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Association between acute kidney injury and risk of Parkinson disease

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ABSTRACT

Backgrounds: Worldwide, the incidence of acute kidney injury (AKI) has been increasing. However, information on the long-term incidence of Parkinson disease (PD) in patients with AKI has not been reported.
Methods: A total of 9380 patients with AKI and 37,484 age- and sex-matched patients who did not have AKI were identified during 2003–2011. All patients were tracked until a diagnosis of PD, death, or the end of 2011. Cumulative incidences and hazard ratios (HRs) were calculated.
Results: The mean follow-up time for PD was 6.89 (SD = 3.30) years in the AKI cohort and 6.78 (SD = 3.29) years in the non-AKI cohort. The overall incidence densities of PD were significantly higher in the AKI cohort than in the non-AKI cohort (6.04 vs. 3.99/1000 person-years), with an adjusted HR of 1.47 (95% confidence interval [CI] = 1.18–1.83). Compared with the patients in the non-AKI cohort aged ≤64 years, the relative risk (95% CI) of PD was 2.17 (1.12–4.18), 14.1 (9.16–21.8), and 14.1 (8.43–23.6) for the patients in the AKI cohort aged ≤64, 65–79, and ≥80 years, respectively.
Conclusion: Patients with AKI were associated with a higher long-term risk of PD.

1. Introduction

Parkinson disease (PD), affecting approximately 1%–2% of the population worldwide, is the second most common neurodegenerative disorder after Alzheimer disease [1]. PD has a broad spectrum of symptoms such as progressive motor dysfunction and psychiatric disturbances, which gradually reduce a patient's ability of self-care [2]. The onset of PD typically occurs in the sixth decade, and its prevalence increases with age. Approximately 77% of patients have a poor outcome 10 years after the diagnosis of PD [3]. With the worldwide phenomenon of population aging [4], PD is expected to impose an increasing economic and social burden on medical care systems. In patients with PD, the proposed pathologic mechanisms of selective dopaminergic neuron loss in the substantia nigra are mitochondrial dysfunction, oxidative stress, and protein mishandling [5]. The susceptibility genes PARK 1–15 have been identified to play a role in the pathogenesis of PD. Over the decades, epidemiologic studies have reported that nongenetic factors (occupational exposure, dietary factors, and inflammation) [6] and disease (diabetes [7], abnormal heart rate variability [8], end-stage renal disease [9], hypertension [10], and depression [11]) are associated with the risk of PD development.

Acute kidney injury (AKI), of which the incidence proportionately increased over the decades, is a common complication of medical illness and surgical procedures in hospitalized patients. [12,13]. Recent studies have revealed that the consequences of AKI are considerably broad and encompass short-term and long-term major organ damage in addition to kidney damage [14,15]. Studies on experimental animals have demonstrated that AKI leads to an increase in microvascular permeability in the brain, induces proinflammatory chemokines, and causes inflammation and functional changes of the blood–brain barrier [16]. Wu et al. reported that AKI is associated with a 1.25-fold higher risk of de novo stroke [17]. These findings suggest that AKI has remote effects on the central nervous system (CNS). However, whether AKI causes long-lasting neurodegenerative effects within the CNS remains unknown. Furthermore, the results of animal studies lack clinical relevance. Thus, the association between AKI and neurodegenerative disorders, such as PD, requires epidemiologic evidence obtained using a large-scale cohort study design.

The Taiwan National Health Insurance (NHI) Research Database (NHIRD) provides longitudinal and comprehensive medical claims

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data on approximately 23 million people. Several studies have used the NHIRD to investigate AKI or PD, and the data are reliable [18–21]. We used data from the NHIRD to examine whether AKI is associated with the risk of long-term PD.

2. Methods

2.1. Data source

Data for the subjects sampled in this retrospective cohort study were obtained from the Longitudinal Health Insurance Database 2000 (LHID2000). On March 1, 1995, Taiwan implemented the NHI program and enrolled nearly 99% of all residents [22]. The LHID2000 consists of all original medical claims for a random sample of 1000,000 NHI beneficiaries from the 2000 Registry of Beneficiaries compiled using a systematic sampling method for research purposes. The details of the NHI program and LHID2000 have been previously described [23,24]. This study was approved by the Institutional Review Board of China Medical University (CMUH104-REC2-115).

2.2. Study population

The AKI cohort was identified during January 1, 2000 to December 31, 2011. We included patients with newly diagnosed acute renal failure (ICD-9-CM codes 584.5–584.9) and set the index date as the date of AKI diagnosis. We used a 1-year period prior to the index date to identify preindex comorbidities and AKI. Patients with a history of chronic kidney disease (CKD; ICD-9-CM code 585), end-stage renal disease (ESRD; ICD-9-CM code 585), and PD (ICD-9-CM code 332) before the index date were excluded. The diagnosis of primary PD is based on ICD-9 code (332 except 332.1), while the diagnosis of secondary PD is based on ICD-9 code (332.1). The non-AKI cohort, comprising patients without any kidney disease (ICD-9-CM codes 580–589), was randomly identified from the LHID2000 during the same period of 2000–2011, with exclusion criteria identical to those applied to the AKI cohort. With each AKI patient, 4 non-AKI subjects were frequency-matched by age (every 5-year span), sex, and the year of the index date. The patients in both cohorts were followed until PD was diagnosed, they were censored for withdrawal from the NHI program, or December 31, 2011.

