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Factors Associated With the Development and Severity of Polycystic Liver in Patients With Autosomal Dominant Polycystic Kidney Disease

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ABSTRACT

Background: Factors related to the development and severity of polycystic liver disease (PLD) have not been well established. We aimed to evaluate the genetic and epidemiologic risk factors of PLD in patients with autosomal dominant polycystic kidney disease (ADPKD).
Methods: Adult patients with inherited cystic kidney disease were enrolled from May 2019 to May 2021. Demographic, clinical, and laboratory data were collected at the initial study visit. The severity of PLD was graded based on the height-adjusted total liver volume: < 1,000 mL/m (Gr1), 1,000–1,800 mL/m (Gr2), and > 1,800 mL/m (Gr3). Targeted exome sequencing was done by a gene panel including 89 ciliopathy-related genes. We searched out the relative factors to the presence and the severity of PLD using logistic regression analysis.
Results: Of 602 patients with typical ADPKD, 461 (76.6%) patients had PLD. The patients with PLD showed female predominance and a higher frequency of other ADPKD-related complications. The genetic variants with truncating mutation of PKD1 (PKD1-protein-truncating [PT]) or PKD2 commonly affected the development and severity of PLD. An older age, female sex, and higher kidney volume with Mayo classification 1C-1E was significantly associated with the development of PLD, but not with the severity of PLD. On the other hand, higher body mass index, lower hemoglobin, and higher alkaline phosphatase (ALP) were the significant risk factors of severe PLD (≥ Gr2).
Conclusion: Hepatic involvement in ADPKD could be related to kidney manifestations and genetic variants including PKD1-PT or PKD2. Monitoring hemoglobin and ALP and evaluating the genetic variants might help predict severe PLD.

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Keywords: Polycystic Kidney; Autosomal Dominant; Polycystic Liver Disease; Risk Factors; Genotype

INTRODUCTION

Polycystic liver disease (PLD) is the most common extrarenal manifestation of autosomal dominant polycystic kidney disease (ADPKD).[1,2] It is characterized by multiple fluid-filled cysts developed from bile ducts.[3] Liver cysts rarely develop before age 20 but become prominent as age increases, and cyst burden is more significant in women, especially with multiple pregnancies and deliveries.[4,5] Increased number and size of liver cysts lead to hepatomegaly, which is closely related to gastrointestinal symptoms, including abdominal pain.[6] In addition, a large liver volume negatively affects the quality of life and nutritional status.[7,8]

In contrast to the progressive deterioration of kidney function, the hepatic function is usually maintained irrespective of liver volume. However, local complications such as cyst infection, hemorrhage, and rupture are commonly reported, which closely affect the life quality of the patients. Although hepatic failure or decompensated liver cirrhosis have rarely been reported among patients with PLD,[9] biliary tract disease and malnutrition associated with massive PLD have been recognized. In contrast to the assertive effort to evaluate the prognostic marker and therapeutic option for kidney function, there was a lack of evidence to predict the development and prognosis of PLD in ADPKD patients.[10,11] Considering these unavoidable disease burdens of PLD, more attention should be paid to the risk factors for PLD among patients with ADPKD.

The genetic factor is the most potent predictor of renal prognosis among patients with ADPKD. Several studies have also shown the genetic association with the severity of PLD, but there is still a controversy about the effect of genotype on PLD severity.[12,13] A previous study demonstrated that ADPKD genotypes were not associated with the severity or growth rate of PLD.[12] On the other hand, a recent study showed that a PKD1 nonsense mutation was associated with liver cyst severity in patients with ADPKD.[13] In this regard, more studies need to be addressed the association between liver cysts or PLD severity and genetic variants.

In this study, we aimed to evaluate the distinct factors associated with the presence of liver cysts and the severity of PLD. We also analyzed the relative clinical and genetic factors associated with massive PLD in Korean patients with ADPKD.

METHODS

Study populations

This study was conducted with a prospective multicenter cohort of patients with inherited cystic kidney disease (Clinical Research Information Service: KCT0005580). We only included Korean patients, all participants were Asian. A total of 812 participants with three or more renal cysts in both kidneys were recruited between May 2019 and May 2021. We excluded subjects who were drop-out by withdrawing consent or aged < 18 years old, or without abdominal computed tomography (CT) scan, or atypical ADPKD.

