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Original Article

Long-term risk of dementia following acute kidney injury: A population-based study

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Abstract

Objective: Adverse neurological effects may be common following acute kidney injury (AKI). The purpose of our study was to investigate the long-term risk of dementia following AKI and temporary dialysis during hospitalization. **Materials and Methods:** The study was based on data from the National Health Insurance Research Database of Taiwan. Patients 18-year-old and older who were withdrawn from temporary dialysis because of AKI and survived for at least 90 days following discharge were included in our acute-dialysis-recovery group. Patients without AKI and dialysis were the control group. A Cox proportional-hazards regression model was applied to determine the risk of dementia. **Results:** Of 2905 acute-dialysis patients, 689 (23.7%) survived for at least 90 days following recovery from acute dialysis. The Cox proportional-hazards regression model showed that the acute-dialysis-recovery group had an increased long-term risk of dementia (hazard ratio [HR], 2.01; $P = 0.01$) compared with the control group. The conditional effects plot showed that the risk of dementia was amplified in patients who were older than 58 years. The development of dementia following recovery from acute dialysis was associated with an increase in all-cause mortality (HR, 2.38; $P < 0.001$). **Conclusions:** Patients with acute dialysis have a greater risk for the subsequent development of dementia after recovery than patients without AKI and dialysis, and patients who develop dementia after recovery from temporary dialysis are at increased risk for mortality.

Keywords: *Acute kidney injury, Chronic kidney disease, Dementia, Dialysis, End-stage renal disease*

Introduction

The number of people affected by cognitive decline, including cognitive impairment and dementia, is increasing worldwide [1]. Dementia is a syndrome characterized by a catastrophic, progressive global deterioration in intellectual function, and is one of the main causes of disability among elderly people [2]. Recent estimates suggested that 25 million people worldwide were affected by dementia in 2000, and the data suggested that this figure will increase to 42 million by 2020 [1]. Dementia carries a substantial economic burden globally. Therefore, the identification of predictors of dementia is of significant importance.

Acute kidney injury (AKI) is a major contributor to morbidity and mortality in hospitalized patients [3]. Recent study showed that survivors of critical illness are associated with higher risk of cognitive impairment. Long-term cognitive impairment is a growing public health problem [4]. Although AKI was once considered a reversible condition, mounting evidence indicates that it may have a negative impact on subsequent renal function and the long-term prognosis despite the level of recovery of kidney function [5]. Cyclical hemodynamic stress related to hemodialysis combined with the extensive vascular disease may accelerate the cognitive deficits that are characteristic of cerebral microvascular disease [6].

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Severe AKI causes uremic encephalopathy. In animal studies, AKI adversely affects the brain, presumably through the distant effects of AKI-induced inflammation [7]. Previous studies have shown that chronic kidney disease (CKD) and end-stage renal disease (ESRD) are associated with an increased risk of dementia [8,9]. However, the relationship between AKI and dementia remains unclear. Therefore, the purpose of this study was to investigate the long-term risk of developing dementia following recovery from temporary dialysis.

Materials and methods

Data source

The data for our population-based study were retrieved from the Longitudinal Health Insurance Database (LHID) and were randomly selected from the claims records of the Taiwan National Health Insurance (NHI) program by the National Health Research Institute (NHRI), and released for research purposes in 2000. The LHID was provided to the public for research purposes. This database provided information including age, sex, dates of hospital admission and discharge, the International Classification of Disease, 9th edition, Clinical Modification (ICD 9-CM) codes of diagnosis and procedures, medical institutions providing services, and outcomes at hospital discharge. The NHI program provides health care to all Taiwanese residents, and it covered more than 99% of the population in Taiwan in 2010. The LHID is updated annually and consists of all the original claims data and registration files for 1 million residents of Taiwan who were randomly sampled from the 2000 Registry for Beneficiaries of the NHI program.

Ethical considerations

Informed consent was originally obtained by the NHRI, and since patients were anonymous in the present study, informed consent was not required. In addition, since the identification numbers of all individuals in the NHRI databases were encrypted to protect their privacy, this study was exempt from a full ethical review by the institutional review board of National Taiwan University Hospital (201212021RINC).

