Acute Kidney Injury Is Associated With an Increased Risk of Dementia

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There is growing evidence that acute kidney injury (AKI) is associated with adverse long-term outcomes, including an increased risk of developing chronic kidney disease, end-stage kidney disease, cardiovascular events, and death.[1] The acute neurological complications of AKI are well described and include attention deficits, decreased mental status, seizures, and hyperreflexia.[2] The long-term consequences of AKI on neurologic outcomes are unclear. We tested the hypothesis that AKI, even with complete renal recovery, is associated with a higher risk of developing dementia.

We performed a retrospective propensity score–matched study using data from Intermountain Healthcare, a nonprofit organization that serves Utah and Idaho and averages more than 130,000 admissions annually. We included adult patients hospitalized between January 1, 1999, and December 31, 2009, with complete clinical and administrative data. We excluded patients with a history of dementia or chronic kidney disease (CKD) determined by *International Classification of Diseases, Ninth Revision* (ICD-9) code. AKI was defined by ICD-9 codes and Kidney Disease: Improving Global Outcomes definitions of AKI based on serum creatinine levels.[3,4] The Kidney Disease: Improving Global Outcomes definition of AKI included an increase in serum creatinine to $\geq$1.5 times baseline.[4] AKI with complete recovery was defined as discharge creatinine $<$1.10 times the preadmission baseline value. Demographic, baseline creatinine, prior inpatient visits, season of admission, and all components of the Charlson Comorbidity index[5] were used to generate the propensity score. The primary outcome was time to dementia as determined by ICD-9 codes 290 to 290.4 and 331.[3] The Cox proportional hazard model was used to compare time to dementia among patients with and without AKI. All statistical analyses were performed with SAS software, version 9.14 (SAS Institute, Cary, NC).

Using a pool of more than 6977 patients with complete data, we identified 1041 patients with AKI followed by complete recovery. We propensity score–matched 1041 patients with AKI patients with 1041 patients without AKI during the index admission. After propensity score matching, covariates were well balanced between the groups (Table 1). The mean (SD) age and baseline creatinine was 61 $\pm$ 16 years and 0.9 $\pm$ 0.2 mg/dl, respectively. More than 90% of the participants were white and nearly half were women. During a median (interquartile range) follow-up time of 5.8 (2.0–7.7) years, 97 patients developed dementia. More patients with AKI developed dementia (7.0% vs. 2.3%). The median (interquartile range) time to dementia was slightly shorter in patients with AKI compared with patients without AKI (1.9 [0.2–4.1] years vs. 2.0 [0.5–3.3] years). Patients with AKI had a more than 3-fold increased risk of developing dementia compared with those without AKI (hazard ratio: 3.4; 95% confidence interval: 2.14–5.40). Because there were more deaths in the AKI group (480 vs. 355), we also examined the association of AKI with the composite outcome of dementia or death. AKI increased the risk of the composite outcome of dementia or death by 60% (hazard ratio: 1.60; 95% confidence interval: 1.40–1.84).

Our study adds to the growing literature that AKI is associated with long-term adverse outcomes. We found a significant increased risk of dementia following AKI in patients without a previous history of cognitive dysfunction. Cognitive dysfunction is a well-known complication of CKD,[6] but long-term cognitive dysfunction in AKI is not well described. Several studies have found that cognitive function declines as kidney

function declines.[6] Although cardiovascular disease risk factors, such as hypertension and diabetes, which are highly prevalent in patients with CKD, lead to lower cognitive function, studies have found that the risk of dementia is independent of these risk factors in patients with CKD.[6] Similarly, in our study of patients with AKI, those with AKI had a higher risk of dementia despite being matched to those without AKI on these cardiovascular risk factors. A previous study performed in Taiwan of 2905 patients with AKI requiring dialysis who recovered and survived for at least 90 days found results similar to our study; patients with AKI had greater risk for subsequent development of dementia than those without AKI independent of cardiovascular risk factors.[7] Notably, this study did not report the degree of kidney function recovery.

How AKI may lead to cognitive dysfunction is unclear, but increased inflammation, oxidative stress, and endothelial dysfunction are all described complications of AKI.[2,8,9] In animal models, ischemic AKI resulted in inflammation and functional changes in the brain.[9] Specifically, compared with sham mice, those with AKI had increased neuronal pyknosis and microgliosis in the brain.[9] In addition, the mice with AKI had significant microvascular dysfunction in the brain. Whether these changes occur in humans has not been determined and further study is required.

Our study has limitations. First, because it is an observational study, we are unable to determine causality or determine the mechanism by which AKI leads to an increased risk of dementia. Dementia was determined by ICD-9 code and hence misdiagnosis may have occurred. In addition, although we did have follow-up data on these patients, including ICD-9 codes for CKD, we did not have serum creatinine levels following hospital discharge. Finally, although we included a large number of covariates in the propensity score matching, there may be other confounders that were not included.

Notwithstanding these limitations, our study also has several strengths. It includes a large cohort of patients from the largest health care provider in the Intermountain West. We had complete laboratory and administrative data and thus were able to propensity score match more than 1000 patients with AKI to those without AKI. The use of propensity score matching is a strength, as it reduces bias due to confounding variables.

Our study suggests that in addition to an increased risk of death, CKD, and cardiovascular events, AKI leads to an increased risk of dementia. Our findings suggest that after AKI, patients should be monitored more closely for cognitive impairment, which is a change in current clinical practice. How frequently patients should be screened for cognitive impairment after AKI is unknown, and larger prospective studies are needed to answer this question and to confirm our findings. Although we currently do not have any therapeutic strategies to reduce long-term consequences of AKI, close monitoring of patients after AKI may result in less morbidity and mortality.

Table 1. Propensity score matching of patients with and without AKI

Characteristic	AKI $n = 041$	No AKI $n = 1041$
Age (yr)	61 ± 17	62 ± 16
Race, *n* (%)		
White	957 (91.9)	961 (92.3)
Black	7 (0.7)	7 (0.7)
Hispanic	47 (4.5)	47 (4.5)
Hypertension, *n* (%)	716 (68.8)	733 (70.4)
Diabetes, *n* (%)	363 (34.9)	365 (35.1)
Congestive heart failure, *n* (%)	317 (30.5)	298 (28.6)
Acute myocardial infarction, *n* (%)	177 (17.0)	175 (16.8)
Chronic obstructive pulmonary disease, *n* (%)	498 (47.8)	492 (47.3)
Cerebrovascular disease, *n* (%)	182 (17.5)	171 (16.4)
Peripheral vascular disease, *n* (%)	167 (16.0)	147 (14.1)
Liver disease, *n* (%)		
Mild	235 (22.6)	221 (21.2)
Severe	35 (3.4)	30 (2.9)
Mixed connective tissue disease, *n* (%)	80 (7.7)	79 (7.6)
Peptic ulcer disease, *n* (%)	126 (12.1)	113 (10.9)
Paralysis, *n* (%)	54 (5.2)	52 (5.0)
HIV, *n* (%)	1 (0.1)	2 (0.2)
Metastatic cancer, *n* (%)	263 (25.3)	279 (26.8)
Prior inpatient visits	3.1 ± 3.5	3.1 ± 4.9
Baseline creatinine (mg/dl)	0.93 ± 0.2	0.93 ± 0.2

AKI, acute kidney injury.
All values are mean ± SD or number and percentage.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Methods.

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