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Title:

Acute Kidney Injury Requiring Dialysis in Severe Sepsis

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Author's Contributions:

AS contributed to conception and design of the study and drafted the initial manuscript. AS, GK and RSN participated in data analysis. All authors participated in data interpretation, revisions of draft for critically important intellectual content and approval of final version of the manuscript. All authors agree to be accountable for all aspects of the work.

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At a Glance Commentary:

Scientific Knowledge on the Subject: The incidence of severe sepsis hospitalizations has increased over the years in last decade but mortality has continued to decrease. Acute kidney injury is the most common organ failure in those with severe sepsis and is associated with high mortality. Previous literature suggests that incidence of acute kidney injury is also increasing over time.

What this study adds to the field: In this study using a nationally representative database we found that the incidence of acute kidney injury requiring dialysis in those with severe sepsis has increased over the last decade, but the associated mortality has declined. We

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also found that the odds of mortality associated with acute kidney injury requiring dialysis in those with severe sepsis have decreased over time.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

ABSTRACT:

RATIONALE: Understanding the changing incidence and impact of acute kidney injury requiring dialysis in patients with severe sepsis will allow better risk stratification, design of clinical trials and guide resource allocation.

OBJECTIVES: To assess the longitudinal incidence of acute kidney injury requiring dialysis and its impact on mortality in patients with severe sepsis.

METHODS: Retrospective, cohort study of adults (≥20 years) hospitalized with severe sepsis from 2000-2009 in United States using a nationally representative database.

MEASUREMENTS: We calculated the incidences of acute kidney injury requiring dialysis and mortality over time. We used linear regression to assess temporal trends. We used logistic regression to estimate the odds of acute kidney injury requiring dialysis and mortality.

MAIN RESULTS: Of the estimated 5,257,907 hospitalizations with severe sepsis, 6.1% had acute kidney injury requiring dialysis. The odds of acquiring acute kidney injury requiring dialysis increased by 14% in 2009 compared to 2000. Mortality in patients with acute kidney injury requiring dialysis was higher (43.6% vs 24.9%; p<0.001). After multivariable adjustment, odds of mortality declined 61% by the year 2009. Acute kidney injury requiring dialysis remained an independent predictor of mortality in patients with severe sepsis, though its influence of mortality declined with time.

CONCLUSIONS: Incidence of acute kidney injury requiring dialysis in patients with severe sepsis has increased over time, conversely associated mortality has declined. The likelihood of demise from acute kidney injury requiring dialysis in patients with severe sepsis has also declined.

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INTRODUCTION:

Severe sepsis – the systemic inflammatory response syndrome caused by an infection in the presence of at least one organ failure is a common and often fatal condition. Estimates of incidence have steadily risen over the past several years such that approximately 1 in 40 hospitalizations in the year 2007 were complicated by severe sepsis.(1) Moreover the incidence of severe sepsis is much higher than many common diseases such as breast cancer and HIV infection. Conversely case fatality rates have improved but mortality still remains unacceptably high (approximately 27% in 2007). (1)

Acute Kidney Injury (AKI) is common in patients with sepsis. Using data from the Australian New Zealand Intensive Care Society Adult Patient Database (ANZICS APD), Bagshaw et al(2) reported an AKI incidence of 42.1% in patients with sepsis. Similarly, Kumar et al(1) found that AKI represented the most frequent organ failure in persons with severe sepsis. Correspondingly, two multicenter studies suggested that over 40% of all AKI in critically ill patients could be attributed to sepsis(3, 4). Similar to other illnesses, development of AKI in persons with severe sepsis independently predicts worse outcomes and is associated with increased costs(2, 5).

AKI is a broad term that represents a syndrome across a continuum of graded renal injury; the most severe of which requires intervention in the form of dialysis. Several investigations have now demonstrated a substantial rise in the incidence of AKI in different clinical settings including in critically ill patients(6, 7). However, it is unclear whether the rising incidence is due to constant refinements in definitions and better coding practices or

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enhanced recognition or both. AKI requiring dialysis (AKI-D), however, we believe would be less likely to be affected by these factors. Although it is reasonable to hypothesize that with enhanced attention to AKI, health care providers would institute measures to prevent ongoing kidney injury earlier in the course of illness thereby mitigating the need for dialysis, a recent study found that the incidence of AKI-D was rising in concert with the incidence of AKI(8). Although epidemiological investigations have investigated the occurrence and associated outcomes of AKI in persons with sepsis(2, 3), estimates of the incidence and outcomes of AKI-D and their evolution over time are currently unknown. As both severe sepsis and AKI-D are expensive, resource intensive and associated with worse outcomes, it is important to obtain knowledge of these estimates. This would enable health care planners and policy makers to appropriately allocate resources to large fraction of hospitalizations. Moreover, such information would be helpful in prognostication, risk stratification and design of future clinical trials.

We therefore sought to describe AKI-D in persons with severe sepsis. The goals of our study were to 1) determine the longitudinal incidence (years 2000-2009) of AKI-D in persons with severe sepsis and 2) assess the longitudinal impact of AKI-D on mortality in persons with severe sepsis during the same time period. We used a large nationally representative database maintained by the Agency of Health Care Research and Quality (AHRQ) to enhance the external validity of our results.

METHODS:

Study Design and Data Source

We performed a retrospective study using national data from the Healthcare Cost and Utilization Project - Nationwide Inpatient Sample (NIS). NIS is the largest all-payer inpatient care database publicly available in the US that contains data from 20-percent stratified sample of U.S. community hospital(9). Each hospitalization is treated as an individual database entry and information regarding common demographic variables - age, race and sex along with primary insurance, hospital characteristics - teaching status, location (rural vs. urban), size of hospital and hospital region is available. Data from first 10 years of this millennium - 2000-2009 was used for this study. We used the provided principal diagnosis, secondary diagnoses and procedural diagnoses associated with each hospitalization in the database for this study.

