Young-Adult Polycystic Kidney Disease is Associated with Major Cardiovascular Complications

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Abstract: Background: Patients with polycystic kidney disease (PKD) might have a risk of cardiovascular diseases because several cardiovascular risk factors are occasionally associated with PKD patients. Data on the association between PKD and the risk of cardiovascular events, including acute coronary syndrome (ACS), stroke, and congestive heart failure (CHF), are scant. Methods: Patients aged ≥20 years who were newly diagnosed with PKD (International Classification of Diseases, Ninth Revision, Clinical Modification codes 753.12 and 753.13) between 2000 and 2011 were selected as a PKD cohort (N = 5157). The association between PKD and cardiovascular events was analyzed. Results: We randomly selected a comparison cohort of people without PKD, who were frequency-matched by sex, age, and index date of diagnosis. At the end of 2011, the PKD cohort had a 1.40-fold greater incidence of ACS compared with the comparison cohort (8.59 vs. 6.17 per 1000 person-years), in addition to a 1.40-fold greater incidence of stroke, a 1.49-fold greater incidence of CHF, and a 1.64-fold greater incidence of mortality. Conclusions: This retrospective cohort study shows that patients with PKD have an increased risk of cardiovascular events including ACS, stroke, and CHF as well as mortality, particularly in younger patients. Early identification is necessary to attenuate the risk of cardiovascular complications in patients with PKD.

Keywords: polycystic kidney disease; acute coronary syndrome (ACS); stroke; congestive heart failure (CHF); survival

1. Background

Polycystic kidney disease (PKD), a multisystem disorder of ciliary proteins, is occasionally complicated by extra-renal manifestations [1]. The most prevalent PKD in adulthood is autosomal dominant PKD (ADPKD), which is also the most common detrimental monogenetic disorder [1,2].
Although large interfamilial and intrafamilial variations exist in patients with PKD, mutations of the PKD1 (chromosome region 16p13.3, approximately 85% of cases) and PKD2 (4q21, approximately 15% of cases) genes account for most PKD cases [2].

Previous study suggested that polycystins are associated with the vascular abnormality of blood vessels [3].

Polycystin 1 (PC1) and polycystin 2 (PC2), the defect proteins in ADPKD, are found in both vascular smooth muscle cells (VSMC) and endothelial cells that are involved in all major vessels including the aorta and intracranial arterials [4–6]. The interactions between PC1/PC2 and VSMCs are complex. Previous data indicated that the dysregulation of Ca\(^{2+}\) homeostasis, which resulted from the mutation of PC1/PC2, may lead to an increase in VSMC proliferation and apoptosis resembling the Pkd-mutant phenotype [7].

Moreover, several lines of studies suggested that the mTOR signaling pathway is involved with patho-physiological changes of VSMCs including proliferation, differentiation, and migration with increased extracellular matrix protein synthesis [8].

VSMCs after injury are frequently prone to abnormal proliferation and matrix synthesis which eventually contributes to intimal hyperplasia and lumen narrowing in vessels [9].

The mTOR pathway inhibitor is shown to be effective in the attenuation of intimal hyperplasia in an animal model and clinical trials [10,11].

There is overwhelming evidence for the hyperactivity of mTOR signaling in PKD [12,13]. Edelstein et al. firstly found that mTOR could involve the progression of cyst changes in the Han: SPRD rat model of PKD [14]. In addition, Shillingford et al. further demonstrated a substantial role of mTOR contributing to the pathogenesis of human PKD and suggested that patients with PKD are likely to be associated with an aberrant activity of mTOR [15].

Accordingly, it is reasonable to suppose that PKD is associated with a higher risk of vascular complications because of the hyperactivity of mTOR resulting from a PC1/2 deficiency.

In patients with PKD, the underlying defect in the connective tissue matrix has been associated with various extrarenal manifestations including intracranial aneurysms, hepatic cysts, diverticulosis, spontaneous coronary artery dissection (SCAD), atrial fibrillation [16], and other cardiovascular abnormalities [17].

