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Original Article

ORIGINAL ARTICLE

Prevalence of pericardial effusion in autosomal dominant polycystic kidney disease

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ABSTRACT

Background. Autosomal dominant polycystic kidney disease (ADPKD) has numerous extrarenal manifestations. Pericardial effusion (PE) may be an underrecognized complication with a reported prevalence of up to 35%. Our study is the first to systematically evaluate the prevalence of PE and associated risk factors in an ADPKD cohort outside the USA.
Methods. Clinically stable ADPKD patients from a specialized outpatient clinic were evaluated retrospectively. Magnetic resonance tomography and computed tomography scans were analysed regarding the presence of PE (≥4 mm). Imaging results were linked to clinical characteristics.
Results. Of 286 ADPKD patients, 208 had computed tomography or magnetic resonance imaging suitable for evaluation of PE. In this group we detected PE in 17 patients (8.2%). The overall prevalence of PE was 6.3%, with more females being affected (prevalence of PE was 7.8% in females and 3.8% in males). The PE mean size was 6.8 ± 3.3 mm. The prevalence of autoimmune diseases was higher in the patients with PE (11.8% versus 2.1%, $P = .022$), while the presence and size of PE was not associated with signs of rapid progressive disease, ADPKD genotype, patient age, body mass index and other clinical parameters. Exploratory investigation of individual characteristics of PE patients by regression tree analysis suggested renal functional impairment, sex and proteinuria as candidate variables.

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Conclusions. PE prevalence in our cohort was lower than previously reported and showed a clear female preponderance. Our data suggest that patients with PEs >10 mm deserve further attention, as they may have additional non-ADPKD-related pathologies.

LAY SUMMARY

Autosomal dominant polycystic kidney disease (ADPKD) has numerous extrarenal manifestations. Pericardial effusion (PE) may be an underrecognized complication, with a reported prevalence of up to 35%. Our study evaluates the prevalence of PE and associated risk factors in an ADPKD cohort outside the USA. In 208 clinically stable ADPKD patients we detected PE in 17 patients (8.2%). The overall prevalence of PE was 6.3%, with more females being affected. The PE mean size was 6.8 ± 3.3 mm. The prevalence of autoimmune diseases was higher in the patients with PE, while the presence and size of the PE was not associated with signs of rapid progressive disease, ADPKD genotype, patient age, body mass index and other clinical parameters. Exploratory investigation by regression tree analysis suggested renal functional impairment, sex and proteinuria as candidate variables for PE. Our data suggest that patients with PEs >10 mm deserve further attention, as they may have additional non-ADPKD-related pathologies.

Keywords: autosomal dominant polycystic kidney disease, extrarenal manifestation, female preponderance, pericardial effusion, prevalence

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, affecting up to 12.5 million people of all races worldwide [1, 2]. The disease-defining manifestation is the formation of renal cysts, leading to structural defects, enlargement of the kidneys and a decrease in renal function [3]. Additionally, ADPKD is associated with numerous extrarenal cystic and non-cystic manifestations. The most common include arterial hypertension, hepatic and pancreatic cysts, intracranial vascular aneurysms and cardiac valvular complications. There are also less-common complications such as vascular dissections, coronary artery aneurysms and aneurysms of the splenic or popliteal arteries [4, 5]. In 2007, pericardial effusion (PE) was first described as an extrarenal manifestation with a prevalence of up to 35% [6]. Recently, Liu *et al.* [7] reported a second US cohort exhibiting a PE prevalence of 21%.

The aetiology of PE in ADPKD is poorly understood. Qian *et al.* [6] found no association between PE and renal dysfunction and suggested that defects in polycystin-1, a large integral glycoprotein encoded by the *PKD1* gene, and in polycystin-2 protein, a non-selective calcium channel encoded by the *PKD2* gene, are directly involved in the molecular pathogenesis of PE [2, 8]. Polycystins are expressed not only in renal tubules, but also in other epithelial and endothelial cells throughout the body and have important roles in cell adhesion and extracellular matrix regulation, explaining the risk for connective tissue defects in ADPKD patients [9].

