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Regional Variation in the Incidence of Dialysis-Requiring AKI in the United States

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Summary

Background and objectives Little is known about geographic differences in the incidence of AKI. The objective of this study was to determine if regional variation exists in the population incidence of dialysis-requiring AKI in the United States.

Design, setting, participants, & methods Data from the Nationwide Inpatient Sample, a US nationally representative sample of hospitalizations, were used to determine the incidence rates of dialysis-requiring AKI between 2007 and 2009 among the four US Census-designated regions. Cases were identified using validated discharge codes. Poisson regression models were used to estimate overall regional rates, accounting for the data's sampling scheme.

Results In 2007–2009, the population incidence rates of dialysis-requiring AKI differed across the four Census-designated regions ($P=0.04$). Incidence was highest in the Midwest (523 cases/million person-yr, 95% confidence interval=483 to 568) and lowest in the Northeast (457 cases/million person-yr, 95% confidence interval=426 to 492). The pattern of regional variation in the incidence of dialysis-requiring AKI was not the same as the pattern of regional variation in the incidence of renal replacement therapy-requiring ESRD (obtained from the US Renal Data System). In-hospital mortality associated with dialysis-requiring AKI differed across the four regions, with the highest case fatality in the Northeast (25.9%) and the lowest case fatality in the Midwest (19.4%).

Conclusions Significant regional variation exists in the population incidence of dialysis-requiring AKI in the United States, and additional investigation is warranted to uncover potential causes behind these geographic differences.

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Introduction

AKI is an increasingly common condition associated with high morbidity, mortality, and resource use (1–3). In recent years, it has also become well recognized that AKI is associated with poor long-term outcomes, such as accelerated progression of CKD, need for chronic dialysis, and higher mortality after hospital discharge (4–6). Despite the public health burden of AKI, relatively little is known about the population epidemiology of AKI in the United States (for example, regarding regional or geographic variation in disease incidence or case fatality).

With regard to disease incidence, historically, the incidence of AKI has usually been described as cases per 100 hospitalizations (or intensive care unit stays). This approach makes comparisons across geographic regions problematic, because there are potential differences in admission thresholds across regions.

To address these gaps in the literature, we combined a nationally representative database of hospital discharges with census data to determine whether there was significant regional variation in the incidence of dialysis-requiring AKI. We also quantified regional variation in the case fatality rates of dialysis-requiring

AKI. Finally, we explored various potential correlates with regional variation in incidence of AKI, including regional variation in incidence of ESRD and regional variation in nephrology workforce.

Materials and Methods

Data Sources

We examined 2007–2009 data from the Nationwide Inpatient Sample (NIS), a nationally representative database of hospitalizations in the United States (7). The NIS includes patient-level data from approximately 1000 hospitals and is designed as a 20% stratified sample of all short-term, nonfederal, nonrehabilitation hospitals. It was developed as part of the Healthcare Cost and Utilization Project, sponsored by the Agency for Healthcare Research and Quality. The NIS sampling strata were defined based on the following five hospital-level characteristics: geographic region, control (public versus private), location (urban versus rural), teaching status, and bed size. The geographic region stratification is defined the same way as the four US Census-designated regions: Northeast (Connecticut, Maine, Massachusetts, New Hampshire, New Jersey,

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New York, Pennsylvania, Rhode Island, and Vermont), Midwest (Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin), South (Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia), and West (Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming); therefore, we were able to use sampling weights that accompany each patient-level observation to derive accurate regional estimates in the population incidence of dialysis-requiring AKI. The NIS sampling scheme does not allow for individual state-level analyses.

Population totals for each region during the study period were obtained from the US Census Bureau (8). We used data from the US Renal Data System (USRDS) to determine the regional incidence rates of ESRD requiring renal replacement therapy from 2007 to 2009 (9). We used data from the American Boards of Internal Medicine and Pediatrics to determine the number of board-certified nephrologists by region. Workforce data used in this study include all valid board-certified nephrologists (adult and pediatric) as of 2011. The state of practice for each physician was based on the most recent addresses reported by practitioners to their respective boards. The study protocol was examined by the Committee on Human Research of the University of California, San Francisco, and was deemed exempt, because the study involved the use of publicly available, deidentified data.