However, data regarding the relationship between PKD and the risk of cardiovascular events such as coronary artery disease and cerebral vascular disease remain limited, particularly for acute coronary syndrome (ACS) characterized by unstable angina with a non-ST-segment elevation myocardial infarction and ST-segment elevation myocardial infarction, which is a life-threatening condition [18,19].

In the current study, we used the large claims database of the Taiwan National Health Insurance (NHI) program to conduct a nationwide cohort study to investigate the risk of cardiovascular events, including ACS and stroke, in patients with PKD.

2. Materials and Methods

2.1. Data Source

The NHI program covers more than 99% of the population of Taiwan (http://www.nhi.gov.tw/english/index.aspx). The Bureau of National Health Insurance authorized the Taiwan National Health Research Institutes to manage the electronic medical records of patients enrolled in this program and establish the National Health Insurance Research Database (NHIRD) for research purposes. Information available in the database includes the demographic status of insurants; medical diagnoses, treatment procedures, and drug prescriptions for inpatient and outpatient services; and healthcare facilities providing care services to patients. For this study, we used a subset of the NHIRD containing health care data including files of inpatients claims, and the Registry of Beneficiaries. To ensure the privacy of personal information, unique encrypted identification numbers are used for all patients. All claimed data sets can be linked using these anonymous identification numbers. All diagnoses
were defined using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

2.2. Data Availability Statement

The dataset used in this study is held by the Taiwan Ministry of Health and Welfare (MOHW). The Ministry of Health and Welfare must approve our application to access this data. Any researcher interested in accessing this dataset can submit an application form to the Ministry of Health and Welfare requesting access. Please contact the staff of MOHW (Email: stcarolwu@mohw.gov.tw) for further assistance. Taiwan Ministry of Health and Welfare Address: No. 488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan (R.O.C.). Phone: +886-2-8590-6848. All relevant data are within the paper.

2.3. Ethics Statement

The NHIRD encrypts patient personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claims information, including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2-115-CR2). The IRB also specifically waived the consent requirement.

2.4. Study Patients

Figure 1 shows the selection process of the participants in the 2 study cohorts. From the inpatient database, we chronologically identified 5721 patients aged ≥20 years who were newly diagnosed with PKD (ICD-9-CM codes 753.12 and 753.13) between 2000 and 2011. The diagnosis date was designated as the “start date” of the follow-up period (in years). For each PKD patient, we randomly selected 4 controls frequency-matched by sex, age, start date, and comorbidities of hypertension (ICD-9-CM codes 401–405), diabetes (ICD-9-CM code 250), chronic obstructive pulmonary disease (COPD; ICD-9-CM codes 491, 492, and 496), chronic kidney disease (CKD; ICD-9-CM code 585), hyperlipidemia (ICD-9-CM code 272), and end-stage renal disease (ESRD; ICD-9-CM code 585 with catastrophic certification). We gave the controls (non-PKD cohort) the same start year as cases (PKD cohort) and then randomly assigned months and days to the controls as the start date of the controls. The study populations in both cohorts were followed from the start dates until the development of ACS or other events of interest, until they were censored for loss to follow-up or withdrawal from the NHI program, or until the end of 2011. The primary goal of this study was to compare the risk of 3 outcomes and mortality between patients with and without PKD: (1) ACS (ICD-9-CM codes 410, 411.1, and 411.8) including unstable angina (ICD-9-CM code 411.1), NSTEMI (ICD-9-CM codes 410.70–410.72), and STEMI (ICD-9-CM codes 410.0–410.9, except for codes 410.70–710.72); (2) stroke (ICD-9-CM codes 430–438) including hemorrhagic stroke (ICD-9-CM codes 430–432) and ischemic stroke (ICD-9-CM codes 433–438); and (3) heart failure (ICD-9-CM code 428) as well as patient death. Patients identified with these disorders were excluded at the baseline.
A cohort from people enrolled in the National Health Insurance program
N=23,750,000

Newly diagnosed polycystic kidney disease in 1998-2011. (n=7,747)
Excluded patients with ACS, stroke, and heart failure before index date (n=1,737), under 20 years of age (n=285) and missing information about age or sex (n=4)

Subjects without polycystic kidney disease
Using the same exclusion criteria as the polycystic kidney disease cohort with a approximately 1:4 case:control ratio matched with age, sex, comorbidities, and index year

Polycystic kidney disease cases without stroke at baseline. (n=5,721)

Finally 22,857 controls were selected

Figure 1. Shows the selection process of the participants in the 2 study cohorts.

