Original Article

Polycystic kidney disease increases the stroke incidence in Taiwan: A retrospective population-based cohort study using National Health Insurance Database

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A B S T R A C T

Background: Few studies documented incidence rates of different types of stroke among patients with polycystic kidney disease (PKD).

Methods: We conducted a retrospective cohort study based on the National Health Insurance (NHI) Database of Taiwan. The PKD cohort comprised patients aged ≥20 years diagnosed with PKD using inpatient claims from 1998 to 2011, excluding prior stroke. The reference cohort was established by inpatients without PKD using 1:4 frequency-matched with age, gender, and baseline comorbidities. The two cohorts were followed-up until stroke hospitalization, death, withdrawal from the NHI program, or the end of 2012. To account for competing risks of death, we used multivariable competing risks regression models to estimate sub-distribution hazard ratio (SHR) adjusted for age, gender, baseline comorbidities and end stage renal disease.

Results: 7837 PKD patients and 31,211 reference subjects were followed up through 2012. A total of 955 cases of stroke were identified in the PKD cohort, including 441 ischemic stroke
Polycystic kidney disease (PKD) is a prevalent inherited renal cystic disease, and autosomal dominant polycystic kidney disease (ADPKD) is the most common form. Few studies documented incidence rates of different types of stroke among patients with PKD.

**What this study adds to the field**

We illustrated the incidence rates of stroke among inpatient of PKD. The incidence rates of overall stroke, ischemic stroke, intracranial hemorrhage, and subarachnoid hemorrhage were 21.3, 10.2, 6.8, and 1.7 per 1000 person-years, respectively. The PKD patients had a significantly increased risk of all kinds of stroke after adjusting baseline comorbidities.

**Introduction**

Polycystic kidney disease (PKD) is a prevalent inherited renal cystic disease [1], and autosomal dominant polycystic kidney disease (ADPKD) is the most common form, occurring in approximately 1 in every 400 to 1000 people [2]. Cerebrovascular complications are the major problems resulting in morbidity and mortality among PKD patients. Stroke is the second leading cause of death worldwide, and the overall global burden of stroke is great and increasing [3]. An early report analyzed the causes of death among PKD patients to find 12% from a neurologic event; these were ruptured intracranial aneurysms in 6%, hypertensive intracranial hemorrhage in 5%, and ischemic stroke in 1% [4]. PKD patients have an increased risk for intracranial aneurysms, which had a prevalence of about 5–10% [5,6]. A ruptured cerebral aneurysm, resulting in a subarachnoid hemorrhage (SAH) or intracranial hemorrhage (ICH), is the most serious complication of PKD. About 2% of PKD patients had asymptomatic intracranial arterial dolichoectasia [7], which may be a cause of stroke. The prevalence of cerebral microbleeds is about one-fourth of PKD patients, indicating the fragility of cerebral small vessels [8].

Relatively few studies have evaluated risk of different subtypes of stroke among PKD patients [8]. PKD has been well known to be associated with increased risk of hemorrhagic stroke due to existence of intracranial aneurysms [9,10]. A recent cohort study using primary patients covered by Medicare in the United States demonstrated an increased risk of intracranial hemorrhage among ADPKD patients on maintenance dialysis [11]. However, there is limited research for the association between PKD and ischemic stroke except that PKD was found to be associated with new onset of atrial fibrillation, a risk factor of ischemic stroke [12]. In the present study, we aimed to determine the risk of stroke and its subtypes among PKD patients through a nationwide population-based cohort study using the inpatient claims from the National Health Insurance (NHI) databases in Taiwan.

**Material and methods**

**Data source**

We conducted a retrospective population-based cohort study based on data obtained from the NHI Database (NHID), which are a nationwide, electronic database containing the longitudinal medical records of beneficiaries enrolled in the NHI program in Taiwan. The NHI program, a mandatory single-payer social health insurance launched in 1995, provides universal health care coverage to more than 99% of the population in Taiwan (about 23 million people) [13]. Large computerized databases derived from this system by the National Health Insurance Administration, Ministry of Health and Welfare, and maintained by the Health and Welfare Data Science Center [14], are provided to scientists in Taiwan for research purposes. The NHI databases provide encrypted patient identification numbers, gender, date of birth, dates of admission and discharge, the medical institutions providing the services, the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, and information regarding the health care services provided for each patient, including all payments for outpatient visits, hospitalizations, prescriptions, rehabilitation, and long-term home care visits. The NHI includes the Registry for Catastrophic Illness Patients (RCIP) to protect vulnerable beneficiaries by exempting these patients from copayments for the corresponding medical services. The Taiwan Government created a list of the catastrophic illnesses, including all cancer, end stage renal disease (ESRD), among others. Registration for catastrophic illness requires a diagnosis made by a physician and confirmation by image studies or other supporting medical information; these documents are formally reviewed by...
the NHI Administration. To protect privacy, the patients’ personal information has been encrypted and the NHI databases provide researchers with anonymous identification numbers associated with relevant claims information. Therefore, written informed consent from the patients involved was not necessary. The study was approved by the Institutional Review Board of the National Health Research Institutes (EC1040418-E).