Study Population

We included hospitalizations with severe sepsis with age≥20years in this study. In accordance with previous literature(1, 10) we defined severe sepsis as either 1) use of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for severe sepsis or septic shock or 2) use of ICD-9-CM codes for septicemia, bacteremia or fungemia with at least one organ dysfunction. We provide detailed codes in Table E1A & B.

We defined AKI-D using ICD-9-CM code for acute kidney injury (584.X) along with the procedure code for hemodialysis (39.95). These codes have demonstrated excellent positive and negative predictive value to identify admissions with AKI-D in administrative databases(11). We excluded patients who died within 24 hours of hospital admission because they would not have

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had enough time to develop AKI-D (5.5% of all severe sepsis hospitalizations). We also excluded patients on maintenance dialysis.

Study Variables

We identified demographic characteristics (age, sex and race), hospital characteristics (teaching status, location, bed-size and region) and primary payer using appropriate variables from NIS database. We then divided hospitals into tertiles based on the yearly volume of severe sepsis discharges (<195, 195-412, >412 hospitalizations for severe sepsis per year). We used Deyo's modification of Charlson's comorbidity index to identify the burden of comorbid diseases. (12). We identified persons receiving mechanical ventilation using ICD-9-CM procedure codes 96.70, 96.71 and 96.72. Discharges with missing data were excluded except for race, which was missing in about 20% of discharges. We included missing race as a separate subgroup of race for analyses. Overall, less than 1% observations were excluded secondary to missing data.

Outcomes

Our primary outcomes of interest were all cause in-hospital mortality and the independent influence of AKI-D on mortality in those with severe sepsis. We also assessed the longitudinal incidence of AKI-D in those with severe sepsis from the years 2000 to 2009. During the same time period we also report the longitudinal risk of acquiring AKI-D as well as the longitudinal impact of AKI-D on mortality.

Statistical Analysis

We performed all statistical analysis using STATA 13.1 (College Station, TX). Using the weights provided in NIS database, we generated national estimates for the number of overall severe sepsis hospitalizations and hospitalizations in each age category (20-44yr, 45-64yr, 65-79yr and ≥80 yr) and gender. We used chi square test to compare categorical variables and linear regression to assess significance of trends over time.

We used multivariable logistic regression model to estimate odds of AKI-D and odds of all-cause inpatient mortality. All clinically relevant variables were included in the final multivariable models that were adjusted for age, sex, race, primary payer, Charlson's score, hospital teaching status, hospital location, hospital region, hospital volume (small, medium and large), hospital bedsize, individual organ dysfunctions, mechanical ventilation use and year of admission. The model with mortality as dependent variable was also adjusted for AKI-D as a predictor variable. To assess if there is a differential effect of year on mortality between those with AKI-D and those without we checked for an interaction between AKI-D status and year. We then used linear combination of estimates to determine the independent effect of AKI-D on mortality for each individual year studied.

As characteristics of those with AKI-D were different from those without AKI-D, we used a propensity score matching approach to adjust for differences in the two cohorts. We used a multivariable logistic regression model to calculate the likelihood that a person with severe sepsis would develop AKI-D. This model included factors (detailed in Table 1) that might result in AKI-D regardless of their individual statistical significance. Each hospitalization in the AKI-D group was then matched with the hospitalization in the non AKI-D group using 1:1 nearest

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neighbor matching with 0.01 calipers and without replacement. The final matched cohort had 65,833 matched pairs (total 131,666 observations). All baseline variables had standardized differences <10% (Fig E1) after propensity matching. Sandwich covariance estimator was used to adjust for correlation between matched pairs in the logistic regression model in propensity-matched sample.

To better understand the effects of readmissions on our results we performed an additional sensitivity analysis where potential multiple admissions of same patient were identified using hospital records with similar age, sex, race, primary payer, hospital identification code and year of admission. This technique has been previously used to identify potential readmissions using the NIS database (13, 14). We then restricted our analyses to the cohort with unique observations and excluded any duplicate observations. We assessed the odds for AKI-D, mortality and independent effect of AKI-D on mortality for each individual year using regression models as for the original cohort of patients.

RESULTS

Patient Characteristics and Incidence of AKI-D (Table 1)

There were an estimated 5,257,907 (95% CI: 5,048,945 – 5,466,869) hospitalizations with severe sepsis over the study period. Of those, estimated 323,120 (95% CI: 305,522 – 340,717) had AKI-D for an overall crude cumulative incidence of 6.1%. Lower proportions of those aged 80 and older with severe sepsis developed AKI-D as compared to those without AKI-D (17.1% vs 29%) (Table1). Persons developing AKI-D were more often males, and were more likely to be admitted to teaching hospitals, hospitals with larger bed-sizes and hospitals with higher volumes

of severe sepsis (Table 1). Persons with AKI-D were also more likely to require mechanical ventilation (56.1% vs 34.2%; p<0.001), have septic shock (43.3% vs 35.9%; p<0.001) and other organ dysfunctions than those without AKI-D (Table 1).

Trends of AKI-D

The proportion of patients with severe sepsis who developed AKI-D steadily rose over the time period of study (5.2% in 2000 and 6.6% in 2009) with an annualized increment of 2.1% (Fig 1A). This increase was consistent across all age groups as well as sex, although the rise did not meet statistical significance in the age group ≥80 year old (Fig 1B and Fig 1C). In adjusted analyses, after accounting for potential confounding variables, the odds of acquiring AKI-D in those with severe sepsis increased by 14% (Fig 3A).