Definition of Primary Outcome

Cases of dialysis-requiring AKI were identified using validated International Classification of Diseases, 9th Revision, Clinical Modification codes (10,11). Dialysis-requiring AKI was defined as the presence of any of the following diagnostic codes: 584.5 (acute renal failure [ARF] with lesion of tubular necrosis), 584.6 (ARF with lesion of renal cortical necrosis), 584.7 (ARF with lesion of renal medullary necrosis), 584.8 (ARF with other specified pathologic lesion in kidney), or 584.9 (ARF, unspecified) and presence of any of the following procedure codes: 39.95 (hemodialysis), V45.1 (renal dialysis status), V56.0 (extracorporeal dialysis), or V56.1 (fitting and adjustment of extracorporeal dialysis catheter). To avoid inclusion of patients admitted for initiation of chronic maintenance hemodialysis, we excluded the cases with procedure codes for arteriovenous fistula creation or revision (39.27, 39.42, 39.43, and 39.93). This algorithm has been shown to be sensitive and specific, producing high positive and negative predictive values (all $\geq 90\%$) (10).

Statistical Analyses

Data were analyzed using Stata/SE 12.0 (College Station, TX). We estimated the number of hospitalizations with dialysis-requiring AKI for the combined 2007–2009 period, applying appropriate weights to account for the complex sampling scheme. Poisson regression models were used to estimate overall regional incidence rates using the total number of NIS discharges for each region and the corresponding population totals for each region during the study period. Although we used Poisson regression routines, the survey sampling methods in Stata use robust SEMs and

hence, do not make distributional assumptions. We used the adjusted Wald test to test for significance of differences in incidence rates across regions. We fitted additional Poisson regression models using region-, sex-, and age-specific categories to see if regional differences in incidence rates were accounted for by differences in underlying patient demographics. Owing to the large proportion of hospital discharges with missing race data, we did not include race/ethnicity in our analysis (11).

We examined in-hospital mortality associated with dialysis-requiring AKI across the four regions. Regional incidence rates of dialysis-requiring AKI were also compared with regional incidence rates of renal replacement therapy-requiring ESRD that were obtained from the USRDS (9). Regional incidence rates of renal replacement therapy-requiring ESRD were calculated using combined incidence counts from USRDS and regional population totals obtained from the US Census Bureau for the 3-year study period.

Lastly, we created logistic regression models using dialysis-requiring AKI as the outcome and region as the main predictor to assess the risk of dialysis-requiring AKI per hospitalization in each region. We were also able to estimate the overall hospitalization rates (for all diagnoses) in each region using the NIS sampling scheme. Therefore, we are able to see if patterns of regional variation in the population incidence of dialysis-requiring AKI (case per million person-years) are similar or different from the patterns of regional variation in the in-hospital incidence of dialysis-requiring AKI (case per hospitalization).

Results

From 2007 to 2009, we identified 448,755 hospitalizations (95% confidence interval [95% CI]=423,788 to 473,721) with dialysis-requiring AKI in the United States. The demographic characteristics of patients hospitalized with dialysis-requiring AKI are listed according to geographic region in Table 1.

Regional Variations in In-Hospital Incidences May Not Accurately Reflect True Disease Distribution

The West region had the highest incidence of dialysis-requiring AKI per hospitalization (0.43% of hospitalizations) (Figure 1). Using Northeast as the referent group, the odds ratios (ORs) for developing dialysis-requiring AKI among hospitalized patients in the other regions were (in ascending order) South (OR=1.15, 95% CI=1.05 to 1.25), Midwest (OR=1.17, 95% CI=1.05 to 1.31), and West (OR=1.32, 95% CI=1.17 to 1.49).

However, when AKI incidence was expressed per population, the West region does not have a particularly high population incidence rate of dialysis-requiring AKI (Figure 1). The reason for this finding is because hospitalization rates are lowest in the West (0.106 hospitalizations/person-yr versus 0.135 [South], 0.137 [Midwest], and 0.141 hospitalizations/person-yr [Northeast]).