Based on the family history of ADPKD and typical image results, typical ADPKD was defined. A significant number of kidney cysts were different depending on age in subjects with family history.[14] Additionally, we defined typical ADPKD based on the presence of 10 or more cysts in each kidney in individuals without a family history of the disease. We divided subjects into two groups according to the presence of PLD. Of those subjects with a PLD, we measured total liver volume and adjusted it for the height of the patient.

Data collection and measurement

We collected demographic data such as age, sex, smoking, and alcohol-drinking status. Anthropometric data, including height, weight, and blood pressure, were obtained at the time of enrollment. In addition, we investigated renal (hematuria, proteinuria, urinary tract stone) and extrarenal complications (intracranial aneurysm), and major comorbidities, including hypertension and diabetes. We obtained laboratory data, including complete blood counts, kidney and liver function, and urinalysis. In addition, we collected data concerning pregnancy, delivery, and hormonal replacement therapy through the questionnaire survey. Detailed methodology for data collection was described in the previously reported protocol manuscript.[15] Proteinuria was defined by urine protein to creatinine ratio (uPCR) ≥ 0.3 g/gCr. The presence of PLD was defined by observed cysts ≥ 3 in the abdominal CT scan. We measured liver volume based on the CT image using semiautomatic volumetry software (ImageJ version 1.5a, https://imagej.nih.gov/ij/)[16,17] by one professional radiologist. Total liver volume (TLV) was adjusted for height, and it was classified into four grades as suggested in the previous study: no cyst (Gr0), height-adjusted total liver volume (HtTLV) < 1,000 mL/m (Gr1), HtTLV 1,000–1,800 mL/m (Gr2), HtTLV > 1,800 mL/m (Gr3).[2] In addition, patients with HtTLV ≥ 1,000 mL/m were defined as severe PLD. Total kidney volume was also measured by volumetry, which was classified based on the Mayo classification criteria.[16] Kidney function was determined by the estimated glomerular filtration rate (eGFR) calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.[18]

Genetic analysis and classification

We performed targeted exome sequencing by gene panel, including 89 genes related to cystogenesis or ciliopathy.[15] The major type of genetic mutation was classified into PKD1, PKD2, and others. Among the detected variants, nonsense and frameshift mutations were grouped as protein-truncating (PT) mutations, whereas nonsynonymous missense, non-frameshift indel, or non-canonical splicing mutation were grouped as non-truncating (NT) mutations. Finally, we divided into 5 categories for the genetic variants: PKD1-PT, PKD1-NT, PKD2, others, and no detected variants.

Statistical analysis

We used the Student's *t*-test, analysis of variances (ANOVA), and χ^2 tests to compare the groups. Continuous variables were described as the mean ± standard deviation, and categorical variables were described as numbers with percentages. Two-sided *P* values were derived by setting the significance level at 0.05. In ANOVA analysis, we performed post-hoc analysis using the Tukey methods. As a cross-sectional study, we performed a logistic regression analysis to determine the relative factors for the presence of PLD and the severity of PLD (≥ grade 2). For the multivariate analysis, we included variables showing $P < 0.05$ in the univariate analysis. Statistical analyses were performed using SPSS (version 23.0; IBM Corp., Armonk, NY, USA).

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Ethics statement

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of each participating center: Seoul National University Hospital (H-1907-067-1047), Chonnam National University Hospital (CNUH-2019-276), Kangbuk Samsung Hospital (KBSMC 2019-07-029), Inje University Busan Paik Hospital (19-0151), Seoul Metropolitan Government-Seoul National University Boramae Medical Center (30-2019-104), Hallym University Kangnam Sacred Heart Hospital (2019-07-015), Keimyung University Dongsan Hospital (DSMC 2019-07-055-008), and Seoul National University Bundang Hospital (19-0151). Informed consent was received from all participants at the time of enrollment for the study.