Outcomes

The overall all-cause inpatient mortality for those with severe sepsis was 26.1%. Crude mortality in persons with AKI-D was significantly higher than those without AKI-D (43.6% vs 24.9%; p<0.001). Despite lower incidences of AKI-D in the cohort aged 80 years and older, overall crude mortality as well as crude mortality in people developing AKI-D was significantly higher in this cohort (Fig 2A). Mortality was also higher in males in both overall and AKI-D cohorts (Fig 2B).

There was a steady decline in both overall case fatality rates as well as case fatality rates in the cohort acquiring AKI-D (Fig 1A). However the magnitude of this decline was approximately

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half that observed in the entire cohort (19.2% versus 41.6%). Decrements in mortality rates were observed across all age categories and sex (Fig 2A & 2B).

On multivariable analysis, the odds of mortality for persons with severe sepsis declined by 61% from 2000 to 2009 (OR 0.39; 95% CI 0.37-0.41) (Fig 3A). After adjustment for potential confounding factors, AKI-D remained an independent predictor of in-hospital mortality. In the year 2000, the odds of mortality in those with severe sepsis who developed AKI-D were twice than those who did not have AKI-D (OR 2.00; 95% CI 1.84-2.18). These odds of mortality declined as evidenced by significant interaction term between year of admission and AKI-D (interaction p=0.002) but still remained significant during the time period of our study, such that by the year 2009 the odds of mortality in those with AKI-D were 1.74 times (OR 1.74; 95% CI 1.64-1.85) (Fig 3B).

On propensity-matched analysis, our results were similar. AKI-D remained an independent predictor of mortality with OR 1.78 (95% CI: 1.59-2.00) in the year 2000. Overall odds of mortality in persons with severe sepsis decreased by 64% from 2000 to 2009 (Fig E2a) and impact of AKI-D on mortality also decreased with time (interaction p=0.01 – Fig E2b). We observed similar trends for odds of AKI-D, mortality (Fig E2c) and impact of AKI-D over time (interaction p<0.001 - Fig E2d) when only unique observations were analyzed.

DISCUSSION

We show that though the incidence of AKI-D complicating severe sepsis is rising, the associated mortality is declining. These findings were remarkably similar across age groups and sex. We found that after adjustment for confounding variables, that the risk of developing AKI-D complicating severe sepsis in 2009 was 14% higher than that in 2000. Conversely, the risk of AKI-D on mortality from severe sepsis was 61% lower in 2009 relative to 2000. Our results for mortality and the declining impact of AKI-D on mortality were similar when we adjusted for the likelihood that people with severe sepsis would acquire AKI-D and matched people who acquired AKI-D to people who were AKI-D free.

Our results are in agreement with earlier reports demonstrating increasing incidences of AKI with time(6, 8, 15, 16). Our study can be most readily compared to the study by Bagshaw SM et al(6), which examined the incidence and outcomes of AKI in all ICU admissions using ANZICS APD. These authors used an acute serum creatinine elevation to ≥1.5mg/dL and urine output <410ml in 24 hours to define AKI. They found that although the incidence of AKI progressively increased over the study period that extended from 1996 to 2005; associated mortality decreased. These authors, however, only accounted for patients who developed AKI during the first 24 hours of ICU admission and were unable to provide estimates of acute renal replacement therapy. In contrast we restricted our attention to AKI requiring dialysis, thereby capturing a population that may have developed AKI several days after hospital admission. Moreover using our scheme of patient inclusion (AKI and the need for renal replacement therapy), we probably mitigated influences that may artificially inflate the incidence of AKI secondary to heightened awareness and more complete capture from proper coding practices.

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More recently, Hsu RK et al(8) used the NIS database to estimate the national incidence and trends of AKI-D in all hospitalizations over the last decade and found that the population incidence rate increased from 222 to 533 cases per million person years. They also found that mortality declined from 29.1% in 2000 to 23.5% in 2009. In addition, they showed that the odds of AKI-D increased by 7% annually (OR 1.07; 95% CI: 1.06-1.07) on adjusted analysis. In our study, using year as a continuous variable in we found, a 1% increase in annual odds (OR 1.01; 95% CI: 1.00-1.01) of AKI-D in those with severe sepsis (results not shown). Differences in these results are likely due to different populations studied; Hsu RK et al included all hospital admissions but we restricted our sample to those ≥20 years with severe sepsis that survived the first day of hospitalization. In addition, we performed much more rigorous adjustments to the logistic regression model than the previous study.

We also found that those aged ≥80 years with severe sepsis had lower incidence and risk of AKI-D even on adjusted analysis. These findings may reflect physician, patient and/or family preferences to not initiate renal replacement therapy in the very elderly; a hypothesis supported by the fact that the highest incidence of all AKI occurred in those ≥80 years (53.0% vs 50.1% in 65-79yr vs 47% in 45-64yr vs 39.2% in 20-44 yr old; $p<0.001$).

Our data sources do not provide a ready explanation for the increasing incidence of AKI-D and improving mortality. The increasing incidence of AKI-D could reflect the overall increasing complexity of patients with severe sepsis as was shown by Kumar G et al(1). Progressively earlier initiation of dialysis for AKI in those with severe sepsis is potentially

another explanation for these results. In addition, increased investigative procedures using iodinated contrast in form of CT scans could also contribute to the same though it is difficult to capture and thus study their impact reliably using ICD-9-CM codes. The outcomes for severe sepsis have improved since early part of last decade that has been thought to be due to better understanding of the pathophysiology of severe sepsis and improved care of patients. The improvement in mortality in those with AKI-D is likely a reflection of overall improvement in care of patients with severe sepsis.