2.5. Statistical Analysis

Distributions of sex, age (20–49, 50–64, and ≥65 years), and comorbidities (yes and no) were compared between the cohorts with and without PKD. We used the Chi-squared test to examine categorical variables and the Wilcoxon rank-sum test to examine the skewed age distributions between the groups. For events significantly associated with PKD, we used the Kaplan–Meier method to calculate and plot the cumulative incidences of such events and examined the differences between the cohorts by using the log-rank test. We also calculated the overall incidence rates of each study event in both cohorts. Because mortality was a critical factor affecting the estimation of ACS, stroke, and heart failure risk, we considered the event of death as a competing event to estimate subhazard ratios (SHRs) and 95% confidence intervals (CIs) by using the standard univariable and multivariable Cox proportional hazards regression models [20]. Cox regression models were used to calculate the crude hazard ratios (HRs) and 95% CIs of PKD-related mortality in the PKD and non-PKD cohorts. We also used events with a significant crude SHR (cSHR) or crude HR to calculate the relative adjusted SHR (aSHR) or adjusted HR (aHR) of the events associated with PKD through multivariable Cox regression analysis after controlling the baseline characteristics. The joint effect between PKD and the comorbidities was also measured for outcome events that were significantly associated with PKD. SAS 9.3 statistical software (SAS Institute, Inc., Cary, NC, USA) was used for all statistical analyses. The 2-sided significance level was set at 0.05.

3. Results

Table 1 presents the baseline data of the PKD and comparison cohorts; the baseline characteristics were similar in both cohorts. As shown in Figure 2, the cumulative incidence rates of ACS, stroke, congestive heart failure (CHF), and mortality were all greater in the PKD cohort than in the non-PKD cohort.

Table 1. Characteristics of patients between patients with and without polycystic kidney disease (PKD).

| Age, Year | Polycystic Kidney Disease | p-Value |
|-----------|---------------------------|---------|
|           | Yes (N = 5721)            | No (N = 22,857) |       |
|           | N | % | N | % |       |
| 20–49     | 2080 | 36.4 | 8308 | 36.4 | 0.99 |
| 50–64     | 1676 | 29.3 | 6695 | 29.3 |       |
| ≥65       | 1965 | 34.4 | 7854 | 34.4 |       |
| Median (IQR) ^ | 56.0 (45.1–70.3) | 56.1 (45.1–70.5) | 0.76 |
Table 1. Characteristics of patients between patients with and without polycystic kidney disease (PKD).

| Age, Year | Polycystic Kidney Disease | p-Value |
|-----------|--------------------------|---------|
|           | Yes (N = 5721)           | No (N = 22,857) |         |
|           | N  %                    | N  %    |         |
| Gender    | 0.99                    |
| Female    | 2250 44.6               | 10,192 44.6  |
| Male      | 3171 55.4               | 12,665 55.4  |
| Comorbidity |                        |         |
| Hypertension | 2504 43.8            | 10,006 43.8  |
| Diabetes  | 610 10.7                | 2432 10.6  |
| Hyperlipidemia | 236 4.13            | 933 4.08  |
| COPD      | 327 5.72                | 1293 5.66  |
| Chronic kidney disease | 1234 21.6 | 4915 21.5 |
| ESRD      | 564 9.86                | 2239 9.80  |

Chi-square test; # Wilcoxon signed rank test. IQR: interquartile range. COPD: chronic obstructive pulmonary disease. ESRD: end-stage renal disease.

Figure 2. Cumulative incidence of acute coronary syndrome (A); stroke (B); congestive heart failure (C); and mortality (D) for polycystic kidney disease cohort (dashed line) and comparison cohort (solid line).

