

Long-Term Validation of E-selectin Gene S128R Polymorphism as a Predictor of Cyst Growth in Autosomal Dominant Polycystic Kidney Disease

Bennur Esen

bennuresen@yahoo.com

Sağlık Bilimleri Üniversitesi

Ahmet Engin Atay

Sağlık Bilimleri Üniversitesi

Tarik Sayin

Sağlık Bilimleri Üniversitesi

Ferdi Karagoz

Sağlık Bilimleri Üniversitesi

Halit Akbas

Harran University

Research Article

Keywords: autosomal dominant polycystic kidney disease, cyst progression, 10-year follow-up, E-selectin S128R polymorphism

Posted Date: July 9th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10282405/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at BMC Nephrology on September 11th, 2026. See the published version at <https://doi.org/10.1186/s12882-026-05349-3>.

Abstract

Objective:

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive cyst formation and kidney enlargement, ultimately leading to chronic kidney disease. Although E-selectin has been shown to play a role in endothelial dysfunction and inflammation during disease progression, the long-term prognostic effects of serum E-selectin levels and the SELE S128R (rs5361) gene polymorphism have not been clearly established. The aim of this study was to investigate the association of baseline serum E-selectin levels and SELE S128R polymorphism with long-term structural and functional disease progression in patients with ADPKD.

Methods:

In this prospective longitudinal study, 20 patients with ADPKD who completed a 10-year follow-up period from an initial cohort of 76 patients were included. Clinical, biochemical, and imaging data from baseline and follow-up periods were compared. Total kidney volume (TKV), height-adjusted total kidney volume (htTKV), and dominant renal cyst volume were evaluated using magnetic resonance imaging (MRI)-based Mayo classification. Serum E-selectin levels were measured using an enzyme-linked immunosorbent assay (ELISA) method, and the SELE S128R gene polymorphism was analyzed using the polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) method. Patients were grouped according to AA and AC + CC genotypes.

Results:

During follow-up, TKV and htTKV significantly increased ($p = 0.001$ for both), whereas renal function worsened, as demonstrated by an increase in serum creatinine levels and a significant decline in estimated glomerular filtration rate (eGFR). Left dominant cyst volume also increased significantly ($p = 0.013$). Serum E-selectin levels remained stable over time. No significant differences were observed between the AA and AC + CC genotype groups in terms of imaging or biochemical parameters at baseline or at follow-up. However, changes in TKV and htTKV over time were significant only in patients with the AA genotype ($p = 0.008$ for both). Similarly, changes in serum creatinine ($p = 0.023$), eGFR ($p = 0.009$), and parathyroid hormone (PTH) ($p = 0.021$) levels over time were significant only in patients with the AA genotype.

Conclusion:

The AA genotype of the S128R polymorphism in the E-selectin gene was associated with significant changes in TKV and htTKV compared with AC and CC genotypes. In addition, changes in dominant cyst

volume were associated with the AA genotype. Furthermore, longitudinal changes in serum creatinine, eGFR, and PTH levels were more prominent in patients with the AA genotype. However, no significant association was found between serum E-selectin levels and cyst progression.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common inherited causes of end-stage kidney disease and is characterized by progressive renal cyst development, an increase in total kidney volume (TKV), and a gradual decline in kidney function (1). The disease primarily results from mutations causing loss of function in the PKD1 and PKD2 genes, which encode polycystin-1 and polycystin-2 proteins, respectively. These mutations lead to increased tubular epithelial cell proliferation, impaired fluid secretion, and consequently cyst formation and enlargement (2).

In recent years, ADPKD has been recognized not only as a structural cystic kidney disease but also as a disease associated with endothelial dysfunction, chronic inflammation, and microvascular abnormalities that contribute to disease progression (3). During endothelial activation, the expression of adhesion molecules such as E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) increases. This increase is considered an important marker of endothelial activation (3, 4).

The Ser128Arg (S128R, rs5361) polymorphism in the SELE gene is a missense variant resulting in the substitution of the serine amino acid with arginine at position 128 of the E-selectin protein. The potential role of E-selectin and the S128R polymorphism in ADPKD progression has been investigated in several studies. Clinical studies have demonstrated that circulating soluble E-selectin levels are higher in patients with ADPKD compared with healthy controls, supporting the potential role of endothelial activation in the pathophysiology of the disease (3, 4). The S128R polymorphism, which is an important genetic regulator of endothelial inflammatory response, has also been associated with endothelial function in various inflammatory and vascular diseases (4, 5). However, evidence regarding the impact of this polymorphism on cyst progression, increase in kidney volume, and long-term loss of kidney function in ADPKD remains limited.

In a previous study, the relationship between serum E-selectin levels, the SELE S128R polymorphism, and renal cyst growth during a one-year follow-up period in patients with ADPKD was evaluated. In this analysis, patients with the CC genotype demonstrated a more pronounced increase in total kidney volume, and the risk of cyst growth was 1.32-fold higher compared with the AA genotype; however, this association did not reach statistical significance (6).