RESULTS

Baseline characteristics of the study population

A total of 602 subjects were finally included in this study (**Fig. 1**). The mean age was 45.3 years old, and 46.8% were male. There were 455 (75.6%) and 23 (3.8%) subjects with hypertension and diabetes, respectively. Genetic variants were detected in 433 (71.9%) subjects, and the most common variant type was PKD1-PT (n = 202, 33.6%). There were 461 (76.6%) subjects with PLD. Compared to the subjects without PLD, those with PLD showed older age, a higher proportion of females and complications such as hypertension and intracranial aneurysm. Subjects with PLD showed higher kidney volume classified into Mayo classification 1C-1E and a higher proportion with PKD1-PT and PKD2 in the distribution of genetic variant types. Subjects with liver cysts showed lower hemoglobin, lower serum calcium, higher serum creatinine, lower eGFR, lower uric acid level, and lower serum albumin (**Table 1**).

Characteristics according to PLD groups

Of 461 subjects with PLD, 112 (24.3%) and 69 (15.0%) subjects showed grade 2 and 3 PLD, respectively. The subjects with a higher grade of PLD showed older age, more females, non-smokers, non-alcoholics, lower body mass index (BMI), a higher number of pregnancies and

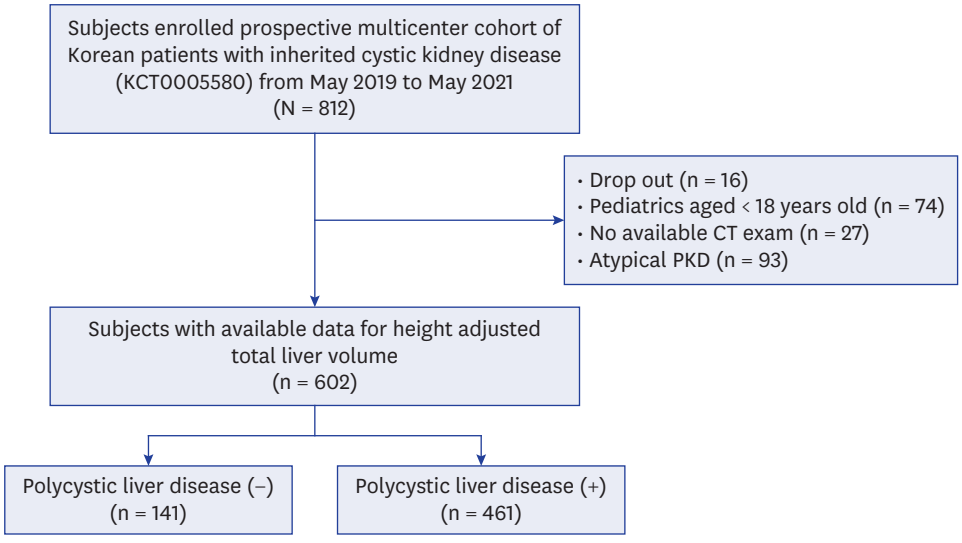

Fig. 1. Study populations.
CT = computed tomography, PKD = polycystic kidney disease.

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Table 1. Baseline characteristics according to the presence of PLD