Table 2 shows the overall incidence rates of the 3 events between the PKD and non-PKD cohorts as well as the cSHRs of the events in these cohorts. The PKD patients were at a higher risk of all events than the comparisons. Overall, comparing the PKD and non-PKD cohorts revealed that the PKD cohort had a higher incidence of ACS (8.59 vs. 6.17 per 1000 person-years), unstable angina (1.98 vs. 1.26 per 1000 person-years), stroke (21.5 vs. 16.1 per 1000 person-years), hemorrhagic stroke (6.16 vs. 2.97 per 1000 person-years), ischemic stroke (15.3 vs. 13.2 per 1000 person-years), and CHF (16.3 vs.
11.1 per 1000 person-years), corresponding to cSHR values of 1.40 (95% CI = 1.22–1.61), 1.41 (95% CI = 1.05–1.89), 1.40 (95% CI = 1.28–1.53), 2.12 (95% CI = 1.78–2.53), 1.20 (95% CI = 1.08–1.33), and 1.49 (95% CI = 1.34–1.65), respectively. The sex-specific PKD-to-non-PKD cohort relative risk of ACS was significant for men (cSHR = 1.47, 95% CI = 1.24–1.74). Furthermore, the age-specific PKD-to-non-PKD relative risk of ACS was high for all age groups. Notably, in the group aged 20–49 year-old, a 1.61-fold increased risk of ACS (95% CI = 1.18, 2.21), 1.65-fold in stroke (95% CI = 1.32, 2.07), and 1.82-fold in CHF (95% CI = 1.37, 2.42) was noted.

**Table 2.** Incidence and hazard ratio of outcome between patients with and without polycystic kidney disease.

| Variable          | Polycystic Kidney Disease | Crude SHR † (95% CI) |
|-------------------|---------------------------|-----------------------|
|                   | Yes                       | No                    |
|                   | N Event PY Rate #         | N Event PY Rate #     |
| ACS               |                           |                       |
| All               | 5721 252 29,323 8.59      | 790 126,080 6.17      | 1.40(1.22, 1.61) |
| Unstable angina   | 58 1.98                   | 161 1.26              | 1.41(1.05, 1.89) |
| NSTMI             | 2 0.92                    | 77 0.60               | 0.94(0.59, 1.50) |
| STMI              | 69 2.35                   | 238 1.86              | 1.14(0.88, 1.49) |
| Gender            |                           |                       |
| Female            | 2550 72 14,002 5.14       | 10,192 59,827 4.10    | 1.26(1.08, 1.50) |
| Male              | 3171 180 15,322 11.8      | 12,665 68,253 7.99    | 1.47(1.24, 1.74) |
| Age, year         |                           |                       |
| 20–49             | 2080 54 12,584 4.29       | 8308 51,120 2.56      | 1.61(1.18, 2.21) |
| 50–64             | 1676 84 8865 9.48         | 6695 38,289 5.64      | 1.67(1.30, 2.15) |
| ≥65               | 1965 114 7874 14.5        | 7854 38,671 11.5      | 1.28(1.04, 1.57) |
| Comorbidity §     |                           |                       |
| No                | 37 2 268 7.47 148 7 1101 6.36 | 1.11(0.23, 5.24) |
| Yes               | 5684 250 29,055 8.60 22,709 783 126,978 6.17 | 1.40(1.22, 1.61) |
| Stroke            |                           |                       |
| All               | 5721 609 28,395 21.5      | 22,857 2002 124,216 16.1 | 1.40(1.28, 1.53) |
| Hemorrhagic stroke| 175 28,396 6.16 369 124,216 2.97 | 2.12(1.78, 2.53) |
| Ischemic stroke   | 434 28,396 15.3           | 1633 124,216 13.2     | 1.20(1.08, 1.33) |
| Gender            |                           |                       |
| Female            | 2550 237 13,533 17.5      | 10,192 677 58,390 11.6 | 1.62(1.40, 1.88) |
| Male              | 3171 372 14,863 25.0      | 12,665 1325 65,826 20.1 | 1.29(1.15, 1.45) |
| Age, year         |                           |                       |
| 20–49             | 2080 108 12,419 8.70      | 8308 265 50,742 5.22  | 1.65(1.32, 2.07) |
| 50–64             | 1676 176 8628 20.4        | 6695 537 37,243 14.4  | 1.41(1.19, 1.67) |
| ≥65               | 1965 325 7349 44.2        | 7854 1200 36,231 33.1 | 1.35(1.19, 1.52) |
| Comorbidity §     |                           |                       |
| No                | 37 4 254 15.7 148 17 1060 16.0 | 0.98(0.33, 2.89) |
| Yes               | 5684 605 28,142 21.5      | 22,709 1985 123,156 16.1 | 1.41(1.28, 1.54) |
| Congestive heart failure |                           |                       |
| All               | 5721 471 28,987 16.3      | 22,857 1410 126,905 11.1 | 1.49(1.34, 1.65) |
| Gender            |                           |                       |
| Female            | 2550 171 13,806 12.4      | 10,192 531 59,153 8.98 | 1.43(1.21, 1.69) |
| Male              | 3171 300 15,181 19.8      | 12,665 879 67,751 13.0 | 1.52(1.34, 1.73) |
| Age, year         |                           |                       |
| 20–49             | 2080 69 12,585 5.48       | 8308 150 51,123 2.93  | 1.82(1.37, 2.42) |
| 50–64             | 1676 116 8866 13.1        | 6695 336 37,950 8.15  | 1.46(1.18, 1.80) |
| ≥65               | 1965 286 7537 38.0        | 7854 924 37,832 24.4  | 1.57(1.38, 1.80) |
| Comorbidity §     |                           |                       |
| No                | 37 0 276 0.00 148 7 1107 6.32 | -                     |
| Yes               | 5684 471 28,711 16.4      | 22,709 1403 125,798 11.2 | 1.50(1.35, 1.66) |