**Study population**

To investigate a potential association between the risk of stroke and PKD, we constructed a PKD cohort and a reference cohort. The PKD cohort comprised patients aged 20 years and older who were diagnosed with PKD using ICD-9-CM codes 753.12 (polycystic kidney, unspecified type) and 753.13 (polycystic kidney, autosomal dominant) from the inpatient claims and validated with the RCIP of the NHID from 1998 to 2011. The index date of the PKD patients was defined as the date of the first diagnosis for PKD in hospital admission. Patients with a prior history of stroke (ICD-9-CM 430–438) in hospital admission before the index date of PKD diagnosis were excluded (N = 1128).

The reference cohort comprised patients without PKD from the inpatient claims, frequency matched by age (in 5-year group), sex, and baseline comorbidities at a ratio of 1:4. The baseline comorbidities included hypertension (ICD-9-CM 401–405), chronic obstructive pulmonary disease (COPD) (ICD-9-CM 491, 492, and 496), congestive heart failure (ICD-9-CM 428), diabetes (ICD-9-CM 250), chronic kidney disease (ICD-9-CM 585), and hyperlipidemia (ICD-9-CM 272) identified by hospital admissions.

End stage renal disease (ESRD) recorded in the RCIP was considered as a risk factor for stroke [15] in the natural history of PKD, and the study subjects were categorized as (1) no ESRD, (2) ESRD before PKD, and (3) ESRD after PKD. The study subjects were followed-up until diagnosis of stroke in hospital admission, death, withdrawal from the NHI program, or the end of this study, December 31, 2012 [Fig. 1].

**Outcome variables**

Our outcome of interest, the incidence of stroke, was based on assessment of NHI inpatient claims for any of the following ICD-9-CM codes: (1) subarachnoid hemorrhage (SAH): 430, (2) intracranial hemorrhage (ICH): 431 and 432, (3) ischemic stroke (IS): 433, 434, and 436, (4) other stroke: 435, 437, and 438.

**Statistical analysis**

Descriptive data were presented as mean ± standard deviation (SD) for continuous variables and frequency and percentage for categorical variables. Chi-square test was applied to compare categorical variables. Mann–Whitney test was used to compare the median age of the PKD cohort with the reference cohort. Because stroke was usually a nonfatal outcome and could be precluded by the occurrence of death, death was modeled as a competing risk in competing risks regression [16]. The PKD-to-comparison-cohort subdistribution hazard ratio (SHR) and the 95% confidence intervals (CIs) for overall stroke and its subtypes (SAH, ICH, IS) were estimated using multivariable competing risks regression models. The multivariable regression models were concurrently adjusted for age, gender, ESRD, and baseline comorbidities of hypertension, COPD, congestive heart failure,
diabetes, chronic kidney disease, and hyperlipidemia. Cumulative incidence rates of developing overall stroke over time in the PKD and non-PKD cohorts stratified by baseline ESRD were plotted. Gray’s test for subdistribution hazards was applied to compare the difference between groups [17].

Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC). A 2-sided p < 0.05 was considered statistically significant.

Results

The PKD cohort included 7837 patients, and the reference (non-PKD) cohort included 31,211 patients. The median age was 55 years, and 56.4% were males in both cohorts. Their baseline demographic characteristics and frequency of comorbidities are summarized in [Table 1]. The most common comorbidities in the PKD cohort included hypertension (36.66%), chronic kidney disease (19.75%), and diabetes (9.23%). The two cohorts were comparable in distributions of age, gender, and baseline comorbidities. However, a higher proportion of ESRD was observed among the PKD patients compared with the comparison cohort without PKD (32.7% vs. 11.0%, p value < 0.001).