Characteristics	Total (n = 602)	No PLD (n = 141)	PLD (n = 461)	*P* value
Age, yr	45.34 ± 13.35	39.57 ± 16.06	47.11 ± 11.87	< 0.001
Male	282 (46.8)	93 (66.0)	189 (41.0)	< 0.001
Smoking				0.552
Non-smoker	411 (68.3)	91 (64.5)	320 (69.4)	
Current-smoker	68 (11.3)	18 (12.8)	50 (10.8)	
Ex-smoker	123 (20.4)	32 (22.7)	91 (19.7)	
Alcohol drinking				0.952
Yes	289 (48.0)	68 (48.2)	221 (47.9)	
Body mass index, kg/m^2	24.16 ± 3.66	24.91 ± 4.70	23.93 ± 3.26	0.022
< 23	255 (42.4)	52 (20.4)	203 (79.6)	0.220
≥ 23, < 25	126 (20.9)	29 (23.0)	97 (77.0)	
≥ 25	221 (36.7)	60 (27.1)	161 (72.9)	
Systolic blood pressure, mmHg	131.62 ± 38.11	130.57 ± 14.43	131.94 ± 42.82	0.709
Pregnancy number[a]				0.591
None	65 (20.3)	9 (18.8)	56 (20.6)	
1–2	152 (47.5)	26 (54.2)	126 (46.3)	
≥ 3	103 (32.2)	13 (27.1)	90 (33.1)	
Delivery number[a]				0.980
None	73 (22.8)	11 (22.9)	62 (22.8)	
1–2	211 (65.9)	32 (66.7)	179 (65.8)	
≥ 3	36 (11.2)	5 (10.4)	31 (11.4)	
HRT[a]	40 (12.5)	2 (4.2)	38 (14.0)	0.058
Comorbidities				
Hypertension	455 (75.6)	87 (61.7)	368 (79.8)	< 0.001
Diabetes	23 (3.8)	9 (6.4)	14 (3.0)	0.070
Hematuria	99 (16.4)	19 (13.5)	80 (17.4)	0.470
Proteinuria	112 (18.7)	20 (14.2)	92 (20.1)	0.116
Urinary tract stone	56 (9.3)	13 (9.2)	43 (9.3)	0.969
Aneurysm	37 (6.2)	1 (0.7)	36 (7.8)	0.002
Mayo classification				< 0.001
1A–1B	245 (40.7)	82 (58.2)	163 (35.4)	
1C–1E	357 (59.3)	59 (41.8)	298 (64.6)	
Genetic mutation				< 0.001
PKD1-PT	202 (33.6)	36 (25.5)	166 (36.0)	
PKD1-NT	117 (19.4)	33 (23.4)	84 (18.2)	
PKD2	85 (14.1)	5 (3.5)	80 (17.4)	
Others	29 (4.8)	9 (6.4)	20 (4.3)	
No detected variants	169 (28.1)	58 (41.1)	111 (24.1)	
Laboratory results				
Hemoglobin, g/dL	13.24 ± 1.69	14.02 ± 1.83	13.00 ± 1.58	< 0.001
Platelet, ×10^3/μL	230.43 ± 63.08	239.46 ± 60.74	227.67 ± 63.59	0.052
Calcium, mg/dL	9.28 ± 0.45	9.40 ± 0.46	9.24 ± 0.44	< 0.001
Phosphorus, mg/dL	3.53 ± 0.57	3.53 ± 0.56	3.53 ± 0.58	0.964
Blood urea nitrogen, mg/dL	20.14 ± 12.73	18.59 ± 12.09	20.61 ± 12.89	0.098
Creatinine, mg/dL	1.35 ± 1.20	1.18 ± 0.91	1.40 ± 1.27	0.021
eGFR, mL/min/1.73 m^2	76.64 ± 32.74	88.75 ± 32.45	72.93 ± 31.96	< 0.001
Total bilirubin, mg/dL	0.75 ± 0.36	0.76 ± 0.34	0.75 ± 0.37	0.838
Alkaline phosphatase, mg/dL	63.44 ± 41.49	60.55 ± 41.63	64.33 ± 41.45	0.352
Uric acid, mg/dL	5.54 ± 1.64	6.00 ± 1.89	5.40 ± 1.53	0.001
Albumin, g/dL	4.50 ± 0.41	4.57 ± 0.40	4.48 ± 0.41	0.023
Total cholesterol, mg/dL	175.66 ± 39.27	179.87 ± 47.24	174.38 ± 36.45	0.148
Urine specific gravity	1.00 ± 0.11	1.01 ± 0.09	1.00 ± 0.11	0.350
uPCR, g/gCr	0.30 ± 0.96	0.37 ± 1.62	0.28 ± 0.63	0.503

PLD = polycystic liver disease, HRT = hormonal replacement therapy, PKD = polycystic kidney disease, PT = protein-truncating, NT = non-truncating, eGFR = estimated glomerular filtration rate, uPCR = urine protein-creatinine ratio.
[a]The proportion was demonstrated to be limited in female subjects.

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deliveries, higher prevalence of hypertension, lower plasma hemoglobin and platelet count, lower calcium, higher phosphorus, higher BUN, lower eGFR, higher alkaline phosphatase (ALP), lower uric acid, and lower serum albumin (**Supplementary Table 1**). However, there was no significant difference in the distribution of genetic variants according to PLD severity (**Supplementary Table 2**). The mean value of HtTLV was highest in patients with PKD2 mutation, and the overall distribution of HtTLV according to the genetic variants categories is demonstrated in **Supplementary Fig. 1**.