The objective of our study was to evaluate the prevalence of PE in a representative real-world ADPKD cohort outside the USA. By analysing clinical characteristics of affected patients, we further aim to identify potential risk factors for the development of PE.

MATERIALS AND METHODS

Study design and population

Data was acquired from the specialized ADPKD outpatient clinic of Hannover Medical School after approval from the local ethics committee (10429_BO_K_2022). Data and imaging were collected retrospectively for all ADPKD patients with written informed consent and abdominal magnetic resonance imaging (MRI) or computed tomography (CT) scans who presented during the period from December 2012 through December 2021. Scans were run to evaluate patients' kidney volumes and disease progression.

Imaging analysis

All available abdominal MRI and CT images with sufficient inclusion of low cardiac and pulmonary fields were evaluated for the presence of PE in coronal, axial and sagittal sections with the radiology DICOM viewer Visage 7 (Visage Imaging, San Diego, CA, USA). For the evaluation of MRIs, T2-weighted sequences with fat suppression were used. Measurement of PE was performed on several axial levels. A dilation of pericardial fluids ≥4 mm was defined as a significant PE. The PE was quantified by measuring the largest dimension (shown in Fig. 2). In a subgroup of 52 patients (25%), repetitive imaging was available for PE evaluation. Image reading and measurements were carried out by a medical doctoral candidate (J.S.J.) and board-certified radiologist (T.F.K.) as a consensus read.

Laboratory data collection and medical records

The subjects with and without PE were compared based on the following parameters: age, sex, body mass index (BMI), presence of hypertension, intake of antihypertensive therapy (grouped into different classes), presence of autoimmune and systemic inflammatory diseases (e.g. systemic lupus erythematosus, Sjögren's syndrome, sarcoidosis, systemic sclerosis, systemic vasculitis, rheumatoid arthritis, psoriasis arthritis), cardiac (left ventricular hypertrophy, valvular complications, cardiac arrhythmia) and vascular complications (aneurysms, dissections) [10]. If repetitive MRI or CT scans were available, data were collected from the first scan. Serum creatinine, serum cystatin C, serum urea, serum C-reactive protein (CRP), estimated glomerular filtration rate (eGFR) based on serum creatinine/serum cystatin C using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, the decrease in eGFR per year and the decrease in eGFR over 5 years, as well as the presence of proteinuria (>0.12 g/l), were also extracted.

Preferably, characterizing data were collected within ±6 months of imaging.

The Mayo classification was calculated by web-based applications: Mayo Clinic approximation of height-adjusted total kidney volume (ht-TKV; https://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754) and Renal Unit of the Royal Infirmary of Edinburgh, Scotland (https://jscalc.io.calc/EbgTWdRdVXaqRoEk), depending on the availability of sagittal sections. Patients were classified as Mayo class 1A–1E or Mayo class 2. Furthermore, medication with tolvaptan for patients at high risk of a rapid progression of ADPKD as well as genotype data were extracted. Genotype data were obtained from the Department of Human Genetics of Hannover Medical School.

For the PE subjects, additional data, i.e. the exact quantification of proteinuria and albuminuria as well as the presence of malignant tumours, the presence of hypothyroidism, thyroid-stimulating hormone (TSH) level, antinuclear antibodies and intake of drugs with a PE association (e.g. hydralazine, minoxidil, methotrexate and cyclosporine) were evaluated [10].

Statistical analysis

Single variable analysis was done using two-tailed *t*-tests. For categorical parameters, the percentage (count) was calculated and chi-squared tests were used for comparison. A *P*-value $<.05$ was considered statistically significant. The Spearman correlation coefficient was used to assess the correlation between the size of the PE and metric data such as eGFR, age and BMI (data not shown). Continuous parameters are presented as mean ± standard error of the mean (SEM). For *P*-value–based regression tree analysis, we used R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) to examine potential associations of multiple potential cofactors simultaneously. All other analyses were performed using Prism version 5 (GraphPad Software, San Diego, Ca, USA).