[Table 2] shows the incidence of overall stroke with its subtypes, stratified by age, sex, comorbidity, and sub-distribution hazard ratios (SHR) for the patients with PKD compared with those without PKD in the competing risks models. A total of 955 cases of first-ever overall stroke were identified in the PKD cohort, including 441 ischemic stroke (IS), 289 intracranial hemorrhage (ICH), 73 subarachnoid hemorrhage (SAH) and 232 other stroke, while there were 3031 cases in the reference cohort. The incidence rates of overall stroke, IS, ICH, and SAH were 21.3, 10.2, 6.8, and 1.7 per 1000 person-years, respectively, in the PKD cohort. The absolute risk of overall stroke in the PKD patients increased with older age, male gender, those with comorbidity, and ESRD. The SHR for overall stroke in the multivariable competing-risks regression model was 1.39 with 95% confidence interval (CI) 1.28–1.50. The highest SHR, 4.55 (95% CI 3.26–6.37), was for SAH, followed by ICH (1.84) and other stroke (1.24). Although the SHR for IS (1.22) was the lowest among all subtypes, it was statistically significant with 95% CI 1.09–1.36.

[Table 3] reveals sub-distribution hazard ratios (with 95% CI) of potential predictive variables for overall stroke, IS, SAH, and other stroke in the multivariable competing risks regression models. PKD was the independent predictor for overall stroke and all its subtypes in the multivariable models adjusted for age, gender, and baseline comorbidities. PKD was associated with significantly elevated SHR, ranging from 1.22 (95% CI 1.09–1.36) for IS, to 4.55 (95% CI 3.26–6.37) for SAH. For SAH, PKD was the most important independent predictor, and the next one is hypertension with a SHR of 2.30 (95% CI 1.64–3.21). Concerning significant predictors for ICH, hypertension was associated with the greatest SHR of 3.09 (95% CI 2.66–3.59), and then PKD with a SHR of 1.84 (1.59–2.13), followed by ESRD and CKD.

[Fig. 2] shows cumulative incidence rates of overall stroke for the study cohorts stratified by PKD and baseline comorbidity of ESRD. The probability of developing overall stroke was about 18% over a 10-year period after diagnosis of PKD with ESRD at baseline. For those with ESRD at baseline, PKD patients would carry a higher risk of stroke than non-PKD (p < 0.0001). For those without ESRD, PKD was also associated with a significantly higher risk of stroke (p < 0.0001).

Discussion

This nationwide population-based cohort study was of unique strength in its relatively large sample size of total population (23 million) enrolled in a mandatory NHI program [13] during the 15-year follow-up period (1998–2012). Our study documented the absolute risk of each subtype of stroke for the PKD cohort in terms of incidence rate, and its relative risk compared with the comparison cohort matched by sex, age, and baseline comorbidities. The incidence rate of ischemic stroke for the PKD patients was 10.2 per 1000 person-years, which ranked the top among all subtypes of stroke. There is generally a lack of evidence in cohort studies to reveal a definite association between PKD and ischemic stroke. The new finding in our study was that PKD per se was the independent predictor significantly associated with an increased risk of ischemic stroke after adjustment for traditional high-risk comorbidities [18], including hypertension, COPD, congestive heart failure, diabetes, chronic kidney disease, hyperlipidemia, and ESRD. The relative importance of significant predictors for different subtypes of stroke were revealed by SHR.
in the multivariable regression models [Table 3], which could provide useful aid to clinicians in priority setting for preventing stroke in the PKD patients. A comprehensive management of hypertension, chronic kidney disease, and other comorbidities is the key for prevention of stroke in PKD patients.

Sung PH et al. used a partial dataset (one-million patients) of NHID to show an increased risk of both hemorrhagic and ischemic stroke in the ADPKD group compared with the non-ADPKD group selected from the general population matched by sex, age, income and urbanization [19]. However, in their study, the ADPKD group had significantly higher proportion...
of comorbidities associated with stroke risk, including hypertension, diabetes, atrial fibrillation, and chronic kidney diseases, compared to the non-ADPKD group (available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5617446/, [Table 1]). Therefore, it might have a problem of selection bias in that study where it was reasonably expected to observe higher relative risk of stroke among ADPKD patients. We had an intrinsically different study design by using a comprehensive dataset including all the inpatient claims of the whole population enrolled in the NHI program, and selection of comparable group [non-PKD cohort] matched by sex, age and baseline comorbidities. Our advantages included consideration of comorbidities both in selection of the reference cohort and in adjustment applied in the statistical modelling, which may further reduce the potential effect of selection bias. The incidence rate of cerebrovascular accident (ICD-9-CM 430–436) was 9.4 (CI 8.3–10.7) per 1000 person-years in the study of Sung PH et al., which was lower than our estimate of 21.3 per 1000 person-years. It may be explained by at least two reasons: (1) our PKD cohort was composed of inpatients with a higher degree of severity, as demonstrated by 14.6% of them comorbid with the ESRD at baseline [Table 1]; (2) a broader definition of stroke diagnosis (ICD-9 CM 430–438) in our study. Despite using different study design and different dataset, their results corroborated our findings of increased risk of all subtypes of stroke based on the population-based cohort study.