Independent risk factors for developing PLD

Female subjects had 2.01 times higher risk for PLD than male subjects in multivariate analysis. In addition, subjects with Mayo classification 1C-1E showed significantly increased risk of presence of PLD (adjusted odds ratio, 3.00; 95% confidence interval, 1.77, 5.07). The presence of hypertension and intracranial aneurysm increased risk of PLD in univariate analysis, but the significance was attenuated in the multivariate analysis. Among the genetic variant types, PKD1-PT and PKD2 significantly increased the risk of PLD by 2.87 times and 8.09 times compared to the subjects without detected variants, respectively (**Table 2**).

Table 2. Significant relative factors associated with polycystic liver disease

Factors	OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age	1.04 (1.03–1.06)	< 0.001	1.04 (1.02–1.07)	0.001
Female	2.79 (1.88–4.14)	< 0.001	2.01 (1.12–3.59)	0.019
Body mass index				
< 23 kg/m^2	Reference			
≥ 23, < 25 kg/m^2	0.86 (0.51–1.43)	0.556		
≥ 25 kg/m^2	0.69 (0.45–1.05)	0.084		
Systolic blood pressure	1.00 (1.00–1.01)	0.717		
Smoking				
Non-smoker	Reference			
Current-smoker	0.79 (0.44–1.42)	0.431		
Ex-smoker	0.81 (0.51–1.29)	0.371		
Alcohol drinking	0.99 (0.68–1.44)	0.952		
Hemoglobin	0.68 (0.60–0.77)	< 0.001	0.93 (0.77–1.13)	0.458
Platelet	1.00 (0.99–1.00)	0.055		
Calcium	0.42 (0.26–0.66)	< 0.001	0.61 (0.33–1.15)	0.128
Phosphorus	1.01 (0.73–1.40)	0.964		
Blood urea nitrogen	1.02 (1.00–1.03)	0.101		
eGFR	0.98 (0.98–0.99)	< 0.001	1.00 (0.99–1.01)	0.583
Total bilirubin	0.95 (0.55–1.63)	0.838		
Alkaline phosphatase	1.00 (1.00–1.01)	0.353		
Uric acid	0.81 (0.72–0.91)	< 0.001	0.84 (0.72–0.99)	0.031
Albumin	0.51 (0.29–0.91)	0.022	1.61 (0.87–3.00)	0.131
Total cholesterol	1.00 (1.00–1.00)	0.152		
uPCR	0.92 (0.77–1.09)	0.342		
Hypertension	2.46 (1.63–3.70)	< 0.001	1.43 (0.81–2.50)	0.215
Diabetes	0.46 (0.19–1.09)	0.076		
Hematuria	1.35 (0.79–2.32)	0.274		
Urinary tract stone	1.01 (0.53–1.94)	0.969		
Intracranial aneurysm	11.89 (1.62–87.50)	0.015	5.59 (0.73–42.54)	0.097
Mayo classification ≥ 1C	2.54 (1.73–3.74)	< 0.001	3.00 (1.77–5.07)	< 0.001
Genetic variants				
No detected variants	Reference		Reference	
PKD1-PT	2.41 (1.49–3.90)	< 0.001	2.87 (1.58–5.19)	< 0.001
PKD1-NT	1.33 (0.80–2.22)	0.276	1.43 (0.77–2.67)	0.259
PKD2	8.36 (3.21–21.78)	< 0.001	8.09 (2.97–21.99)	< 0.001
Others	1.16 (0.50–2.71)	0.730	1.72 (0.65–4.54)	0.272

OR = odds ratio, CI = confidence interval, eGFR = estimated glomerular filtration rate, uPCR = urine protein-creatinine ratio, PKD = polycystic kidney disease, PT = protein-truncating, NT = non-truncating.

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We additionally evaluated hormonal effects via pregnancy number, delivery number, and hormonal replacement therapy on the development of PLD in female subjects. There was no statistical difference according to the number of pregnancies or delivery, and hormonal replacement therapy (**Supplementary Table 3**).