Midwest Has the Highest and Northeast Has the Lowest Population Incidence of Dialysis-Requiring AKI

On a population basis, the overall population incidence rate of dialysis-requiring AKI in the United States from 2007 to 2009 was 492 cases/million person-yr (95% CI=465 to 519 cases/million person-yr). The population incidence

Table 1. Population characteristics of patients hospitalized with dialysis-requiring AKI by US Census regions from 2007 to 2009

Characteristic	Overall	Northeast	Midwest	South	West	P Value for Difference across Regions
Number of hospitalizations	448,755	75,561	104,661	170,330	98,202	
Age (yr; mean)	63.2	65.2	63.8	62.5	62.1	<0.001
Men (%)	57.3	58.3	56.4	56.8	58.1	<0.001
Race/ethnicity (%)						<0.001
White non-Hispanic	50.4	66.9	39.8	48.7	51.9	
Black non-Hispanic	16.0	17.2	11.7	22.5	8.3	
Hispanic	9.5	7.5	1.1	9.4	20.0	
Other	5.8	6.3	2.2	4.4	12.0	
Missing	18.3	2.1	45.2	15.0	7.8	

rate of dialysis-requiring AKI was highest in the Midwest (524 cases/million person-yr, 95% CI=484 to 568) and lowest in the Northeast (459 cases/million person-yr, 95% CI=427 to 493), with the South and West regions ranking second and third, respectively. The overall difference in crude incidence across the four geographic regions was statistically significant ($P=0.04$). After adjustment for age and sex, the overall difference remained statistically significant ($P<0.001$), with the Northeast region (having the lowest incidence) driving the most pronounced variation relative to the other three regions (Table 2).

Regional Variation in Incidence of Dialysis-Requiring AKI Does Not Follow the Same Pattern as Regional Variation in Incidence of ESRD

We found that the regional variation in incidence of dialysis-requiring AKI was comparable in magnitude but smaller than the regional variation in incidence of ESRD (highest versus lowest region rate ratio was 1.14 versus 1.25) (Figure 2).

The pattern of regional variation for dialysis-requiring AKI does not follow the pattern for ESRD. For example, the Northeast and Midwest have the lowest and highest incidences of dialysis-requiring AKI, respectively, despite having similar incidences of ESRD (Figure 2).

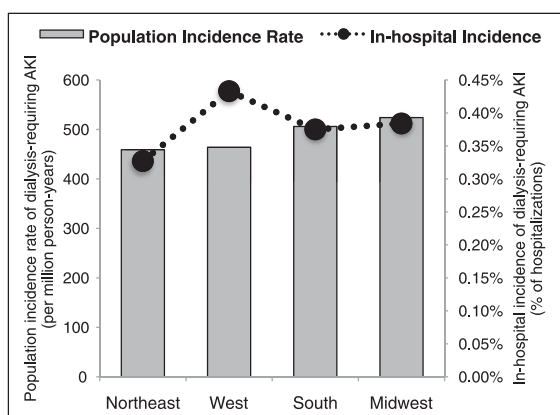


Figure 1. | Population incidence rate of dialysis-requiring AKI and in-hospital incidence of dialysis-requiring AKI by regions from 2007 to 2009.

Regions with Higher Population Incidence of Dialysis-Requiring AKI Have Lower Case Fatality Rates

Case fatality (in-hospital mortality) rate associated with dialysis-requiring AKI also varied across the four regions. Mortality was highest in the Northeast and lowest in the Midwest. Of note, the ranking order in case fatality rate associated with dialysis-requiring AKI across the four regions is directly opposite of the ranking order of the population incidence of dialysis-requiring AKI across the four regions (Figure 3).

Nephrology Workforce

The density of board-certified nephrologists (adult and pediatric) varied across the four regions. Notably, the Northeast region, which had the lowest population incidence of dialysis-requiring AKI, had the highest number of nephrologists per population (3.95 per 100,000 persons), whereas the other three regions had a lower density of nephrologists (2.78 per 100,000 persons for South, 2.72 per 100,000 persons for Midwest, and 2.54 per 100,000 persons for West).

Discussion

To our knowledge, this study is the first to explore geographic differences in the incidence of AKI in the general population in the United States. Its strengths include being nationally representative and having a large sample size, which translate into excellent power to estimate regional incidence rates accurately.

Understanding regional variations in disease incidence has provided useful insights for many medical conditions. For example, well characterized geographic variation in disease incidence and mortality of stroke and acute myocardial infarction (12–14) has helped to generate hypotheses on causation and has driven public health initiatives aimed at decreasing cardiovascular disease in high-risk regions (15,16). Since 2000, the USRDS Annual Data Reports have presented relevant statistics in an atlas format to emphasize geographic differences in disease occurrences and outcomes associated with ESRD (9,17). The use of mapping in publications by the institutions such as the Centers for Disease Control and Prevention and the Dartmouth Atlas Project has been instrumental in identifying geographic disparities in disease burden and mortality (12–14), practice patterns (18), and health care delivery (19).