ACS, acute coronary syndrome. PY, person-years; Rate #, incidence rate per 1000 person-years. Crude SHR †, relative hazard ratio. Comorbidity §: Patients with any one of the comorbidities (including hypertension, diabetes, hyperlipidemia, COPD, chronic kidney disease and ESRD) were classified as the comorbidity group. NSTMI: non-ST elevation myocardial infarction. STMI: ST elevation myocardial infarction.
PKD patients with comorbidities were associated with significantly higher risks of ACS than the non-PKD patients. The PKD cohort was 1.40-fold more likely to develop stroke (95% CI = 1.28–1.53), 2.12-fold more likely to develop hemorrhagic stroke (95% CI = 1.78–2.53), and 1.20-fold more likely to develop ischemic stroke (95% CI = 1.08–1.33) compared with the non-PKD cohort. We compared the risks of stroke and CHF between the PKD and non-PKD cohorts in terms of several variables including sex, age, and the presence or absence of comorbidities. In all stratifications, the risks of stroke and CHF in the PKD cohort were higher than those in the non-PKD cohort, except for patients without comorbidities.

Table 3 shows a significantly high risk of mortality in patients with PKD compared to that in patients without PKD which reached a 1.64-fold increase (95% CI = 1.53–1.75). In stratification with sex and age shows that the sex-specific PKD-to-non-PKD cohort relative risk of mortality was significant for men (cHR = 1.60, 95% CI = 1.47–1.73) as well as that in women (cHR = 1.75, 95% CI = 1.57–1.97). Furthermore, the age-specific PKD-to-non-PKD relative risk of mortality was high for all age groups. Notably, in the group aged 20–49 year-old, a 1.84-fold increased risk of mortality (95% CI = 1.55, 2.18).

Table 3. Incidence and hazard ratio of mortality between patients with and without polycystic kidney disease.