Independent risk factors for severe PLD

In this study, we tried to determine the risk factors for severe PLD (Gr2 and Gr3). Among demographic factors, older age, female sex, and higher BMI increased the risk of severe PLD in the univariate analysis, but the age and sex effect were attenuated in the multivariate analysis (**Table 3**). For the laboratory factors, lower hemoglobin, higher phosphorus, higher blood urea nitrogen, lower eGFR, higher serum ALP, higher uric acid, and lower serum albumin increased the risk of severe PLD in the univariate analysis. However, only hemoglobin and serum ALP were maintained as the independent risk factors after adjustment. Hypertension has a significant association with an increased risk of severe PLD in multivariate analysis. In addition, PKD1-PT and PKD2 were significantly associated with severe PLD compared to subjects without detected genetic variants. We also evaluated the relative risk factors for severe PLD except for subjects without detected genetic variants. We found similar results compared

Table 3. Risk factors associated with polycystic liver disease grade ≥ 2

Factors	OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age	1.04 (1.02–1.06)	< 0.001	1.02 (1.00–1.05)	0.093
Female	1.37 (0.93–2.01)	0.112	1.27 (0.68–2.40)	0.459
Body mass index				
< 23 kg/m^2	Reference		Reference	
≥ 23, < 25 kg/m^2	1.31 (0.79–2.17)	0.295	1.47 (0.80–2.68)	0.216
≥ 25 kg/m^2	2.05 (1.33–3.14)	0.001	2.32 (1.34–4.03)	0.003
Systolic blood pressure	1.00 (0.99–1.00)	0.576		
Smoking				
Non-smoker	Reference		Reference	
Current-smoker	1.12 (0.61–2.04)	0.724	1.20 (0.55–2.62)	0.645
Ex-smoker	0.92 (0.57–1.49)	0.728	1.02 (0.53–1.98)	0.954
Alcohol drinking	0.60 (0.41–0.88)	0.009	0.67 (0.42–1.07)	0.094
Hemoglobin	0.80 (0.71–0.91)	< 0.001	0.79 (0.64–0.96)	0.017
Platelet	1.00 (0.99–1.00)	0.070		
Calcium	0.85 (0.55–1.31)	0.458		
Phosphorus	1.44 (1.04–1.99)	0.030	1.20 (0.75–1.92)	0.451
Blood urea nitrogen	1.02 (1.01–1.04)	0.006	0.99 (0.96–1.02)	0.634
eGFR	0.99 (0.98–0.99)	< 0.001	1.01 (0.99–1.02)	0.362
Total bilirubin	1.14 (0.67–1.92)	0.628		
Alkaline phosphatase	1.02 (1.01–1.02)	< 0.001	1.02 (1.01–1.02)	< 0.001
Uric acid	1.14 (1.01–1.29)	0.032	1.15 (0.97–1.35)	0.100
Albumin	0.59 (0.36–0.96)	0.035	1.02 (0.55–1.89)	0.963
Total cholesterol	1.00 (0.99–1.00)	0.102		
Hypertension	4.69 (2.56–8.58)	< 0.001	3.62 (1.76–7.43)	< 0.001
Diabetes	0.61 (0.19–1.98)	0.410		
Hematuria	2.56 (1.30–5.06)	0.007	1.12 (0.63–2.02)	0.699
Urinary tract stone	1.22 (0.79–1.89)	0.379		
Intracranial aneurysm	1.25 (0.66–2.36)	0.488		
Mayo classification ≥1C	1.22 (0.82–1.81)	0.319		
Genetic variants				
No detected variants	Reference		Reference	
PKD1-PT	1.58 (0.96–2.62)	0.075	2.10 (1.14–3.86)	0.018
PKD1-NT	1.48 (0.82–2.67)	0.197	1.59 (0.80–3.17)	0.189
PKD2	1.87 (1.03–3.39)	0.039	2.43 (1.20–4.91)	0.013
Others	0.72 (0.24–2.15)	0.561	0.86 (0.25–2.93)	0.811

OR = odds ratio, CI = confidence interval, eGFR = estimated glomerular filtration rate, PKD = polycystic kidney disease, PT = protein-truncating, NT = non-truncating.

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to whole enrolled subjects with PLD (**Supplementary Table 4**). Although compared to the subjects with other variants, PKD1-PT tended to increase the risk of severe PLD, there was no statistical significance (**Supplementary Table 4**).

The number of pregnancies and delivery significantly increased the risk of severe PLD, but hormonal use was not associated with PLD severity in univariate analysis. After adjustment with age, significance of the number of pregnancies and delivery was attenuated. Although hormonal replacement therapy was significantly increased the risk of severe PLD, the association was attenuated after adjustment with laboratory result, comorbidity, and genetic variants (**Supplementary Table 5**).