Though we have used a robust, nationally representative database, our study has important limitations. There is no consensus definition of severe sepsis for studies in administrative databases. Though we have used severe sepsis and organ failure codes in accordance with previous studies (1, 10) they may not reliably identify those with severe sepsis. Constant evolution in ICD-9-CM codes, particularly addition of codes for severe sepsis in 2002 and septic shock in 2003 may have also impacted our results but we did see a consistent trend across many years of the study. The NIS database has incomplete data regarding race of admissions thus limiting us in being able to interpret and comment on the racial incidence, impact and trends of AKI-D. Our data source also limited us from identifying outcomes post hospital discharge. As such our results of improvements in mortality may simply reflect a shift from in-patient mortality to demise post discharge. In addition, each hospitalization is treated as a separate observation in NIS database with no variables to help uniquely identify readmissions. We however attempted to exclude potential readmissions by identifying unique observations using patient characteristics, primary payer hospital ID and year of admission and found similar trends in that cohort

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which lends credence to our results. Finally, certain variables such as estimated glomerular filtration rate (eGFR) values, which accurately identify levels of pre-existing renal dysfunction were unavailable in our data source which limit our ability to discern the impact of advanced degrees of renal dysfunction on the decision to initiate dialysis.

The main strength of our study is the use of a large nationally representative database that allows for easily generalizable and accurate estimates to be generated. An additional strength is the use of propensity score matching to make the groups with and without AKI-D similar in baseline characteristics for further analyses. The fact that our results showed similar trends in overall, propensity matched sample and sample with only unique observations argues for the robustness of our results.

To summarize, using a nationally representative and well-characterized database we show hat even though the incidence of AKI-D is progressively rising in those with sever sepsis, the impact of AKI-D on mortality is decreasing. Nevertheless, AKI-D still remains a significant predictor of mortality in those with severe sepsis. Further studies are needed to understand the reasons behind rising incidence of AKI-D and efforts need to be targeted towards mitigating the incidence.

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FIGURE LEGENDS:

Figure 1: Incidence of AKI requiring dialysis (AKI-D) and Mortality in those admitted with severe sepsis

1A) Incidence of AKI-D and Mortality over time

1B) Incidence of AKI-D by Age Groups over time

1C) Incidence of AKI-D by Sex over time

Key: *p<0.001, #p=0.003, ¶p=0.07

Figure 2: Age and sex specific mortality in those admitted with severe sepsis

2A) Mortality by Age Groups in overall cohort and those with AKI-D

2B) Overall Mortality by Sex in overall cohort and those with AKI-D

Key: *p<0.001, §p=0.004

Figure 3: Odds for developing AKI-D and Mortality

3A) Odds for developing AKI-D and Mortality over time

*Adjusted for age, sex, race, primary payer, Charlson's score, hospital teaching status, hospital location, hospital region, hospital volume, hospital bedsize, individual organ dysfunctions, mechanical ventilation use and year of admission

#Adjusted for age, sex, race, primary payer, Charlson's score, hospital teaching status, hospital location, hospital region, hospital volume, hospital bedsize, individual organ dysfunctions, AKI-D status, mechanical ventilation use, year of admission and interaction between AKI-D status and year of admission

3B) Odds of mortality due to AKI-D over time

(Adjusted for age, sex, race, primary payer, Charlson's score, hospital teaching status, hospital location, hospital region, hospital volume, hospital bedsize, individual organ dysfunctions, mechanical ventilation use and year of admission)

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TABLES:

Table 1: Baseline Characteristics of those with and without AKI-D

Characteristic		**AKI-D % (N=323,120)**	**Without AKI-D % (N=4,934,787)**	**p value**
Age Group	20-44	10.9	9.4	<0.001
	45-64	35.3	27.7	
	65-79	36.7	33.9	
	≥80	17.1	29.0	
Sex	Male	57.7	50.0	<0.001
Race	White	51.7	55.4	<0.001
	Black	15.6	11.3	
	Hispanic	9.4	7.0	
	Asian	2.4	2.1	
	Native American	0.5	0.4	
	Others	2.7	2.1	
	Missing	17.5	21.6	
Primary Payer	Medicare	58.3	65.8	<0.001
	Medicaid	12.6	10.3	
	Private	22.8	18.4	
	Self-pay	3.4	3.0	
	No Charge	0.3	0.3	
	Other	2.3	2.3	
Charlson's Score	<3	63.0	74.1	<0.001
	3-4	23.5	15.1	
	≥5	13.5	10.9	
Respiratory Dysfunction		64.7	46.8	<0.001
Respiratory Dysfunction		43.3	35.9	<0.001
Hepatic Dysfunction		13.0	4.9	<0.001
Renal Dysfunction		100.0	45.7	<0.001
Hematological Dysfunction		25.1	17.7	<0.001
Metabolic Dysfunction		28.1	14.7	<0.001
Neurological Dysfunction		13.7	12.2	<0.001
Septic Shock		43.3	35.9	<0.001
Mechanical Ventilation Use		56.1	34.2	<0.001
Hospital Teaching Status	Teaching	53.3	45.5	<0.001
Hospital Bed-size	Small	8.6	11.1	<0.001
	Medium	22.2	24.6	
	Large	69.2	64.3	
Hospital Volume	Small	25.2	33.4	<0.001
	Medium	36.1	34.0	
	Large	38.8	32.7	
Hospital Location	Urban	95.7	89.8	<0.001
Year of Admission	2000	4.3	5.0	<0.001