Table 2. Regional variation in population incidence of dialysis-requiring AKI from 2007 to 2009: crude incidence rate and rate ratios in unadjusted and adjusted models

Region	Crude Incidence Rate ^a (per million person-yr)	95% Confidence Interval	Incidence Rate Ratios			
			Unadjusted	P Value	Age- and Sex-Adjusted	P Value
Nation	492	465 to 519				
Northeast	459	427 to 493	Reference	Reference	Reference	Reference
West	464	422 to 511	1.01	0.85	1.13	0.03
South	506	480 to 534	1.10	0.03	1.18	<0.001
Midwest	524	484 to 568	1.14	0.02	1.18	0.001
Overall comparison across regions ^b				0.04		<0.001

^aIncidence rates expressed in cases per million person-years.
^bP values from adjusted Wald test to test for difference across four regions.

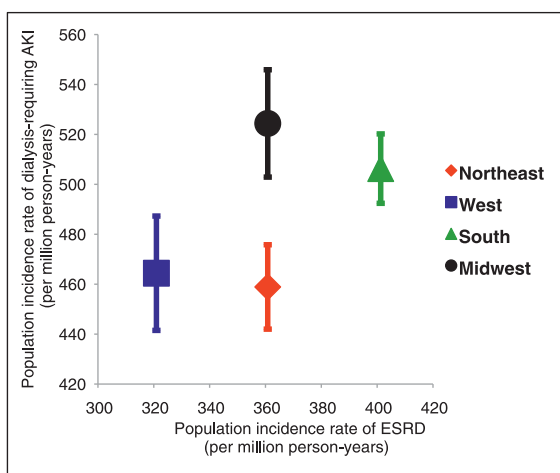


Figure 2. | Population incidence rate of dialysis-requiring AKI versus population incidence rate of ESRD by regions from 2007 to 2009. Error bars represent SEMs. No error bars are given for ESRD, because the population incidence rates for ESRD were obtained directly from the US Renal Data System and therefore, are not estimates.

Our investigations led to several novel findings. Using nationally representative hospital discharge data, we found significant geographic variation in the population incidence rate of dialysis-requiring AKI across the four US Census-designated regions, with highest incidence in the Midwest and lowest incidence in the Northeast in both crude and adjusted models.

We showed that, because of variations in hospitalization rates across regions in the country, variations in incidence of AKI per hospitalization do not accurately reflect true underlying regional variations in AKI in the population. This finding highlights the problematic way in which AKI epidemiology is historically performed (*i.e.*, with AKI incidence expressed as cases per hospitalization rather than cases per underlying population). Inferences drawn by comparing single-center or even multicenter studies (2) that express AKI as a percentage of hospitalizations are confounded by varying thresholds for admission across

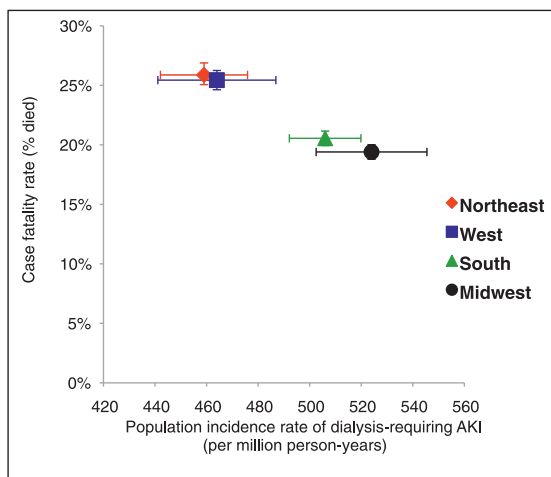


Figure 3. | Population incidence rate of dialysis-requiring AKI versus case fatality rate by regions from 2007 to 2009. Error bars represent SEMs.

hospitals/regions, and therefore, they arguably should be avoided as much as possible in future studies.

