for the development of AKI because no single sCr value corresponds to a given GFR across all patients. Instead, the change in sCr compared to baseline determines risk for AKI.[11] To estimate baseline renal function when sCr is unknown, RIFLE advocates use of estimated Cr_{MDRD} for the GFR of 75 ml/min per 1.73, a lower end of the normal range for healthy individuals.[28] This relative increase in first measured sCr compared to estimated Cr_{MDRD} was an independent risk factor for the development of AKI in a multivariate model where every 10% increase in measured sCr increases the risk for AKI by 8%. Hence in clinical practice an assessment of the relative increase between the first measured sCr and estimated Cr_{MDRD} may offer a valuable prognostic tool for the risk of AKI.

We demonstrated that less severe AKI was not only common among trauma patients but also associated with adverse clinical outcomes. Even mild AKI was associated with a 2.5-fold increase in the risk of dying as calculated in a multivariate regression model that included baseline clinical characteristics, indicators of anatomic and physiologic injury severity in the first 24 hours, the severity of other organ dysfunction and details of early resuscitation. All of these parameters carry clinical significance and the results are easily generalized for physicians caring for trauma patients. Although many of the covariates have been previously shown to be associated with in-hospital mortality[29-31] the association of each stage of AKI with increased in-hospital mortality is demonstrated for the first time in this study. Future studies should

focus on identifying patients at the highest risk for death even earlier, preferably within the first 12 to 24 hours after trauma.

The failure to identify any significant differences in blood leukocyte expression between patients with and without AKI is not surprising. Compared to healthy controls, trauma induced a genome-wide reprioritization of leukocyte gene expression, with greater than 60% of the leukocyte transcriptome changing within the first 12 hours. These changes were comparable to or greater than the changes seen after administration of microbial products to healthy volunteers.[32] We found only modest differences in genome-wide expression in the trauma patients who experienced AKI, regardless of the RIFLE score. This lack of difference may reflect the overall genomic response to the severity of the traumatic injury, rather than as a predictor for the differential physiological responses leading to AKI.

Acute kidney injury should no longer be viewed as an indicator of overall severity of illness but instead the injured kidney can exhibit independent effects on other organs, including the lungs.[33-35] The kidneys receive a higher blood flow per unit mass than other organs but the fraction of extracted oxygen is low due to the presence of abundant diffusional arterial-to-venous (AV) shunting in the cortex and medulla.[36] This AV shunting accounts for up to 50% of the oxygen removal from arterial blood before the glomerular capillaries, rendering the kidney very sensitive to conditions of hypoperfusion.[36] During experimental hemorrhagic shock, the oxygenation status in kidneys may be impaired in spite of the preserved blood flow.[37] At the same time hypoxia may limit renal use of lactate for anaerobic metabolism.[38] The oxygen supply to the renal tissue may become impaired even earlier during acute normovolemic

hemodilution, such as during resuscitation with large quantities of crystalloid solutions after trauma.[39] Once initiated, AKI incites a cascade of inflammatory processes both locally and systemically.[40] Because of this susceptibility for hypoxia and early development of kidney injury, the use of more sensitive markers of kidney injury after trauma may be a useful tool for identifying patients at risk for AKI as well as other organ dysfunctions and dying.

Our study has several limitations. This is a retrospective analysis of prospectively collected data from which causal inference cannot be derived and which is subject to bias from unmeasured factors. Although we attempted to control for selection bias with multivariate statistical method and risk adjustment, we could not completely eliminate the potential for residual confounding. Second, we did not have access to information related to survival after hospital discharge; therefore, our risk estimates for discharged patients might represent the lower limit of the true risk. Finally, our analysis addressed the relationship between all-cause sCr increase and subsequent adverse events. The etiology of AKI after trauma is usually multifactorial and the strong association of even mild AKI with hospital mortality was demonstrated regardless of the etiology of AKI.[9] No conclusive data exist to demonstrate that two traditional etiological categories of AKI, prerenal azotemia and acute tubular necrosis, have meaningful prognostic differences, or, despite common clinical practice, differing rates of response to therapy.[41] A recent report from the Acute Kidney Injury Network has favored the concept of volume-responsive AKI, and they have suggested a research agenda to address the clinical significance of this type of AKI in future studies.[42]

In conclusion, in a large multi-center prospective cohort of trauma patients with no previous kidney disease, AKI was associated with an independent risk of hospital death. This risk was evident in a dose-response manner and even patients with the mild AKI had a 2.5-fold increase in adjusted risk for death compared to patients without AKI. Future studies need to address whether early identification of patients with less severe AKI will provide a window for therapeutic interventions that may reverse adverse clinical outcomes.

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BIOGRAPHICAL SKETCH

Azra Bihorac is an assistant professor in anesthesiology, surgery and medicine in the University of Florida's College of Medicine, Department of Anesthesiology. After completing medical school in 1990 she spent several years in Turkey where she trained in internal medicine and nephrology. She moved to the United States in 1999 to continue her research training in nephrology and then completed internal medicine, nephrology and critical care medicine training at the University of Florida. She has a very active research group with a primary interest in clinical and translational research in acute kidney injury, including sepsis and shock. She was awarded an NIH K23 award in 2010, and in 2011 completed her Master of Science with a concentration in clinical and translational science while a scholar in the UF CTSI's Advanced Postgraduate Program in Clinical Investigation.