| Variable     | Polycystic Kidney Disease |                      | Crude HR † (95% CI) |
|--------------|---------------------------|----------------------|---------------------|
|              | Yes                       | No                   |                     |
|              | N | Event | PY | Rate # | N | Event | PY | Rate # |
| All          |   | 5721  | 1217 | 30,045  | 40.5 | 22,857 | 3218 | 130,270 | 24.7 | 1.64(1.53, 1.75) |
| Gender       |   |       |     |        |     |        |     |         |      |                |
| Female       |   | 2550  | 416  | 14,224  | 29.3 | 10,192 | 1012 | 60,548  | 16.7 | 1.75(1.57, 1.97) |
| Male         |   | 3171  | 801  | 15,822  | 50.6 | 12,665 | 2206 | 69,721  | 31.6 | 1.60(1.47, 1.73) |
| Age, year    |   |       |     |        |     |        |     |         |      |                |
| 20–49        |   | 2080  | 191  | 12,778  | 15.0 | 8308   | 421  | 51,648  | 8.15 | 1.84(1.55, 2.18) |
| 50–64        |   | 1676  | 347  | 9154    | 37.9 | 6695   | 875  | 38,931  | 22.5 | 1.69(1.50, 1.92) |
| ≥65          |   | 1965  | 679  | 8113    | 83.7 | 7854   | 1922 | 39,690  | 48.4 | 1.73(1.59, 1.89) |
| Comorbidity §|   |       |     |        |     |        |     |         |      |                |
| No           |   | 37    | 7    | 276     | 25.3 | 148    | 13   | 1122    | 11.6 | 2.14(0.86, 5.38) |
| Yes          |   | 5684  | 1210 | 29,769  | 40.7 | 22,709 | 3205 | 129,148 | 24.8 | 1.64(1.53, 1.75) |

PY, person-years; Rate #, incidence rate per 1000 person-years. Crude HR †, relative hazard ratio. Comorbidity §: Patients with any one of the comorbidities (including hypertension, diabetes, hyperlipidemia, COPD, chronic kidney disease and ESRD) were classified as the comorbidity group.

Table 4 presents the calculated cSHRs and aSHRs of the 3 PKD-related events and cHRs and aHRs of the mortality after adjustment for sex, age, and baseline comorbidities. Men were at higher risks of ACS, stroke and mortality than women. The hazard of heart failure was higher for patients aged 50–64 years than for those aged 20–49 years. Hypertension, diabetes, CKD, and ESRD were associated with increased risks of ACS, stroke, CHF, and mortality.
Table 4. Hazard ratios of outcome in association with gender, age and comorbidities in univariable and multivariable competing risk models.

| Variable               | ACS                  | Stroke               | Congestive Heart Failure | Mortality          |
|------------------------|----------------------|----------------------|-------------------------|--------------------|
|                        | Crude SHR † (95% CI) | Adjusted SHR ‡ (95% CI) | Crude SHR † (95% CI) | Adjusted SHR ‡ (95% CI) | Crude SHR † (95% CI) | Adjusted SHR ‡ (95% CI) | Crude HR † (95% CI) | Adjusted HR ‡ (95% CI) |
| PKD                    | 1.40(1.22, 1.61)     | 1.40(1.22, 1.62)     | 1.40(1.28, 1.53)       | 1.39(1.27, 1.52)    | 1.49(1.34, 1.65)     | 1.51(1.36, 1.68)       | 1.64(1.53, 1.75)     | 1.71(1.60, 1.83)      |
| Gender (Men vs. women) | 1.58(1.39, 1.79)     | 1.55(1.36, 1.77)     | 1.30(1.20, 1.40)       | 1.27(1.17, 1.38)    | 1.07(0.98,1.17)      | 1.03(0.94, 1.13)       | 1.84(1.73, 1.96)     | 1.42(1.33, 1.51)      |

| Age, years             |                      |                      |                         |                    |
| 20–49                  | 1(Reference)         | 1(Reference)         | 1(Reference)           | 1(Reference)       | 1(Reference)         | 1(Reference)           | 1(Reference)         | 1(Reference)         |
| 50–64                  | 1.37(1.03, 1.82)     | 1.19(0.89, 1.59)     | 1.28(1.04, 1.57)       | 1.04(0.84, 1.28)   | 1.79(1.40, 2.29)     | 1.45(1.13, 1.84)       | 2.69(2.44, 2.96)     | 2.32(2.11, 2.56)      |
| ≥65                    | 1.23(0.99, 1.54)     | 1.08(0.87, 1.35)     | 1.25(1.07, 1.46)       | 1.12(0.96, 1.30)   | 1.31(1.08, 1.58)     | 1.10(0.91, 1.33)       | 5.78(5.29, 6.32)     | 5.16(4.72, 5.65)      |