RESULTS

Prevalence of pericardial effusion

A total of 286 patients diagnosed with ADPKD according to the Pei criteria were evaluated [11, 12]. A total of 208 patients, ages 19–77 years, had suitable scans (88% MRI, 12% CT), i.e. in which all four heart chambers were visible, while 78 patients were excluded from further analysis due to a lack of adequate imaging (shown in Fig. 1, baseline characteristics shown in Supplementary Table 1). Clinical characteristics did not differ in the excluded patients except for a lower prevalence of hypertension (shown in Supplementary Table 1). Repetitive imaging was available for 52 patients over a mean period of 47.3 ± 44.4 months.

Imaging analysis revealed PE in 17 patients, 2 of whom had previously recorded PE linked to underlying diseases apart from ADPKD (i.e. rheumatic disease/lymphoma and pericarditis). Six of the patients with PE had repetitive imaging, which showed persisting PE for four patients, while in two patients the PE had vanished in the longitudinal scan. After exclusion of the four patients with previously recorded and vanished PE, PE prevalence was 6.3% (13/208 subjects).

In our cohort, the mean PE size was 6.8 ± 3.3 mm ($n = 17$). PE size is generally considered mild when <10 mm, moderate when 10–20 mm and large when >20 mm [10]. The 4 patients with previously recorded or vanished PE showed mild to moderate PE size (10.5 ± 2.4 mm), whereas the remaining 13 patients had a PE size of 5.6 ± 0.4 mm (shown in Supplementary Table 2).

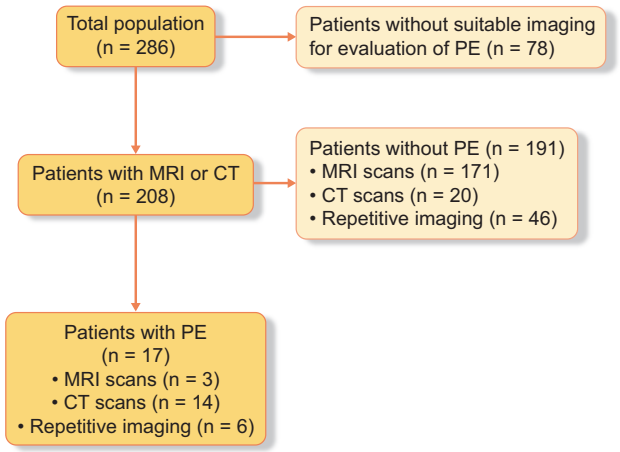

Figure 1: Study flow chart.

Sex and other cofactors

We observed a female preponderance in patients with PE (82.3%; shown in Fig. 3a) when compared with the overall sex ratio of our cohort (62.0% female). Even when discounting the four patients with previously recorded or vanished PE, who were all female, we found a 76.9% female:male ratio among the remaining PE patients. Considering all examined patients, this corresponded to a PE prevalence of 7.8% in females and 3.8% in males.

Among the subjects with PE, more patients suffered from autoimmune diseases (11.8% versus 2.1%, $P = .022$). Of note, a diagnosis of autoimmune disease was generally established independent of the diagnosis of PE, which was only detected retrospectively in the current study. No differences were found in age, BMI and renal function between subjects with and without PE (shown in Table 1). Within the patients with PE we found no correlation of PE size with these metric variables. Neither the longitudinal decrease in renal function nor Mayo subclasses (grouped as Mayo subclasses 1A + B versus 1C + D + E) indicated an association with PE (shown in Table 1 and Fig. 3b and c). While the frequency of recorded hypertension was similar, patients with PE showed a trend towards receiving more classes of antihypertensive drugs (25.0% versus 11.5% had four or more classes) and more frequent use of loop diuretics (18.8% versus 6.4% of patients with hypertension) (shown in Table 1).