Participant selection

We identified patients 18-year-old and older who were hospitalized and received the first-time dialysis for AKI between January 1999 and December 2008. AKI was diagnosed when there was a rapid reduction of renal function, as measured by serum creatinine or reduction in urine output [10]. Since the diagnosis of AKI is often underreported during hospitalization if only AKI codes are used, we identified AKI if the admissions claim data included a dialysis code (procedure codes). This method to identify AKI-dialysis patients has been utilized previously and has a high accuracy rate since the Taiwan NHI database is claims-based and procedure codes are always linked to reimbursements, which would not be missed by physicians [11]. We excluded patients with a history of dementia, and those who had undergone dialysis, or were diagnosed with AKI within 1 year preceding the index hospitalization. We defined the "index hospitalization" as the first admission during the observation period. We also excluded patients who had undergone kidney transplantation or who were hospitalized for longer than 180 days before the index hospitalization. Patients who died during the index hospitalization or within 90 days of the discharge date were excluded from the study. As in our previous study, we chose 90 days to reduce the possibility of survivor-treatment bias [11]. Figure 1 shows the patient selection process. Of the remaining patients with AKI requiring dialysis, 2 subgroups were identified. One group was the patients who continued receiving dialysis; the other group was the patients who were withdrawn from dialysis. The second group comprised our AKI-dialysis recovery group. We chose patients who survived for at least 90 days following hospital discharge to reduce the possibility of immortal time bias [12-14].

The control group patients, who were hospitalized without a history of dementia, AKI or dialysis within 1 year preceding the index hospitalization, were randomly selected from the remaining NHI beneficiaries. The study group to control group ratio was 1: 4. To determine the primary outcome of developing dementia, we tracked all patients until December 31, 2009. In both the outpatient department and during hospitalization, the first appearance of dementia was identified according to ICD-9-CM codes (290.X, 290.XX, 294.X, 294.XX, 331.X). The diagnosis was mostly done by board-certified neurologists or psychiatrists after excluding dementia or delirium due to other medical illnesses and brain organic lesions.

Research variables

We collected the demographic and clinical characteristics of the study individuals, including age, sex, and comorbidities. To identify comorbidities, we used the criteria of at least 1 admission or at least 3 outpatient visits for the treatment of a certain disease during the year preceding the index admission. The "CKD" comorbidity was defined according to ICD-9-CM coding (provided in supplementary file 1) rather than the estimated glomerular filtration rate (eGFR). This method demonstrated fair validity in estimating the CKD prevalence and has also been utilized in past reports [15,16]. We also collected the diagnosis and procedure codes during hospitalization, including mechanical ventilation use, intensive care unit admission, and long-term outcomes. Charlson comorbidity index scores were based on pre-existing conditions from a patient's medical records.

Statistical analysis

All statistical analyses were performed using the R computer program, Version 2.14.1 (Free Software Foundation, Boston, MA, USA). Chi-squared tests were performed to examine the differences in the categorical data, and the unpaired *t*-test or Mann–Whitney U test was used for the analysis of continuous data as appropriate. Two-sided $P < 0.05$ was considered to represent a statistically significant difference.

A propensity score to account for baseline differences and reduce selection bias between the two groups was used [17]. A nonparsimonious multivariable logistic regression analysis was applied to produce propensity scores for predicting the probability of AKI requiring dialysis during the index hospitalization. The goodness of fit was assessed using the modified Hosmer-Lemeshow test. The discriminative power was assessed using the area under the receiver operating characteristic (AUROC) curve.

A Cox proportional multivariable regression hazards model was used to estimate the long-term risk of dementia after the index hospitalization based on the hazard ratios (HRs).