DISCUSSION

In this study, we identified relative factors associated with cystic involvement in the liver in ADPKD. In addition, we secured the independent risk factors for severe PLD among ADPKD patients with PLD. Although specific factors influencing each outcome were different, genetic variants with PKD1-PT or PKD2 commonly affected the development and severity of PLD. Older age, female, and higher kidney volume with Mayo classification 1C-1E were significantly associated with the presence of PLD, but it was not related to the severity of PLD. Although higher BMI, lower hemoglobin, higher serum ALP, and the presence of hypertension did not associate with the development of PLD but increased the risk of TLV ≥ 1,000 mL/m in subjects with PLD.

As a major extrarenal manifestation of ADPKD, PLD does not affect liver function. Still, it was usually represented by heterogeneous structural changes of the biliary tree development and caused subjective discomfort related to mass effects when liver volume significantly increased.[19,20] The frequency of liver cysts increased with age, especially in women, related to exposure to estrogen.[3] In this regard, it has been reported that PLD usually worsens during pregnancy or under estrogen replacement therapy.[5,21,22] In this study, we found that the female sex significantly impacted the development of liver cysts. Although the number of pregnancies or delivery did not affect the development of PLD, it incrementally increased the risk of severity of PLD in the univariate analysis. The impact of the number of pregnancies and delivery on the severity of PLD was attenuated after adjustment with age, and it could be related to the hormonal change associated with menopause and inversed effect of age on liver growth.[23] Considering the limitation as one of the epidemiological studies, further experimental study would be warranted to reveal the exact relationship between pregnancy, hormonal status, and the severity of PLD.

Hepatic cysts have been regarded as the most common extrarenal manifestation, but there was scarce data to suggest risk factors for hepatic cysts. As traditional risk factors, in addition to female and pregnancy factors, kidney function and severity of kidney lesions were also related to the presence of liver cysts.[4,24] In this study, we also found that higher kidney volume represented by Mayo classification 1C-1E significantly associated with the development of PLD. However, there was no association between kidney function and liver cysts or volume with the severity of PLD. The frequency of hepatic cysts increases with age,[25] and its late onset time for the clinical phenotype of liver cysts could be related to this association between liver cysts and an advanced stage of kidney disease with higher kidney volume.

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Hypertension is a major comorbidity of ADPKD, which usually develops before a loss of kidney function.[26] Early onset hypertension before age 35 is associated with a poorer kidney prognosis in ADPKD.[24] Moreover, hypertension lead decline in renal blood flow parallels kidney volume increases, and precedes loss of kidney function with structural and functional deterioration.[27] In PLD, architectural changes occur due to cystic formation, leading to capillarization of the hepatic sinusoids and elevated hepatic resistance connected to portal hypertension.[25,28] In the process of vasodilation with restoring the functional blood volume followed by portal vein stretching, the renin-angiotensin system is broadly involved.[29] Although the direct association between hypertension and liver cyst has not been evaluated yet, we suggest that both portal hypertension and activation of the renin-angiotensin system are systemically involved in the development of hypertension and the severity of PLD. In addition to the liver factor, hypertension could be initially related to kidney function. Liver cysts usually developed after increased total kidney volume, and we also found a negative association between kidney function and the severity of PLD. A further pathophysiological study would be warranted to support the complicated relationship between hypertension and the severity of PLD.

Hemoglobin was significantly associated with the severity of PLD in this study. Anemia is one of the major hematological abnormalities, and it was reported in approximately 75% of patients with chronic liver disease.[30] In addition, iron deficiency could be related to liver conditions such as nonalcoholic fatty liver disease.[31] Cyst formation in the liver interrupts the remodeling of the ductal plate, leading to portal hypertension.[32] Moreover, mass effects with hepatomegaly and portal hypertension also could be linked to iron deficiency anemia.[33] Meanwhile, considering the normal hepatic function in patients with ADPKD, anemia could be related to decreased kidney function. The patient with liver cysts showed lower eGFR, and the kidney function was incrementally lower in according to the higher total liver volume. As a retrospective observational cohort, we could not determine the causal relationship, but we suggested that lower hemoglobin and severe PLD bidirectionally influenced each other, and also related to the decreased kidney function.