Genotype data, which was available for a subgroup of patients (31%), was grouped in *PKD1* and *PKD2* (likely) pathogenic variants and into truncating and non-truncating variants (shown in Table 1). No difference was found in genetics between patients with and without PE. Due to the low availability of genetics in the PE group, genetics were not considered in our statistical regression analysis.

Explorative regression tree analysis

As direct comparison of possible cofactors of PE was uninformative, we performed an explorative regression tree analysis to characterize patients with ADPKD-associated PE ($n = 13$). The analysis classified affected patients into three groups (shown in Supplementary Fig. 1). The first group (node 2) was characterized by a slow decline in renal function. The second and

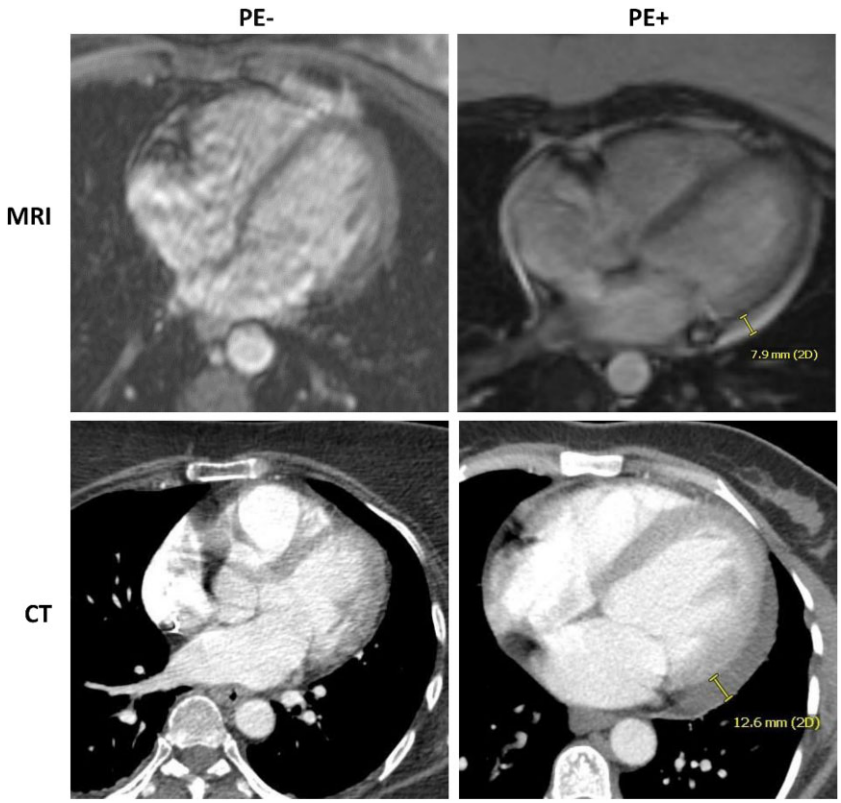

Figure 2: Representative axial scans of the heart showing normal pericardium (left) and pericardial effusion (right). MRI: T2-weighted sequence.