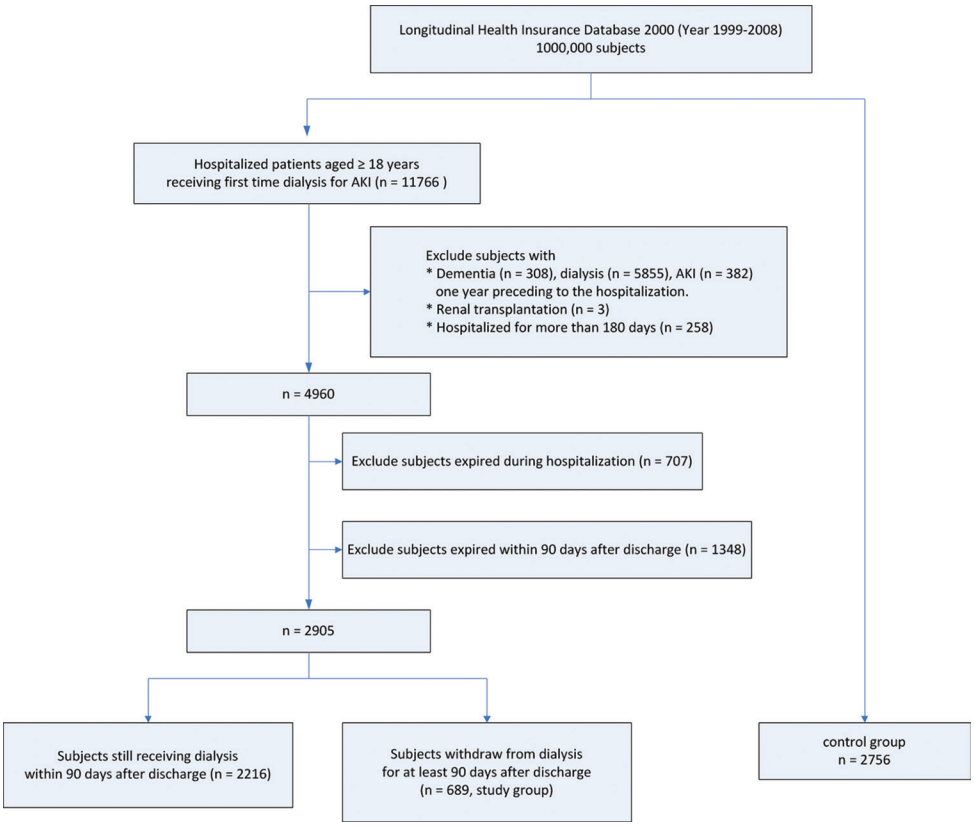

Figure 1: Diagram of the patient selection process

Because CKD and ESRD are strongly correlated with cognition dysfunction [18-21], we used a Cox proportional hazards model with time-varying covariates to evaluate the impact of CKD or ESRD on the risk of dementia, based on the assumption that CKD or ESRD could develop at any time between the hospital discharge date and the diagnosis of dementia. Because dementia is correlated with long-term mortality [8], we made another time-varying Cox regression model to examine whether AKI requiring dialysis was associated with all-cause mortality after discharge.

A conditional effect plot for dementia was drawn based on the fitted results of the regression model to predict dementia. It was a contingency analysis for age with the addition of a covariate for the interaction of age with incident dementia. The model estimated the probability of having dementia against a chosen continuous covariate, with the values of the other discrete and continuous covariates held constant [17,22].

Results

Demographic data and comorbidities

A total of 2905 patients 18-year-old and older who were hospitalized and received first-time dialysis for AKI were identified. Of these, 689 (23.7%) patients who recovered after acute dialysis and survived for at least 90 days following hospital discharge were our study group patients. A total of 2756 patients without AKI or dialysis were our control group. The demographic characteristics and baseline comorbidities of the two groups of patients are shown in Table 1. Compared with the control group, the patients in the AKI-dialysis recovery group were more likely to be male, were older, had higher Charlson scores, had a higher prevalence of comorbidities, and had more acute organ dysfunction, except for acute hematologic disorders. The patients in the recovery group were also more likely to develop CKD or ESRD, compared with the control patients.

Propensity score for acute kidney injury requiring dialysis

Logistic regression analysis showed that age, male sex, hypertension, diabetes mellitus, CKD, moderate or severe liver disease, number of hospitalizations, and acute organ dysfunction, including respiratory, cardiovascular, and hepatic comorbidities, were independent predictive factors to differentiate the two groups [Table 2]. We applied these variables to calculate the propensity score for each patient to eliminate the baseline differences between groups. The validation test showed an adjusted R^2 of 0.685, and the AUROC value was 0.942. The predicted probability derived from this model was used as the propensity score for each patient.

Factors predicting long-term dementia

There were 44 (6.4%) patients in the AKI-dialysis-recovery group and 67 (2.4%) patients in the control group who developed dementia during the study. The incidence rate of dementia was 200/10 000 person-years in the AKI-dialysis-recovery group, and 53/10 000 person-years in the control group. After adjusting for baseline comorbidities, acute organ dysfunction, and the propensity score, patients in the AKI-dialysis-recovery group remained at greater risk of developing dementia (HR, 2.01; 95% CI, 1.19–3.39; P = 0.01) than the control patients [Table 3].