Yoo DJ et al. reported that ADPKD patients with the mean age of 65.3 years on maintenance dialysis in the Medicare primary insurance of the United States had an incidence rate of intracranial hemorrhage (ICD-9 codes 430 and 432) of 10.93 (95% CI 9.64–12.39) per 1000 person-years [11]. A significantly three-fold relative risk of ICH was observed among ADPKD patients. The greater absolute risk of hemorrhagic stroke in their study may correspond to the older age (65.3 vs. 55 years) and everyone receiving dialysis (and mostly hemodialysis) compared with about 32% in our PKD cohort [Table 1], because hemodialysis would generally increase such a risk [20]. The relative risk of SAH, and ICH for PKD patients in our study was about 4.6, and 1.8, respectively, which seemed compatible with their estimates. Therefore, the literature supported that the estimates of incidence rates and relative risks of stroke in our study were reasonable.

This study has the following limitations that should be addressed. First, our study focuses on stroke patients that were hospitalized and did not include those mild ones that were not admitted to hospitals. The Taiwan NHI has a comprehensive coverage for stroke hospitalization as a catastrophic illness for
a month from the onset, and all such patients can have all co-payments waived. Thus, the data quality of the NHI of stroke is very accurate because stroke hospitalization must be under strict review by board-certificated specialists to prevent abuse, and it has been demonstrated acceptable validity (nearly 95%) in ischemic stroke diagnosis using NHID [21]. Because the NHI coverage rate has been generally over 99% since 2002 in Taiwan, it is reasonable to view the stroke cases in our study is of moderate to severe degree of stroke. Second, clinical data related to disease severity in PKD and comorbidities were not available in the NHI databases. In addition, we do not have detailed information on socioeconomic status, smoking habits, family history, or any clinic data regarding lipid profiles, body mass index or blood pressure. Third, evidence derived from a retrospective cohort study is usually of lower quality than that from a prospective type because of potential inherent biases (such as selection bias). However, genetic examination, which is not covered by the NHI program, was not routinely done in Taiwan. The literature has estimated that 15% of patients with ADPKD have a negative family history, which could lead to misclassification [22]. Further study is indicated to extend the scope of PKD to cover the earlier phase of PKD based on genetic information. Fourth, although the general ICD-9 codes for cerebrovascular disease delineates seemingly clear boundaries for diagnostic subgroups, “the other stroke” including ICD 435 (transient ischemic attack), ICD 437 (other and ill-defined cerebrovascular disease), ICD 438 (late effects of cerebrovascular disease), ICD 439 (transient ischemic attack), ICD 437 (other and ill-defined cerebrovascular disease) might be roughly recorded in clinical practice with less precision. It may affect the generalization of overall stroke associated with PKD because the category of the other stroke accounted for around one quarter. This study is based on retrospective data analysis from the NHID in Taiwan, and therefore generalization of our findings is limited. Finally, as the majority of Taiwan’s population is of Chinese ethnicity, the findings of our study may not be applicable to populations of other ethnic backgrounds.

Conclusions

We present the incidence rates of stroke subtypes among the patients with PKD in Taiwan, and we find that, over a 15-year follow-up period, PKD is independently associated with increased risk of all subtypes of stroke, based on this population-based cohort study in Taiwan. In addition, the long-term probability of developing stroke in the PKD patients with ESRD at baseline was about 18% over a 10-year period. Further studies are warranted to determine whether our findings can be generalised to other ethnic populations. Additional studies including genetic information are required to investigate the natural history of PKD to develop cerebrovascular complications over time.

Data availability

Data are available from the Health and Welfare Data Science Center (HWDC) of the Ministry of Health and Welfare, Executive Yuan, Taiwan. Due to legal restrictions imposed by the government of Taiwan in relation to the ‘Personal Information Protection Act’, data cannot be made publicly available. Requests for data can be sent as a formal proposal to the HWDC (https://dep.mohw.gov.tw/DOS/lp-2499-113.html).

Conflicts of interest

None declared.

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