	2001	4.9	5.6	
	2002	6.2	6.5	
	2003	7.4	7.5	
	2004	8.8	9.0	
	2005	10.5	10.3	
	2006	11.5	11.5	
	2007	13.0	13.0	
	2008	15.9	15.3	
	2009	17.3	16.1	

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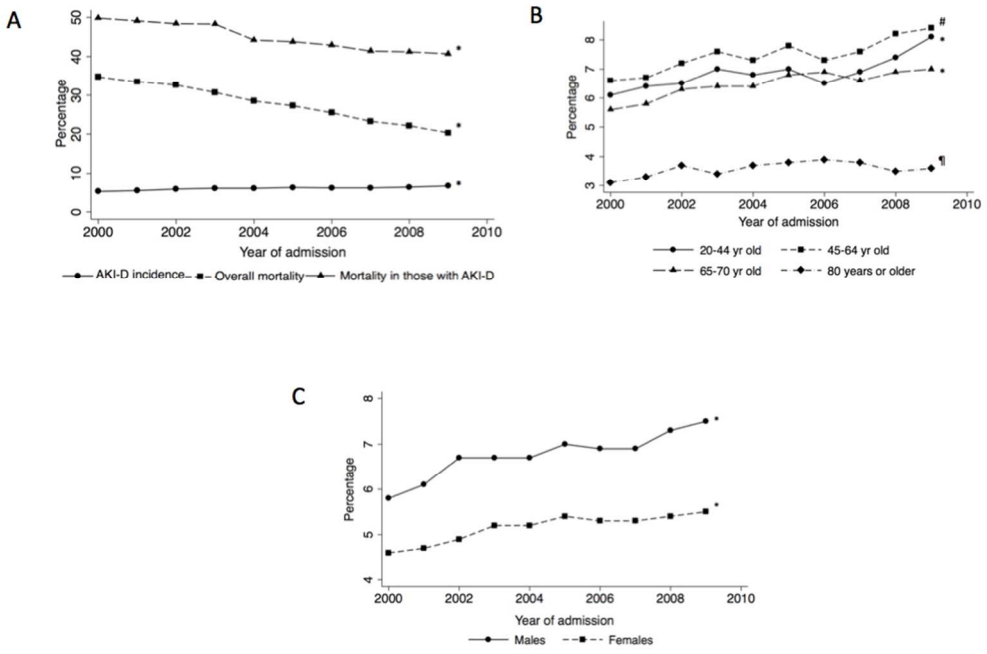