Table 1: Data of patients who recovered from acute kidney injury and control patients without acute kidney injury

	Recovery from acute dialysis (*n*=689), *n* (%)	Control group (*n*=2756), *n* (%)	*P*
Patient characteristics			
Male	400 (58.1)	1249 (45.3)	<0.001
Age (years)	63.33±16.19	46.37±18.4	<0.001
Comorbidities (1 year before admission)			
Charlson score	2.4±2.11	0.34±0.84	<0.001
Myocardial infarction	22 (3.2)	6 (0.2)	<0.001
Congestive heart failure	109 (15.8)	30 (1.1)	<0.001
Peripheral vascular disease	8 (1.2)	4 (0.1)	0.001
Cerebrovascular disease	57 (8.3)	43 (1.6)	<0.001
COPD	65 (9.4)	103 (3.7)	<0.001
Rheumatologic disease	10 (1.5)	11 (0.4)	0.004
Peptic ulcer	109 (15.8)	137 (5)	<0.001
Hemiplegia	7 (1)	3 (0.1)	0.001
Solid tumor	43 (6.2)	59 (2.1)	<0.001
Tumor with metastasis	17 (2.5)	8 (0.3)	<0.001
Diabetes mellitus	296 (43)	179 (6.5)	<0.001
Moderate or severe liver disease	42 (6.1)	86 (3.1)	<0.001
Chronic kidney disease	198 (28.7)	17 (0.6)	<0.001
Hypertension	392 (56.9)	419 (15.2)	<0.001
CAD	156 (22.6)	112 (4.1)	<0.001
Stroke	57 (8.3)	45 (1.6)	<0.001
Hyperlipidemia	115 (16.7)	128 (4.6)	<0.001
Acute organ dysfunction			
Cardiovascular	53 (7.7)	13 (0.5)	<0.001
Respiratory	145 (21)	15 (0.5)	<0.001
Hepatic	16 (2.3)	18 (0.7)	<.001
Neurologic	12 (1.7)	3 (0.1)	<0.001
Hematologic	4 (0.6)	6 (0.2)	0.121
Metabolic	32 (4.6)	0 (0)	<0.001
Operative categories			
Mechanical ventilation	252 (36.6)	63 (2.3)	<0.001
ICU admission during index hospitalization	391 (56.7)	140 (5.1)	<0.001
Long-term outcome			
Post-AKI-related ESRD	125 (18.1)	1 (0)	<0.001
Post-AKI-related CKD	353 (51.2)	39 (1.4)	<0.001
Dementia	44 (6.4)	67 (2.4)	<0.001

Descriptive statistics for categorical variables were expressed as frequency and percentage, while continuous variables were expressed as mean±SD as appropriate. CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, ESRD: End stage renal disease, CKD: Chronic kidney disease, SD: Standard deviation, AKI: Acute kidney injury, ICU: Intensive Care Unit

Other significant risk factors included age (HR, 1.10; 95% CI, 1.08–1.11; $P < 0.001$), neurologic comorbidities (HR, 4.82; 95% CI, 1.15–20.14; $P = 0.03$), and stroke (HR, 1.80; 95% CI, 1.00–3.25; $P = 0.05$). However, the development of ESRD following recovery from AKI requiring dialysis, the time-dependent explanatory variable, was not significantly associated with the development of dementia based on our time-varying model (HR, 0.96; 95% CI, 0.37–2.49; $P = 0.93$). The value of the C-index (0.87) and the adjusted R^2 (0.18) indicated good validity for the model. Postrecovery dementia was also estimated using CKD in the time-varying Cox regression model, and the model results showed that the AKI-dialysis-recovery group had a greater risk of developing dementia (HR, 1.81; 95% CI, 1.02–3.20; $P = 0.04$), compared with control patients.

Sensitivity analyses were done to control for the different baseline characteristics. We made a case–control model matching both groups for age, sex, and diabetes mellitus. The AKI-dialysis recovery group still showed an increased risk of dementia development compared with the control group. (HR 1.8, 95% CI 1.08–2.98, $P = 0.02$) The characteristics of the matched patients and Cox proportional hazards regression results are shown in supplementary file 2.