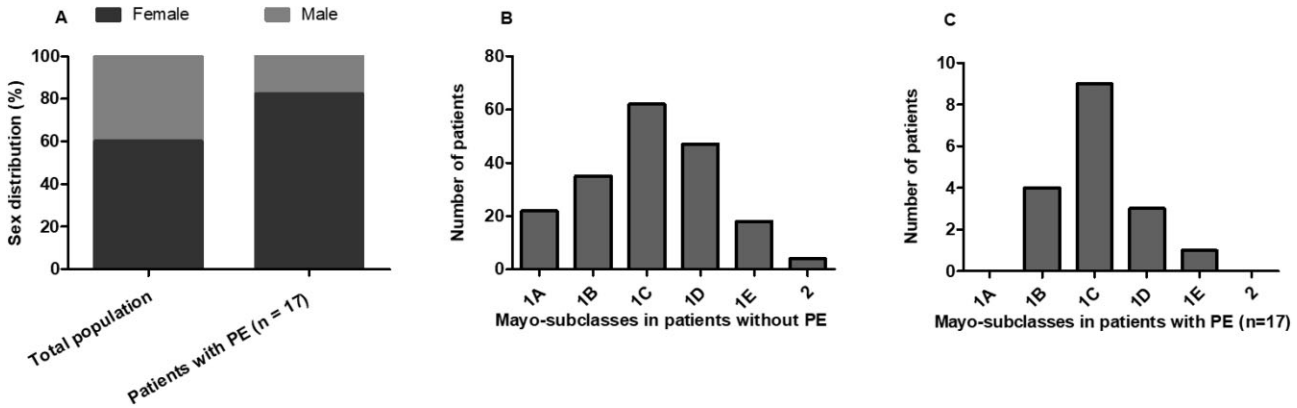

Figure 3: **(A)** Sex distribution in the total study population and patients with PE; females were more likely affected by PE [$n = 14/17$ patients (82.3%)]. **(B)** Distribution of Mayo subclasses in patients without PE. **(C)** Distribution of Mayo subclasses in patients with PE.

third groups (nodes 6 and 9) had more rapid annual loss of eGFR (>2.1 ml/min/1.73 m^2/year) and more advanced CKD (eGFR ≤68 ml/min/1.73 m^2). Additional characteristics included sex, proteinuria and coexisting autoimmune disease.

DISCUSSION

PE is defined as a fluid volume in the pericardial space that exceeds the physiologic amount of pericardial fluid. There is little information about the prevalence of PE in the general population, but an analysis of the Framingham cohort [13] suggested a prevalence of 6.5% in adult men and women and Qian *et al.* [6] reported a prevalence of 4% in healthy kidney donors. In our cohort of 208 ADPKD patients, we observed a PE prevalence of 8.2% or 6.3% (after correction for potential confounders). While this is close to the prevalence in the Framingham cohort, it is higher than the reported prevalence in kidney donors and much lower than the previously published numbers in ADPKD patients. Qian *et al.* [6] reported a prevalence of 35% in 60 ADPKD patients and Liu *et al.* [7] reported a prevalence of 21% in 117 ADPKD patients.

Several differences between the previous ADPKD studies and our study need to be considered when interpreting this discrepancy. First, our cohort consisted of stable ADPKD patients in

Table 1: Baseline characteristics of subpopulations with and without PE ($n = 208$).