We wondered if the pattern of regional variation in population incidence of dialysis-requiring AKI may mirror the regional variation in ESRD incidence but found no correlation. We explored this comparison because of the numerous shared patient risk factors across the spectrum of kidney diseases (such as older age and diabetes mellitus) and the knowledge that underlying CKD itself is a potent risk factor for AKI (20). Our data suggest that determinants of incidence of dialysis-requiring AKI are distributed in a geographically distinct fashion from shared risk factors for kidney disease.

Interestingly, the one region with the most abundant nephrologist workforce is also the one with the lowest incidence of dialysis-requiring AKI (Northeast). At least one previous (nonrandomized) interventional study has shown that early nephrologist involvement in patients with AKI reduces the risk of a further decrease in kidney function (21). Density of nephrologists may also correlate with numerous

other health care system attributes that affect incidence of AKI. A recent multicenter study examining the incidence of AKI associated with acute myocardial infarctions showed significant between-hospital variation in AKI incidence (as well as significant between-hospital variation in use of potentially nephrotoxic medications and intravenous hydration) (22,23). These data suggest that better understanding of practice patterns underlying regional variations in AKI incidence may provide very useful insights into effective measures to reduce AKI incidence, complementing advances made through local interventions (24).

It is notable that the regions with the lowest incidence of dialysis-requiring AKI have the highest case fatality. As we have defined it (and as it has been defined in the prior literature) (5,25), developing dialysis-requiring AKI not only involves the patient having severe AKI but also, the decision by the physician and the acceptance by the patient (and perhaps, family members) to initiate acute dialysis. (We use the term dialysis here to encompass both intermittent hemodialysis as well as continuous renal replacement therapy.) There are no universally accepted thresholds for when renal replacement therapy should be initiated for AKI (26,27). The inverse relationship between population incidence of AKI and the mortality associated with dialysis-requiring AKI suggests the possibility that there may be geographic practice pattern variation on the threshold to perform acute dialysis. Earlier and more pervasive use of acute dialysis on less severely ill patients with AKI may explain why there is higher incidence and lower mortality in some regions. Alternatively, we can also hypothesize that better practice in the care of patients with AKI, such as earlier nephrologist involvement and more optimal performance of dialysis, may be a factor in more favorable in-hospital mortality in some areas versus others. Our database is not sufficient to test these hypotheses.

Our study has several limitations. First, we do not have laboratory measurements, such as serum creatinine, to define and quantify the severity of AKI. Although we relied on the best-validated set of diagnostic and procedure codes currently in the literature to define our primary outcome of dialysis-requiring AKI, it would have been ideal to have clinical data such as serum creatinine to help validate the cases. We cannot exclude the possibility that there are regional differences in coding practices that introduced bias. However, we are not aware of data that indicate any such misclassification would occur systematically by US regions (*i.e.*, consistently coded more so in Midwest versus Northeast). Another limitation of the study is that our results lack geographic granularity; only four regions can be separated out and analyzed. Conducting the analysis at the regional level may result in us missing potentially more dramatic contrasts in AKI incidence at the state level. This shortcoming is imposed by the stratified sampling scheme of the NIS dataset, which uses the Census-designated region rather than individual states as a stratification variable. It is possible that some of the AKI cases that we observed were patients with advanced CKD (in whom small changes in low baseline GFRs translated into large changes in serum creatinine concentration) who were admitted basically to start chronic dialysis, and that there were regional differences in frequency of this type of hospitalization. We could not separate out cases of acute or

chronic renal failure versus *de novo* AKI. Another limitation is that we did not include comorbidities that are AKI risk factors (such as diabetes, CKD, proteinuria, and obesity) in our adjustment model. Our Poisson model approach to determine accurate population incidence prevented us from adding those comorbidities, because doing so would have required incorporation of regional population totals with those prevalent conditions. Determining those figures (*i.e.*, number of men/women in specific age groups in one region with or without CKD, proteinuria, diabetes, and obesity) is not possible with currently available data. Our associations are of an ecological nature (*e.g.*, we did not know that there was a high density of nephrologists working at the hospitals with fewer cases of AKI). Lastly, we quantified nephrology workforce using Board Certification data and do not have confirmation that these practitioners are clinically active.

To conclude, this study contributes novel and provocative information regarding the population of epidemiology AKI. It adds to the growing literature on the importance of geographic variation in kidney disease epidemiology (17,28,29). Additional research is needed to clarify whether geographic differences are because of AKI risk factors, practice pattern differences, or some other cause to develop potential preventative interventions.

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Disclosures.

None.

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