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Trends and outcomes of sepsis hospitalizations complicated by acute kidney injury requiring hemodialysis

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1. Introduction

Sepsis is the 10th most common cause of death in the United States [1]. The incidence of sepsis and the number of sepsis-related deaths are increasing [2]. In addition, sepsis is a huge economic burden with an annual cost of US \$16.7 billion nationally [3]. Acute kidney injury (AKI) develops in around 15% of patients requiring hospitalizations [4]. Its incidence is even more common in septic patients, with nearly 20% of even moderate sepsis being complicated by AKI [5]. Sepsis has been established as one of the most common causes of AKI in critically ill patients with associated increased in-hospital mortality and longer duration of hospital and intensive care unit stay [6]. The most severe form of AKI, that requiring dialysis (AKI-D), has an even worse prognosis with mortality rates approaching 50% [7]. Although AKI frequently occurs in septicemia and is associated with worse prognosis, the impact of AKI-D has not been thoroughly elucidated. We explored the

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epidemiology of AKI-D in septicemia using data from a large, nationally representative database.

2. Methods and statistical analysis

We used the National Inpatient Sample database from 2002 to 2013 to identify adults hospitalized with septicemia using Clinical Classification Software developed by the Agency for Healthcare Research and Quality. We defined AKI using *international Classification of Diseases, Ninth Revision, Clinical Modification*, code 584.xx and dialysis by procedure code of 39.95 or diagnoses code of v45.11, v56.0, or v56.1. To avoid misclassification of hospitalizations for chronic hemodialysis, we excluded those with procedure codes for arteriovenous access creation/revision [8]. We excluded hospitalizations with dialysis codes but no AKI code, assuming that patients were receiving dialysis for end-stage renal disease. This approach has been used previously and has high sensitivity and specificity [9]. We used SAS 9.3 (SAS Institute Inc, Cary, NC) for all analyses.

3. Results

From 2002 to 2013, we had a national estimate of 8 108 048 hospitalizations with septicemia, of which 214185 (2.64%) had AKI-D. There was a substantial increase in the proportion of AKI-D in septicemia hospitalizations, from 1.4% in 2002 to 2.65% in 2013 (Fig. 1). Persons with AKI-D were younger (mean age 64.49 vs 68.86 years; $P < .0001$) and were more likely to be male (56.04% vs 46.85%; $P < .0001$) and African American (15.84% vs 10.98%; $P < .0001$). They also had higher severity of illness as measured by All Patient Refined Diagnosis Related Groups (APRDRG) mortality scale (89.05% vs 37.7% with score of 4; $P < .0001$). They were found to have higher prevalence of comorbidities including chronic kidney disease (CKD) (21.89% vs 14.32%; $P < .0001$), diabetes mellitus (35.41% vs 31.35%; $P < .0001$), hypertension (54.99% vs 49.05%; $P < .0001$), acute/chronic liver failure (28.49% vs 9.16%; $P < .0001$), acute myocardial infarction (11.13% vs 4.75%; $P < .0001$), and primary acute heart failure (32.22% vs 21.92%; $P < .0001$). Procedures such as cardiac catheterizations (1.56% vs 0.74%; $P < .0001$) and mechanical ventilation (58.74% vs 14.56%; $P < .0001$) were more common in AKI-D patients (Table 1). On univariate analysis, AKI-D increased by 4% per year (odds ratio [OR], 1.04; 95% confidence interval [CI], 1.04–1.05; $P < .0001$). After adjusting for demographic factors of age, race, and sex, the increase was attenuated to 2% per year (adjusted OR [aOR], 1.02; 95% CI, 1.02–1.03; $P < .0001$). With further adjustments for comorbidities and procedures, the increase was completely nullified (aOR, 0.98; 95% CI, 0.977–0.99; $P < .0001$). Thus, the increasing trend was completely explained by changes in demographic factors and comorbidities and performed procedures. Mortality was nearly double in patients with AKI-D (39.79% vs 15.06%) with an unadjusted odds of mortality being 3.78 (95% CI, 3.67–3.89; $P < .0001$). After adjusting for various covariates (including demographic factors, hospital-related variables, and APRDRG mortality scale), there remained a significant 2-fold increase in mortality (aOR, 2.08; 95% CI, 2.02–2.14; $P < .0001$). The adjusted odds of mortality decreased per year from 2002 to 2013. However, this was offset by an increase in the incidence of AKI-D, resulting in stable attributable risk percent from 2002 to 2013. Similarly, hospitalizations complicated by AKI-D were associated with 1.71 times higher

adjusted odds of discharge to specialized care (aOR, 1.79; 95% CI, 1.65–1.78; $P < .0001$). In addition, AKI-D was associated with 2.85 times longer length of stay (LOS) (15.60 days vs 5.46 days; $P < .0001$) and 3.75 times higher cost utilization (US \$40 692 vs US \$10 850; $P < .0001$). Although the LOS and inflation-adjusted cost of hospitalization stayed stable from 2002 to 2013 for septicemia hospitalizations both with and without AKI-D, they remained higher for AKI-D for all years. The strongest predictor of AKI-D was the requirement of mechanical ventilation (aOR, 7.10; 95% CI, 6.89–7.32; $P < .01$).