| Baseline comorbidities (yes vs. no) |                      |                      |                         |                    |
| Hypertension            | 1.96(1.74, 2.21)     | 1.76(1.55, 1.99)     | 1.61(1.49, 1.74)       | 1.51(1.39, 1.63)   | 1.69(1.54, 1.85)     | 1.53(1.39, 1.68)       | 1.69(1.59, 1.79)     | 1.21(1.14, 1.28)      |
| Diabetes                | 2.21(1.90, 2.57)     | 1.87(1.60, 2.18)     | 1.79(1.62, 1.98)       | 1.65(1.48, 1.83)   | 2.20(1.97, 2.45)     | 2.00(1.78, 2.24)       | 2.07(1.92, 2.24)     | 1.67(1.54, 1.81)      |
| Hyperlipidemia          | 2.40(1.95, 2.95)     | 1.87(1.51, 2.32)     | 1.41(1.20, 1.67)       | 1.12(0.95, 1.33)   | 1.69(1.41, 2.02)     | 1.33(1.10, 1.59)       | 1.07(0.93, 1.24)     | 0.88(0.76, 1.02)      |
| COPD                   | 1.37(1.10, 1.70)     | 1.16(0.93, 1.44)     | 1.42(1.25, 1.61)       | 1.30(1.14, 1.48)   | 1.72(1.50, 1.98)     | 1.52(1.32, 1.76)       | 2.76(2.51, 3.03)     | 1.60(1.45, 1.76)      |
| CKD                    | 2.20(1.94, 2.49)     | 1.90(1.65, 2.20)     | 1.73(1.60, 1.89)       | 1.64(1.49, 1.81)   | 2.52(2.30, 2.76)     | 2.37(2.14, 2.63)       | 3.36(3.17, 3.56)     | 2.76(2.58, 2.95)      |
| ESRD                   | 2.12(1.78, 2.52)     | 1.32(1.07, 1.61)     | 1.52(1.33, 1.73)       | 1.03(0.89,1.20)    | 2.19(1.92, 2.50)     | 1.29(1.11, 1.50)       | 2.80(2.60, 3.02)     | 1.60(1.47, 1.74)      |

Crude SHR †, relative subhazard ratio; Crude HR †, relative hazard ratio; Adjusted SHR ‡ and Adjusted HR ‡: multivariable analysis including gender, age, and comorbidities of hypertension, diabetes, hyperlipidemia, COPD, chronic kidney disease (CKD), and ESRD.
4. Discussion

In this large population-based cohort study with a long observation period of 27,053 person-years, we noted that PKD patients had a significantly higher risk of ACS as well as CHF when compared with non-PKD patients after adjustment for age, sex, and the associated cardiovascular risk factors included hypertension, diabetes, hyperlipidemia, COPD, and CKD. We also found greater risks of stroke and mortality for the PKD cohort than for the non-PKD cohort. Interestingly, our findings disclosed a significantly increased risk of cardiovascular events including ACS, stroke, and CHF in young patients with PKD, which has never been reported previously for such a relatively young age group.

Cardiovascular complications have surpassed infections among the most common causes of morbidity and mortality in patients with PKD [18,19]. Some cardiovascular risk factors have been suggested to be closely associated with PKD. Hypertension and left ventricular hypertrophy are commonly observed in patients with PKD [19,21]. Early vascular changes have been reported in young patients with normal blood pressure, and patients with PKD are considered to have a higher prevalence of coronary aneurysm (CA) and cardiac valvular abnormalities than the general population does [19]. Nevertheless, diagnosing SCAD is extremely challenging. Even in patients with a strong clinical suspicion, SCAD is difficult to diagnose accurately by using coronary angiography [22]. Previous studies on SCAD associated with PKD are limited to a few case reports and a study with a small sample size [23–25].

In the present study, after adjusting for associated risk factors including hypertension, diabetes, hyperlipidemia, and chronic kidney disease, multivariate analysis revealed a relatively high hazard of ACS as well as stroke in patients with PKD compared with non-PKD patients. Notably, the age-specific risk of ACS was significantly higher for those who were younger, aged 20–49 years (HR = 1.61, 95% CI = 1.18–2.21), and additionally a 1.82-fold increased risk of CHF was observed in young people with PKD. In addition, the trend is consistent in that a 1.65-fold increased risk of stroke was observed.