Conditional effect plots stratified by age and study group

A conditional-effect plot of the estimated risk versus patient age at recovery from AKI requiring dialysis was constructed to demonstrate the probability of developing dementia and compared to that of the control patients [Figure 2]. The turning point is defined as the maximum slope of the tangent line according to the curve. As the turning point shows, patients in the AKI-dialysis-recovery group had an amplified risk of incident dementia after the age of 58 years.

Postdischarge dementia and long-term all-cause mortality

The AKI–dialysis-recovery group had an increase in all-cause mortality after the index hospitalization (HR, 2.84; 95% CI, 2.22–3.64; $P < 0.001$), compared with control patients. The development of postdischarge dementia was also associated with increased all-cause long-term mortality (HR, 2.38; 95% CI, 1.70–3.34; $P < 0.001$), compared with AKI-dialysis-recovery patients who did not develop dementia.

Discussion

Our study reinforces the view that patients recovering from AKI requiring dialysis have a greater risk of developing dementia than control patients. The risk of developing dementia markedly increased in the temporary dialysis patients who were older than 58 years at hospital discharge. Neurological complications of AKI include central nervous system dysfunction with irritability, attention deficits, and diminished mental status. Although AKI is common in hospital patients, the interaction of AKI and the brain remains unclear, especially regarding long-term events. Several mechanisms have been proposed regarding the causal relationship between impaired renal function and the development of dementia [19,20]. Hemodialysis patients have a higher prevalence of brain vessel infarcts, which are frequently associated with white matter disease and severe brain atrophy, which may contribute to subclinical stroke and subsequent cognitive decline [23-25].

A link between inflammation and brain function has been suggested based on the development of fever and so-called sick behavior [26]. Characterized by pyknosis and cell death, the brain lesions observed following AKI appear more severe than the brain pathology observed in sick behavior [27]. The pathophysiology of lesion formation in AKI is poorly understood.

Table 2: Independent predictive factors in logistic regression analysis differentiating the study and control groups

Covariate	OR (95% CI)	*P*
Age	1.02 (1.02-1.03)	<0.001
Male	2.25 (1.70-3.00)	<0.001
Hypertension	1.57 (1.13-2.17)	0.01
Diabetes mellitus	3.42 (2.40-4.86)	<0.001
CKD	16.15 (10.77-24.48)	<0.001
Number of hospitalizations	11.64 (8.44-16.39)	<0.001
Respiratory comorbidities	43.85 (23.96-84.87)	<0.001
Cardiovascular comorbidities	14.97 (6.82-33.86)	<0.001
Hepatic comorbidities	5.90 (2.24-14.45)	<0.001
Moderate or severe liver disease	0.36 (0.17-0.74)	0.01

CI: Confidence interval, CKD: Chronic kidney disease, OR: Odds ratio

Table 3: Independent predictive factors for long-term dementia according to the time-varying Cox regression model

Covariate	Hazard ratio (95% CI)	*P*
Age (year)	1.10 (1.08-1.11)	<0.001
Acute dialysis	2.01 (1.19-3.39)	0.01
Stroke	1.80 (1.00-3.25)	0.05
Neurologic comorbidities	4.82 (1.15-20.14)	0.03
Ongoing ESRD after discharge	0.96 (0.37-2.49)	0.93

CI: Confidence interval, ESRD: End stage renal disease

Potential mechanisms include increased vascular permeability, alterations in the blood-brain barrier, and inflammatory responses [7,27,28]. Cytokines may stimulate brain endothelial cells to produce pro-inflammatory molecules that traverse the blood-brain barrier. The second pathway for distant brain damage in the presence of AKI could be uremic solute retention, which in turn triggers cascades that result in both neuronal cell damage and pro-inflammatory reactions [8].