Table 1
Demographic characteristics and comorbidities in cohorts with and without acute kidney injury.

Variable	Acute kidney injury		*p*-value
	No	Yes	
	N = 37,484	N = 9380	
Age, year			0.99
≤49	6268(16.7)	1567(16.7)	
50–64	7544(20.1)	1886(20.1)	
65–79	13,821(36.9)	3453(36.8)	
80+	9851(26.3)	2474(26.4)	
Mean ± SD†	67.0(16.7)	67.8(16.7)	0.001
Sex			0.99
Female	15,173(40.5)	3797(40.5)	
Male	22,311(59.5)	5583(59.5)	
Urbanization level&			<0.001
1 (Highest urbanization)	10,306(27.5)	2281(24.3)	
2	10,038(26.8)	2536(27.0)	
3	6504(17.4)	1624(17.3)	
4(Lowest urbanization)	10,636(28.4)	2939(31.3)	
Occupation			<0.001
Housekeeping	10,364(27.7)	2785(29.7)	
White collar	8298(22.1)	1571(16.8)	
Blue collar	12,876(34.4)	3368(35.9)	
Others‡	5946(15.9)	1656(17.7)	
Comorbidity			
Diabetes	5265(14.1)	3025(32.3)	<0.001
Hypertension	19,646(52.4)	6351(67.7)	<0.001
Hyperlipidemia	10,220(27.3)	3025(32.3)	<0.001
Anxiety	3608(9.63)	968(10.3)	0.04
Depression	2021(5.39)	755(8.05)	<0.001
Alcohol-related illness	1277(3.41)	1106(11.8)	<0.001
Obesity	391(1.04)	152(1.62)	<0.001
Bipolar disorder	130(0.35)	73(0.78)	<0.001
Schizophrenia	114(0.30)	77(0.82)	<0.001
Head injury	2318(6.18)	900(9.59)	<0.001
Stroke	3224(8.60)	2221(23.7)	<0.001
Hypnotic medication			
Benzodiazepine	14,620(39.0)	4055(43.2)	<0.001
Non-BZD	4425(11.8)	1584(16.9)	<0.001
Anti-psychotic medications	3294(8.79)	1154(12.3)	<0.001

Chi-Square Test; †: T-Test.
&: Urbanization level was categorized according to the population density of the residential area into 4 levels, with Level 1 the most urbanized and Level 4 the least urbanized.
‡Other occupations included primarily retired, unemployed, or low income populations.

2.3. Variables of interest

The sociodemographic variables used in this study comprised age, sex, urbanization level, and occupation. Urbanization level and occupation were defined in detail in a previous paper [25]. The comorbidities included in this study were diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), anxiety (ICD-9-CM code 300.00), depression (ICD-9-CM codes 296.2, 296.3, 300.4, and 311), alcohol-related illness (ICD-9-CM codes 291, 303, 305, 571.0, 571.1, 571.2, 571.3, 790.3, A215, and V11.3), obesity (ICD-9-CM code 278), bipolar disorder (ICD-9-CM code 296), schizophrenia (ICD-9-CM code 295), head injury (ICD-9-CM codes 850–854 and 959.01), and stroke (ICD-9-CM code 430–438), identified at the baseline. In addition, benzodiazepine (BZD) use, non-BZD use, and antipsychotic medication use were compared between the AKI and non-AKI cohorts. Temporary dialysis was defined on the basis of the procedure code (ICD-9-CM procedure 39.95).

2.4. Statistical analysis

The distributions of the sociodemographic data, comorbidities, and medications of the AKI and non-AKI cohorts were compared using the chi-square test to examine categorical variables and Student's *t* test to examine continuous variables. The Kaplan–Meier method was used to estimate the cumulative incidence of PD in both cohorts, with significance based on the log-rank test. The follow-up period in person-years was used to estimate incidence density rate of PD among different risk factors and stratified by age, sex, urbanization level, occupation,

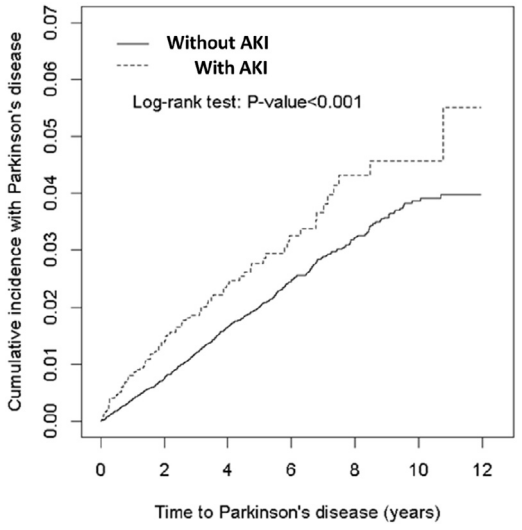

Fig. 1. Cummulative incidence comparison of Parkinson's disease for patients with (dashed line) or without (solid line) acute kidney injury (AKI).

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