More recently, a study on PKD patients indicated that a high prevalence of young-onset hypertension was observed in children with PKD and that may partly support the findings in the present study.

In terms of stratification without co-morbidity, our results showed that the risk of CVD was comparable between patients with and without PKD. The findings may suggest that the associated cardiovascular co-morbidity may contribute more greatly in patients once they have PKD.

Taken together, our findings indicate a higher risk of cardiovascular events in younger patients with PKD that was never previously known.

Previous studies have shown that polycystins are constitutional in normal adult smooth muscle cells [5,6]. Polycystins may play an essential role in maintaining the vascular integrity of the myoelastic structure of the arterial wall [26]. An animal study showed that the null mutation of the PKD1 or PKD2 gene could diffuse vascular rupture and hemorrhage in the vessel tissue, suggesting that polycystins have a role in maintaining vascular integrity [5,27]. Hence, polycystin deficiency is suggested to be directly attributed to the various phenotypes of vascular abnormality in patients with ADPKD, which are independent of the effect of hypertension [6].

Moreover, accumulating evidence indicates that PKD is likely associated with aberrant mTOR activity. Previous study demonstrated that the cytoplasmic tail of PC1 could inhibit mTOR and the loss function of PC1 in ADPKD would eventually lead to a remarkable hyperactivity of mTOR [13,15].

We previously demonstrated that PKD is significantly associated with the risk of cancer, within which mTOR may play an important role [28]. Whether mTOR has a similar role within it needs further elucidation.

Our study results may provide clinical evidence relevant to previous biological evidence.

Previous study has suggested that a rennin-angiotensin blockade was likely associated with a favorable outcome in PKD patients. Therefore, in terms of cardiovascular complications, it should be firstly considered in PKD patients. Certain limitations of the present study should be considered. First, some data on tobacco smoking and kidney function as glomerular filtration rate are relevant
to the risk of ACS but are not provided in the NHIRD. Therefore, we included the confounder of COPD, chronic kidney disease, and end stage renal disease (ESRD) in the multivariable analysis to correct any possible bias. Second, we could not obtain details regarding CA and SCAD. The clinical diagnosis of SCAD is challenging and relies completely on visualizing a radiolucent intimal “flap” in coronary angiography [22,29]. In practice, delineating the coronary wall through ordinary cardiac angiography is difficult, limiting its diagnostic accuracy [22,29,30]. Nevertheless, the diagnoses of ACS and AMI in the study were not biased by this condition. Third, we did not consider the effects of medications including antihypertensive, antiplatelet, and anti-diabetic drugs. This may have led to an underestimation of the risk of ACS in the study. Finally, we could not analyze biological data obtained through genetic analysis including the mutations of the PKD1 and PKD2 genes. We could not examine the individual risks of vascular phenotypes in the study cohort, although this is not necessary for the contemporary diagnosis of PKD or ADPKD.

5. Conclusions

Our study reports for the first time that patients with PKD are at increased risk of ACS as well as other cardiovascular events including stroke, CHF, and mortality.

Most important of all, our findings show that young adult PKD is significantly associated with a higher risk of cardiovascular disease when compared with non-PKD patients. The relatively high risk of cardiovascular events such as stroke and heart failure, as well as mortality, should not be ignored in young patients with PKD, and early recognition of the cardiovascular risk in such patients is required.

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Conflicts of Interest: All authors report no conflicts of interest.

Abbreviations

| Abbreviation | Description                          |
|--------------|--------------------------------------|
| PKD          | polycystic kidney disease             |
| ACS          | acute coronary syndrome               |
| CHF          | congestive heart failure              |
| CI           | confidence interval                   |
| VSMC         | vascular smooth muscle cells          |
| NHIRD        | National Health Insurance Research Database |
| ICD-9-CM     | International Classification of Diseases, Ninth Revision, Clinical Modification |
| HR           | hazard ratio                          |

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