Characteristics	Patients without PE	Patients with PE	P-value
Patients, % (*n*)	91.8 (191)	8.2 (17)	
Male, % (*n*)	39.8 (76)	17.7 (3)	.07
Age (years), mean ± SEM (*n*)	43.7 ± 0.9 (191)	45.6 ± 3.8 (17)	.55
BMI (kg/m^2), mean ± SEM (*n*)	26.1 ± 0.4 (188)	24.4 ± 0.8 (16)	.16
Serum creatinine (µmol/l), mean ± SEM (*n*)	125.5 ± 6.0 (188)	110.4 ± 11.3 (17)	.45
Serum cystatin C (mg/l), mean ± SEM (*n*)	1.3 ± 0.04 (162)	1.3 ± 0.1 (16)	.97
Serum urea (mmol/l), mean ± SEM (*n*)	7.5 ± 0.3 (186)	6.5 ± 0.5 (16)	.33
Serum CRP (mg/l), mean ± SEM (*n*)	2.6 ± 0.3 (185)	2.9 ± 1.0 (16)	.75
eGFR (creatinine, CKD-EPI) (ml/min/1.73 m^2), mean ± SEM (*n*)	63.8 ± 2.0 (191)	70.2 ± 8.3 (17)	.36
eGFR (cystatin C, CKD-EPI) (ml/min/1.73 m^2), mean ± SEM (*n*)	64.9 ± 2.2 (162)	62.1 ± 7.4 (15)	.71
Decrease in eGFR/year (ml/min/1.73 m^2), mean ± SEM (*n*)	6.8 ± 0.4 (134)	6.0 ± 0.9 (15)	.48
Decrease in eGFR over 5 years (ml/min/1.73 m^2), mean ± SEM (*n*)	4.8 ± 0.3 (85)	5.2 ± 1.4 (10)	.64
Mayo subclasses, % (*n*)			
1A–B	29.8 (57)	23.5 (4)	.52
1C–E	66.5 (127)	76.5 (13)	
2	2.1 (4)	0.0 (0)	
Genetics available, % (*n*)	31.9 (61)	29.4 (5)	.83
PKD1 variants	80.3 (49)	80.0 (4)	.99
Truncating *PKD1* variants	57.1 (28)	75.0 (3)	.49
PKD2 variants	26.2 (16)	40.0 (2)	.51
Hypertension, % (*n*)	83.2 (159)	94.1 (16)	.24
Antihypertensive drugs, % (*n*)	98.7 (157)	100.0 (16)	.65
ACE inhibitors/ARBs, % (*n*)	94.9 (149)	100.0 (16)	.36
Calcium channel blockers, % (*n*)	44.0 (69)	43.8 (7)	.98
MCR antagonists, % (*n*)	5.1 (8)	0.0 (0)	.36
β1AR antagonists, % (*n*)	35.7 (56)	31.3 (5)	.72
Thiazides, % (*n*)	21.7 (34)	12.5 (2)	.39
Loop diuretics, % (*n*)	6.4 (10)	18.8 (3)	.07
α1AR antagonists, % (*n*)	4.5 (7)	6.3 (1)	.75
α2AR agonists, % (*n*)	5.7 (9)	18.8 (3)	.051
Vasodilators, % (*n*)	1.3 (2)	0.0 (0)	.65
Antihypertensive drugs (1–3 classes), % (*n*)	88.5 (139)	75.0 (12)	.12
Antihypertensive drugs (≥4 classes), % (*n*)	11.5 (18)	25.0 (4)	
Tolvaptan therapy, % (*n*)	4.2 (8)	5.9 (1)	.74
No tolvaptan therapy, but recommendation, % (*n*)	49.2 (94)	41.2 (7)	.53
Proteinuria >0.12 g/l, % (*n*)	34.6 (66)	29.4 (5)	.67
Autoimmune diseases, % (*n*)	2.1 (4)	11.8 (2)	**.022**
Cardiac complications, % (*n*)	5.2 (10)	5.9 (1)	.91
Vascular complications, % (*n*)	4.7 (9)	5.9 (1)	.83

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; MCR: mineralocorticoid receptor; β1AR: beta-1 adrenergic receptor; α1AR: alpha-1 adrenergic receptor; α2AR: alpha-1 adrenergic receptor.
A *p*-value <.05 was considered statistically significant in bold.

the outpatient clinic. We did not include imaging from hospitalized or acutely ill patients. Instead, imaging was performed for baseline evaluation as a tool to evaluate the risk of rapid ADPKD progression based on the measurement of total kidney volume. It is therefore possible that our patient population had a lower comorbidity load leading to a lower PE risk. Baseline characteristics of the patients with PE, such as age, kidney function and BMI, were comparable between the three studies, except for higher serum creatinine mean values in the study of Qian *et al.* [6], which most likely resulted from single outlier patients [7].

Second, both previous studies were conducted in US cohorts, while our study is the first analysis of a cohort in Europe. It is possible that the higher racial and ethnic diversity in the US cohorts might have played a role. Beyond ethnicity, lifestyle and environmental factors might be involved. Another factor could be the treatment of comorbidities (e.g. hypertension and consecutive left ventricular hypertrophy).