Figure 1

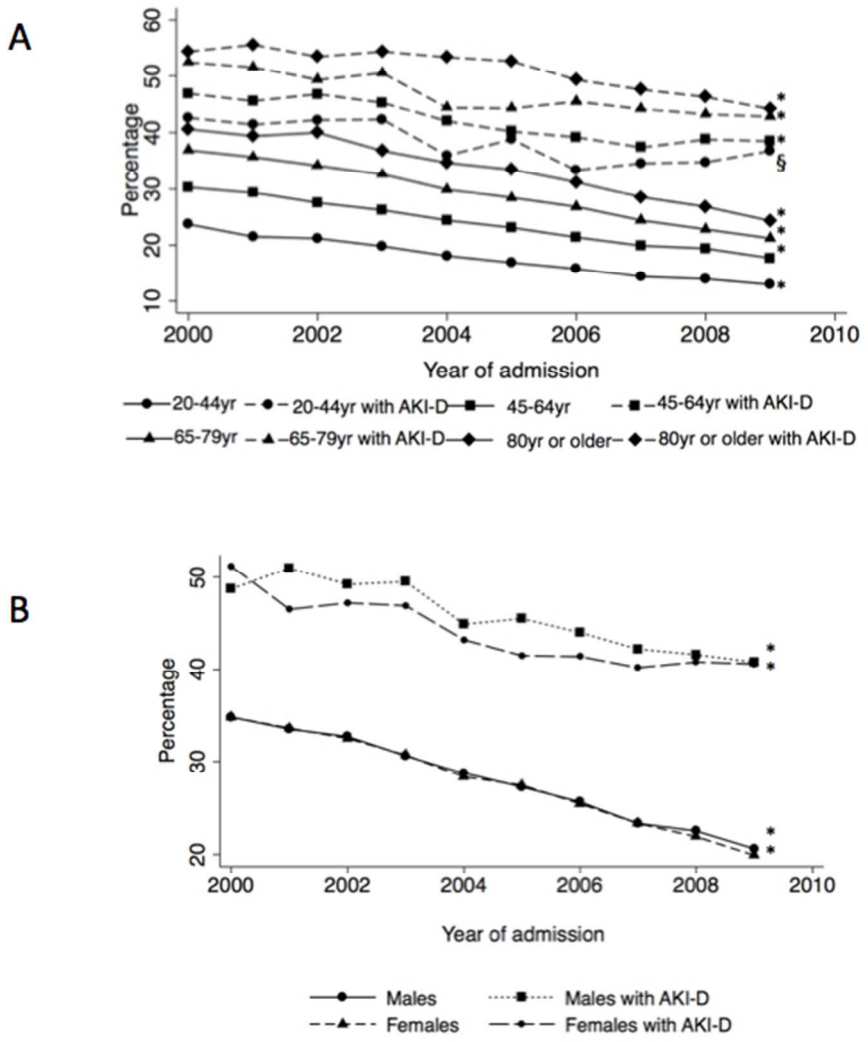

Figure 2

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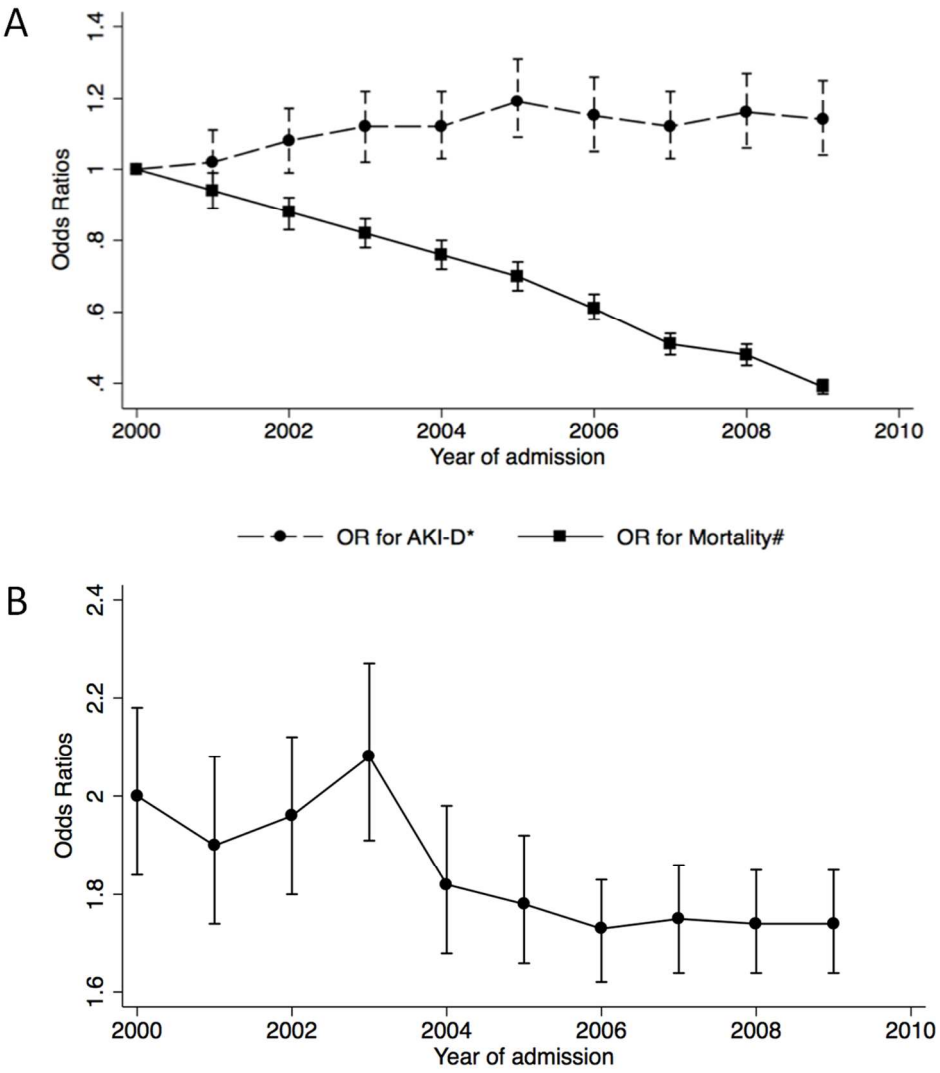

Figure 3
152x194mm (300 x 300 DPI)

Online Supplement

Table E1A: ICD-9-CM odes used to identify admissions with severe sepsis

Septicemia	038.0, 038.10, 038.11, 038.19, 038.2, 038.3, 038.4, 038.40, 038.41, 038.42, 038.43, 038.44, 038.49, 038.8, 038.9
Bacteremia	790.7
Disseminated Fungal Infection	117.9
Disseminated Candidal Infection	112.5
Fungal Endocarditis	115.04, 115.14, 115.94
Candidal Endocarditis	112.81
Candidal Meningitis	112.83
Salmonella Septicemia	003.1
Salmonella Meningitis	003.21
Meningococcal septicemia	036.2
Waterhouse Friedrichson syndrome	036.3
Meningococcal meningitis	036.0
Meningococcal encephalitis	036.1
Meningococcal endocarditis	036.42
Septicemic plague	020.2
Anthrax septicemia	022.3
Gonococcemia	098.89
Gonococcal endocarditis	098.84
Gonococcal meningitis	098.82
Severe Sepsis	995.92
Septic Shock	785.52

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Table E1B: ICD-9-CM codes used for acute organ dysfunction

Organ Failure	ICD-9-CM Code	Description
Respiratory	518.81	Acute respiratory failure
	518.82	Other pulmonary insufficiency, not elsewhere classified. Includes - Acute respiratory distress, Acute respiratory insufficiency, Adult respiratory distress syndrome NEC
	518.85	ARDS after shock or trauma
	786.09	Respiratory distress NOS
	799.1	Respiratory arrest
	96.7, 96.70, 96.71, 96.72	Ventilator management
Cardiovascular	785.5	Shock without mention of trauma
	785.50	Shock unspecified
	785.59	Other shock without trauma (includes Hypovolemic Shock)
	785.51	Cardiogenic shock
	785.52	Septic shock
	458.8, 458.9, 796.3	Hypotension NOS
Renal	584, 584.5, 584.6, 584.7, 584.8, 584.9	Acute Kidney Injury
Hepatic	570	Acute hepatic failure or necrosis
	572.2	Hepatic encephalopathy
	573.3	Hepatitis unspecified
	573.4	Hepatic infarction
Hematologic	286.6	Defibrination Syndrome
	286.7	Acquired coagulation factor deficiency
	286.9	Other coagulation defect
	287.4, 287.5	Thrombocytopenia - secondary or unspecified
Metabolic	276.2	Acidosis – metabolic or lactic
Neurologic	293, 293.0, 293.1, 293.8, 293.81, 293.82, 293.83, 293.84, 293.89, 293.9	Transient organic psychotic conditions
	348.1	Anoxic brain injury
	348.3, 348.30, 348.31, 348.39	Acute encephalopathy
	780.01	Coma
	780.09	Altered consciousness - unspecified
	89.14	EEG