Age remains the strongest major risk factor for dementia [29,30]. After adjusting for age and potential confounders, the conditional-effect plot for our study showed that patients who recovered from AKI requiring dialysis had an increased risk of developing dementia after the age of 58 years compared with the control patients. These results are consistent with those of previous studies, which showed that the incidence of dementia increased exponentially after the age of 65 years [31], suggesting that the effects of AKI and temporary dialysis-associated brain injury amplify the risk of dementia. Approximately, 20% of all the participants were diagnosed with ESRD by the end of the study period. However, we found no increased risk of incident dementia in patients who developed CKD or ESRD following AKI requiring dialysis, compared with patients who recovered from AKI requiring dialysis who did not develop CKD or ESRD. The 3C study [32] showed that the risk of cognitive decline or dementia was not associated with a reduced eGFR at baseline, but was associated with the rate of decline. A more recently published study showed the effect of renal function decline on the risk of dementia remained significant after adjusting for potential risk factors and cardiovascular comorbidities [33]. The inflammation cascade and related brain injury resulting from severe AKI exceeded that of subsequent CKD or ESRD, which was also evidenced from animal study showing severe ischemic AKI caused inflammation and

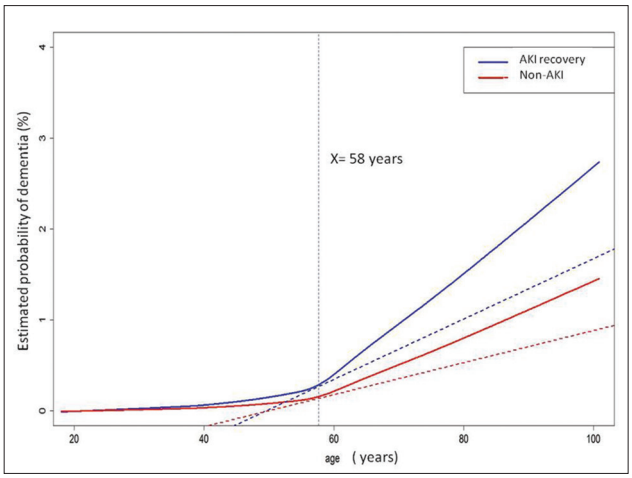

Figure 2: Conditional-effect plots of the estimated risk of dementia versus patient age at withdrawal from dialysis for acute kidney injury and that versus the age of the control patients without acute kidney injury were constructed after adjustment for the propensity score, age, neurologic comorbidities, and stroke

functional changes in the brain [27]. Our data are relevant to the increased risk of dementia in accelerated eGFR decline.

Cognitive impairment in dialysis patients may be an indicator of a poor prognosis. The diagnosis of dementia before the initiation of dialysis has been shown to be an independent risk factor for mortality [34], and the average time to death for dialysis patients with dementia was less than half of that in control dialysis patients. Our results extend poor survival in dementia to temporary dialysis patients by showing that dementia following recovery from AKI requiring temporary dialysis is an independent risk factor for mortality.

The large cohort used in our study contributed to the statistical strength of our findings. As a population-based study, our results may be extended to the general population. Because the primary data were claims information originally taken from the NHI database, which covers 99.7% of the population in Taiwan, information on exposures, outcomes, and covariates were prospectively collected. Thus, missing data or loss to follow-up did not occur. In addition, we randomly selected 4 control patients for every AKI-dialysis-recovery patient, which is statistically sufficient to represent the general population.

Our findings are subject to a number of limitations. First, since the diagnosis of dementia is diagnosis-code based, which may be an insensitive measure for capturing dementia, the majority of dementia cases are likely underdiagnosed. This is especially true in the hemodialysis population, where on average only 4% of dementia cases were diagnosed in previous study [35]. Although this may represent a minority proportion of genuine cases, it will clearly introduce measurement error which could be overcome by having a sufficiently large number of patients, as our study did. Second, we excluded patients with a history of AKI, dialysis, or dementia within the year preceding the index hospitalization, including both inpatient and outpatient diagnoses. However, the actual initiation of cognitive decline likely occurs before sufficient criteria are met for a diagnosis. Thus, it is possible that patients with subclinical dementia may have been included in either the AKI-dialysis-recovery group

or the control group. Third, we could not adjust our regression model based on clinical laboratory results, family history, physical activity status, cigarette smoking, alcohol consumption, and occupation because such potential covariates are not included in the NHI records.

Conclusions

We observed an increased long-term risk of *de novo* dementia in patients who recovered from AKI requiring dialysis during hospitalization which was independent of the development of CKD or ESRD subsequent to hospital discharge. The odds ratio was dramatically amplified in patients older than 58 years. The development of dementia following recovery from AKI requiring dialysis was also associated with a long-term increase in all-cause mortality. Further investigation of the underlying mechanisms of the development of dementia following AKI with dialysis is warranted.

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Conflict of interest

There are no conflicts of interest.

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