ALP is a well-known parameter representing disease progression and somatostatin analogue response in patients with PLD.[21,34] ALP affects the secretory function of cholangiocytes, and it counter-regulates secretory stimulation of cholangiocytes to prevent increased bile pressure.[35] In conditions with PLD, ALP also has a role in counteracting fluid secretion from cholangiocytes lining hepatic cysts and plays a protective role for ductular chlorosis in PLD.[36] The level of ALP was significantly different according to the presence of liver cysts, and it was incrementally increased with the grade of PLD severity in this study. Although more than 90% of patients with liver cysts showed levels of ALP within a normal range, ALP was significantly associated with the progression of PLD. Therefore, more assertive monitoring for ALP needs to be warranted in patients with ADPKD.

There were 433 (71.9%) patients with a significant genetic mutation, of which PKD1 and PKD2 mutations accounted for 73.7% and 19.6%, respectively. The mutation detection rate was slightly lower than the previously reported one, but the proportion of PKD1 including PKD1-PT and PKD1-NT, and PKD2 was comparable to the previously reported one.[37-41] Interestingly, we found that genetic variants in PKD2 showed the highest risk for the presence of liver cysts. Moreover, both genetic variants PKD1-PT and PKD2 mutations increased not only the development of PLD but also the severity of PLD. The evaluation of genetic variants has a role in unraveling severe phenotype, intrafamilial variability, and novel causing

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genotype, thereby providing key information to understand disease pathogenesis in ADPKD.[42] Truncated PKD1 protein has been announced as a poor prognostic marker of end-stage kidney disease in ADPKD patients.[43] However, compared to the apparent correlation between genetic variants and kidney outcome, the association between genetic variants and liver cysts or severity of PLD was not well established. This study is the first report on the significance of genetic variants on the severity of PLD based on the five categories; PKD1-PT, PKD1-NT, PKD2, others, and no detected variant. Among typical ADPKD patients with PLD, genetic variants were not detected in 23.6%. In spite of the advances in the methods to evaluate affected genetic mutation, the undetected mutation rate was still maintained at around 20%. In this regard, we assessed these proportion as a one of subgroup without relative variants or with variant could not be detected usual methods. Based on our results, subjects with genetic variants not only in PKD1-PT but also PKD2 had a higher risk for severe PLD. On the contrary, subjects without detected variants could be considered at lower risk for liver cysts or severe PLD.

This study provided novel aspects to expect the presence of PLD and the severity of PLD using common clinical parameters and genetic variants. Except for the previously reported risk factors such as older age, female sex, and pregnancy, we also found the significance of several factors including serologic parameters such as hemoglobin, ALP, and comorbidity such as hypertension, and genetic variants including PKD1-PT and PKD2. Nevertheless, there are several limitations to be concerned. First, as an observational study, we could not evaluate the causal association and pathophysiology between the factors and outcomes. Second, the sample size was small to provide unwavering evidence. Third, we cannot consider the disease duration and severity of comorbidities. Fourth, we used HtTLV, not the number of liver cysts or the diameter of liver cysts in this study. Fifth, we could not evaluate the menopausal status and specific types of hormonal replacement therapy such as estrogen-only or estrogen with progesterone which could be a significant factor in influencing liver volume. Prospective large cohort study and experimental study would be warranted to solve these limitations.

As a multifarious systemic disease, liver cysts could be related to kidney manifestations and genetic variants. Monitoring hemoglobin and ALP and evaluating the genetic variants, especially PKD1-PT or PKD2 are helpful in predicting severe PLD.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Baseline characteristics according to the severity of polycystic liver disease

Click here to view

Supplementary Table 2

Distribution of HtTLV in according to the genetic variants categories

Click here to view

Supplementary Table 3

Impact of hormone exposure on the development of PLD in female subjects

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Supplementary Table 4

Significant relative factors associated with PLD grade ≥ 2 among the patients with genotypes

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Supplementary Table 5

Impact of hormone exposure on the PLD severity in female subjects

Click here to view

Supplementary Fig. 1

Distribution of HtTLV in according to the genetic variants categories in (**A**) whole population and (**B**) male and female patients.

Click here to view

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