4. Discussion

In our study, we found that, from 2002 to 2013, the proportion of patients with sepsis hospitalizations complicated by AKI-D has increased, reaching a peak in 2009. Males have higher rates of AKI-D in the sepsis population. Potential explanations are related to protective effects of sex hormones. Whites had the lowest rates of AKI-D in sepsis hospitalizations. This may partially be explained by the higher rates of risk factors for AKI such as diabetes, hypertension, and pathological albuminuria in the African American population [10]. We also identified several predictors of AKI-D in septicemia hospitalizations. The predictor with the highest aOR was the requirement of mechanical ventilation. This is likely a surrogate for the severity of illness of the patient, predisposing to both development of and worsening of AKI. Although other comorbidities are also independently associated with AKI-D, CKD was one of the strongest predictors. Because AKI and CKD are likely interconnected [1], this shows the importance of using baseline kidney function for risk stratification of the development of AKI [11,12]. Although these predictors need to be accurately quantified using patient-level data, they could represent a preliminary step toward the creation of a recursive scores. Along with new evidence of biomarkers to differentiate septic from nonseptic AKI, recursive scores can be useful in risk-stratifying septicemia hospitalizations for AKI-D [5]. AKI-D in sepsis hospitalizations was associated with several negative outcomes. Although the trend in cost and LOS has not changed, they remained markedly higher in AKI-D hospitalizations. AKI-D was associated with an excess cost of US \$29 842 per patient, leading to a total cost of US \$6.3 billion attributable to AKI-D over the last decade in septicemia hospitalizations. AKI-D is also strongly associated with discharge to nursing home. Finally, we demonstrate that AKI-D is significantly and independently associated with in-hospital mortality after accounting for confounders. Although the adjusted mortality has decreased every year, which is likely due to better in-hospital care, the attributable risk of mortality and thus its burden has remained stable. Given the near doubling of mortality in sepsis hospitalizations complicated by AKI-D, further studies with more granular data are needed to identify effective prevention and management strategies for early identification of high-risk cases, and potentially mitigate the prognosis of this severe complication.

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Fig. 1.

Temporal trends of septicemia patient hospitalizations complicated by all AKI-D patients. There was a significant increase in the proportion of AKI-D in septicemia hospitalizations from 1.4% in 2002 to 2.65% in 2013.

Table 1

Baseline characteristics of study population stratified by AKI-D

	Septicemia		P
	Without AKI-D	With AKI-D	
Age, mean (SE)	68.86 (0.07)	64.49 (0.12)	<.0001
18–34	4.83	3.64	
35–49	9.34	11.83	
50–64	21.27	31.84	
65	64.56	52.69	
Sex			<.0001
Male	46.85	56.04	
Female	53.15	43.96	
Race			<.0001
White	62.41	56.49	
African American	10.98	15.84	
Hispanic	7.27	9.86	
Others	4.94	5.83	
Missing	14.4	11.98	<.0001
APRDRG mortality scale			<.0001
1&2	30.06	1.08	
3	31.79	9.66	
4	37.7	89.05	
Concurrent diagnosis			
Diabetes mellitus	31.35	35.41	<.0001
Hypertension	49.05	54.99	<.0001
CKD	14.32	21.89	<.0001
HIV	0.68	1.13	<.0001
Acute or chronic liver disease	9.16	28.49	<.0001
Liver or intrahepatic biliary cancer	0.38	0.57	<.0001
Acute myocardial infarction	4.75	11.13	<.0001
Primary acute heart failure	21.92	32.22	<.0001
Cardiac catheterizations	0.74	1.56	<.0001
Mechanical ventilation	14.56	58.74	<.0001
Hospital characteristics Hospital bed size			<.0001
Small	12.82	8.16	
Medium	26.31	23.91	
Large	60.4	67.25	
Hospital location			<.0001
Rural	14.27	5.05	
Urban nonteaching	44.86	43.42	
Urban teaching	40.4	50.85	
Hospital region			<.0001

	Septicemia		<i>P</i>
	Without AKI-D	With AKI-D	
Northeast	18.4	16.36	
Midwest or North Central	21.48	20.95	
South	38.14	38.02	
West	21.11	23.92	
Disposition			<.0001
Home	32.29	12.43	
Discharge against medical advice	0.67	0.37	
Discharge to specialized care	51.73	47.14	
Died	15.06	39.79	
Zip code income (%) [*]			<.0001
0–25 percentile	27.54	29.67	
26–50 percentile	24.47	24.2	
51–75 percentile	22.49	22.96	
76–100 percentile	19.57	18.71	
Primary payer			<.0001
Medicare/Medicaid	77.21	72.07	
Private	16.72	20.88	
Uninsured/self-pay	5.91	6.92	
LOS	5.46 (3.17–9.30)	15.60 (9.64–24.29)	
Cost (\$)	10 850 (6349.09–19571)	40 692 (24 162–70690)	

Both populations were compared using χ^2 test, Wilcoxon rank sum test, and survey regression depending on the distributions of individual variables.

* Quartile classification of the estimated median household income of residents in the patient's ZIP code. These values are derived from ZIP code-demographic data obtained from Claritas.