Third, we chose a stringent cut-off of ≥4 mm, based on radiological criteria, to differentiate between a physiologic amount of pericardial fluid versus a pathologic effusion. The normal pericardial cavity contains physiologically <35 ml of serous pericardial fluid, acting as a lubricant and allowing the two pericardial layers to smoothly slide over each other [14]. A pericardial width, the distance between the two pericardial layers, is pathologic when it is ≥4 mm [14, 15]. Qian *et al.* [6] used a very sensitive categorization and considered a pericardial width ≤3 mm as proof of low-grade PE and >3–<5 mm as medium-grade PE. By subtracting low- and medium-grade PE from their data, PE prevalence drops from 35 to 17%. This is comparable to the 21% prevalence reported for the cohort by Liu *et al.* [7], who considered a fluid signal in the pericardial space of >5 mm.

An important observation of our study was a clear female preponderance among the PE patients. Comparable to our sex ratio, Liu *et al.* [7] reported a similar pattern with 70.8% females among their ADPKD patients with PE. Although the

overall female:male ratio was more balanced in the study by Qian *et al.* [6] (11 females and 10 males), the sex ratio was not reported separately for different grades of PE and it would be interesting to test for an increased female representation in the group with higher-grade PE (>5 mm). There are many different aetiologies for PE, including infectious, autoimmune, neoplastic, metabolic (i.e. hypothyroidism) and drug-related causes [16]. Female preponderance was also observed for diseases apart from ADPKD, i.e. according to Laufer-Perl *et al.* [17] in acute idiopathic pericarditis and myopericarditis with 68% versus 45%. Additionally, autoimmune diseases and hypothyroidism are more common in women and their coexistence in female ADPKD patients could cause a study bias [10, 18]. However, after controlling for all possible aetiologies, the phenomenon of PE remained more common in our female patients.

Apart from autoimmune diseases and sex, we found no striking clinical characteristic in the PE patients in the descriptive statistical analysis but a trend in more frequent use of loop diuretics. This might indicate a state of overall hypervolaemia in the PE patients.

For characterization of PE patients, we employed an explorative regression tree analysis. The analysis suggested three subgroups of patients with a similar likelihood for PE within each group. Potential predictive parameters included annualized eGFR decline, stage of CKD, as well as sex and proteinuria. According to these data, a unifying pathophysiological hypothesis for PE in ADPKD is still lacking. Larger patient numbers will be needed to study these parameters in more detail.

Several limitations of this study must be considered. The first limitation is the relatively small number of patients with PE. For this reason, it is possible that we missed potential predictors of PE occurrence and cannot draw firm conclusions about involved mechanisms. It is a retrospective single-centre cohort study without a control group, thus bias concerning patient selection cannot be excluded. Regarding the imaging modalities, there was no specific cardiac imaging, but we used the cranial section of abdominal MRI (88%) or abdominal CT scans (12%) to evaluate the pericardial field. Although CT, as well as MRI, have an important role in the detection of pericardial pathologies, MRI is the more reliable imaging modality for the detection of cardiac diseases or pericardial abnormalities [19]. We are confident about imaging quality, as we were able to detect small PEs with both modalities and estimate that the risk to ignore medium-sized or large PEs should be relatively low irrespective of the imaging modality (MRI versus CT scans).

Summing up, our study showed a significantly lower prevalence of PE in patients with ADPKD compared with previous studies. Based on our observations in a real-world outpatient cohort, we propose that a PE of at least moderate size (>10 mm) should receive further clinical attention in order to exclude ADPKD independent aetiologies. Therefore, as discussed by Lazaros *et al.* [20], workup of asymptomatic PE should at least consist of medical history, clinical examination, electrocardiography and routine blood tests including CRP, ruling out a bacterial aetiology (including tuberculosis). Finally, echocardiography is recommended as follow-up every 2–4 weeks to 3–6 months depending on the chronicity of the effusion.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

J.S.J., T.F.K., B.A. and J.B. collected the data and performed the analysis. K.M.S.-O., R.S. and V.C.W. conceptualized the project. All authors wrote and reviewed the article.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

CONFLICT OF INTEREST STATEMENT

R.S. received honoraria for scientific lectures from Otsuka Pharmaceutical, AstraZeneca and Bayer. The remaining authors declare no conflicts of interest.

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