SUPPLEMENTARY FIGURE LEGENDS:

Figure E1: The effectiveness of propensity matching in selecting controls

Figure E2: Odds of Mortality in propensity matched sample or sample with only unique observations

E2A) Odds of Mortality over time in propensity matched sample
(Adjusted for age, sex, race, primary payer, Charlson's score, hospital teaching status, hospital location, hospital region, hospital volume, hospital bedsize, individual organ dysfunctions, AKI-D status, mechanical ventilation use, year of admission and interaction between AKI-D status and year of admission)

E2B) Odds of mortality due to AKI-D over time in propensity matched sample
(Adjusted for age, sex, race, primary payer, Charlson's score, hospital teaching status, hospital location, hospital region, hospital volume, hospital bedsize, individual organ dysfunctions, mechanical ventilation use and year of admission)

E2C) Odds for developing AKI-D and Mortality over time in only unique observations
(Odds for AKI-D adjusted for age, sex, race, primary payer, Charlson's score, hospital teaching status, hospital location, hospital region, hospital volume, hospital bedsize, individual organ dysfunctions, mechanical ventilation use and year of admission and odds for mortality adjusted for age, sex, race, primary payer, Charlson's score, hospital teaching status, hospital location, hospital region, hospital volume, hospital bedsize,

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individual organ dysfunctions, AKI-D status, mechanical ventilation use, year of admission and interaction between AKI-D status and year of admission)

E2D) Odds of mortality due to AKI-D over time in only unique observations (Adjusted for age, sex, race, primary payer, Charlson's score, hospital teaching status, hospital location, hospital region, hospital volume, hospital bedsize, individual organ dysfunctions, mechanical ventilation use and year of admission)

SUPPLEMENTARY FIGURES:

Fig E1

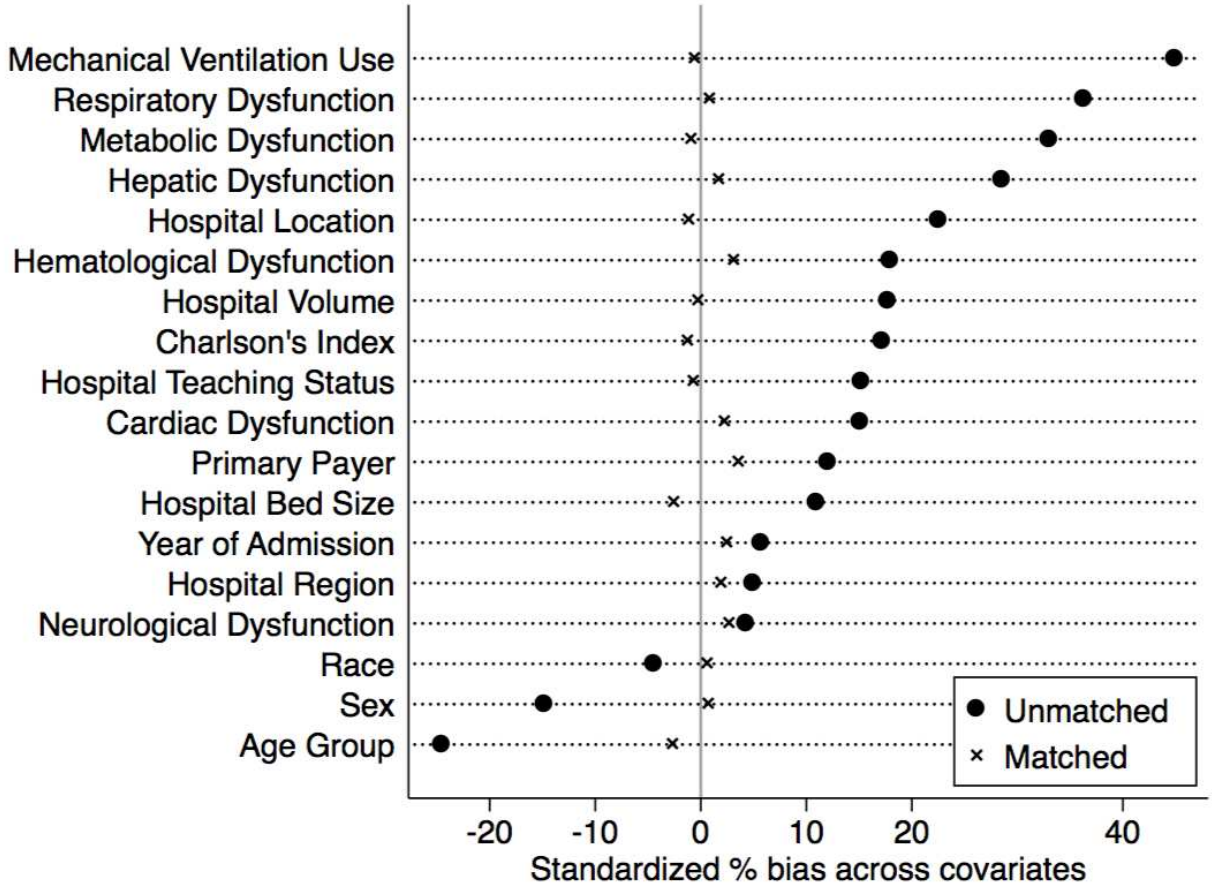

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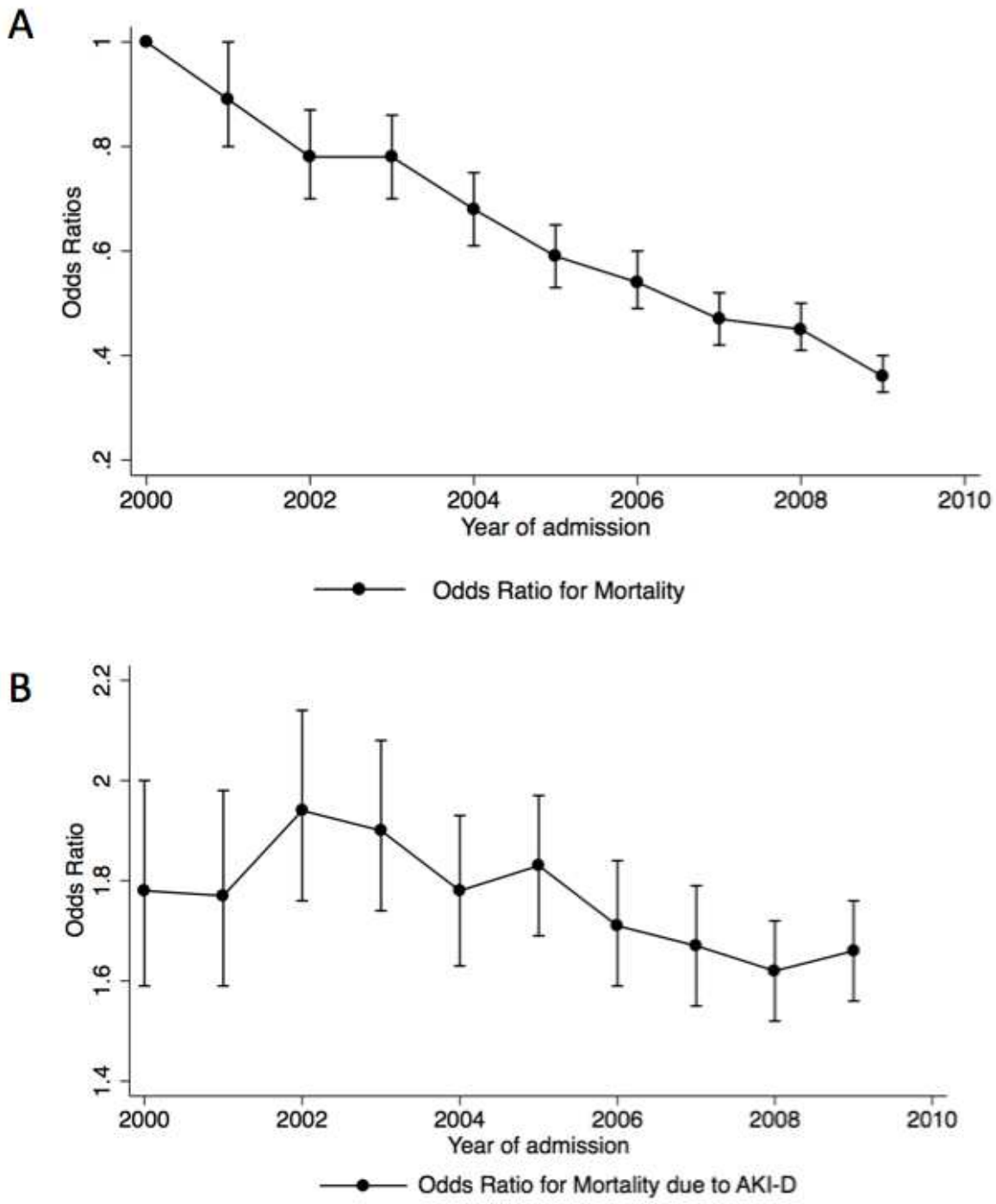
Fig E2



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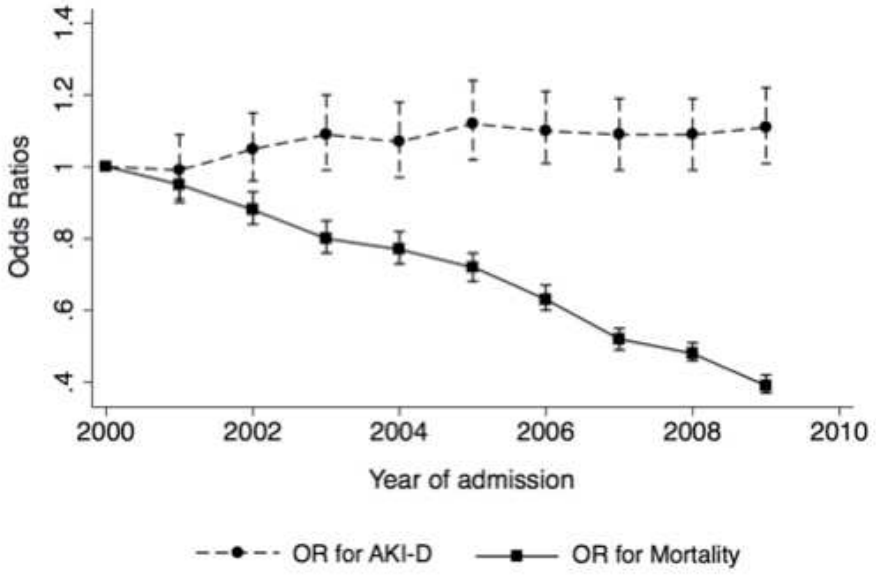

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