In current clinical practice, prediction of disease progression in autosomal dominant polycystic kidney disease is mainly based on clinical parameters such as total kidney volume (TKV) measured by magnetic resonance imaging (MRI), height-adjusted total kidney volume (htTKV), and age-adjusted estimated glomerular filtration rate (eGFR). The Mayo Imaging Classification is considered one of the most reliable radiological methods for classifying patients according to their risk of progression (7, 8).

However, beyond these imaging-based markers, the long-term prognostic value of endothelial biomarkers and genetic variants has not yet been sufficiently elucidated (6, 7).

This study was designed as a 10-year prospective longitudinal follow-up study, representing a continuation of the previous cross-sectional analysis conducted in the same patient cohort, and aimed to evaluate the long-term relationship between the SELE S128R polymorphism and disease progression.

Methods

This study was designed as a 10-year prospective longitudinal follow-up study of a previously established and published ADPKD cohort (6). The study was conducted between January 2026 and June 2026 at the Nephrology Outpatient Clinic of University of Health Sciences Bağcılar Training and Research Hospital. The diagnosis of ADPKD was confirmed according to KDIGO criteria (9), and patients included in 2016 were re-evaluated for long-term follow-up assessment. Baseline clinical, biochemical, and imaging findings were compared with the data obtained at the end of the 10-year follow-up period.

The baseline cohort consisted of 76 patients. During the follow-up period, 8 patients were lost to follow-up, 25 patients could not be re-evaluated because they were followed at different centers, 13 patients could not undergo end-of-study evaluations due to initiation of renal replacement therapy, and 10 patients died. Therefore, 20 patients with complete 10-year follow-up data were included in the final analysis.

The study protocol was approved by the Ethics Committee of Medipol University Faculty of Medicine (approval no: E-10840098-202.3.02-7807; date: 18.11.2025) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Following an overnight fasting period of eight hours, venous blood samples were collected from the participants. Biochemical analyses included glucose, urea, creatinine, uric acid, alanine aminotransferase (ALT), aspartate aminotransferase (AST), electrolytes, total protein, albumin, lipid profile [total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)], and parathyroid hormone (PTH) levels. Biochemical parameters were measured using standard photometric methods with the Siemens Advia 1800 analyzer (Siemens Healthineers, Kobe, Japan). PTH levels were measured using a chemiluminescence immunoassay method with the Siemens ADVIA Centaur analyzer (Siemens Healthineers, USA). For hematological evaluation, blood samples were collected into EDTA-containing anticoagulant tubes, and analyses were performed using the automated hematology analyzer Mindray BC-6800 (Shenzhen Mindray Bio-Medical Electronics Co., Ltd., China).

Serum E-selectin levels were determined using the enzyme-linked immunosorbent assay (ELISA) method. Measurements were performed using the Human E-Selectin (SELE) ELISA kit (E0253Hu, BT LAB, Shanghai Korain Biotech, Shanghai, China) according to the manufacturer's recommended protocols.

Urine analyses were performed according to standard laboratory procedures. Spot urine albumin levels were measured using an immunoturbidimetric method with the Siemens Advia 1800 analyzer, while urine creatinine levels were determined using the Aeroset analyzer (Abbott Laboratories Inc., Abbott Park, IL, USA). The urine albumin-to-creatinine ratio (ACR) was calculated, and an ACR value > 30 mg/g was defined as microalbuminuria in individuals without uncontrolled hypertension or urinary tract infection.

Genotype data for the SELE S128R (rs5361, 561 A > C) polymorphism were obtained from a previously published cohort study (6). DNA isolation and genotyping were performed using the polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) method. For PCR amplification, the primers 5'-ATGGCACTCTGTAGGACTGCT-3' and 5'-GTCTCAGCTCAGATCACCAT-3' were used, and the amplified product length was determined as 248 base pairs (bp). In statistical analyses, the AA genotype was considered the reference group. Due to the limited sample size, individuals carrying the C allele (AC + CC genotypes) were analyzed together to increase statistical power.

Anthropometric measurements were performed using a Tanita body composition analyzer (Tanita Corporation of America, IL, USA). Body weight, height, and body composition parameters were evaluated, and body mass index (BMI) was calculated by dividing body weight (kg) by height squared (m²).

Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation based on serum creatinine (SCr) level, age, and sex. The following formula was used for eGFR calculation:

$$\text{eGFR} = 175 \times (\text{SCr})^{-1.154} \times (\text{age})^{-0.203} \times 0.742 \text{ (for females)}$$

eGFR values were expressed as mL/min/1.73 m².

The size, intensity, and volume of renal cysts were evaluated by the same experienced radiologist at the Department of Radiology, Bağcılar Training and Research Hospital, using T2-weighted magnetic resonance imaging (MRI) examinations. Baseline MRI images obtained in the previous study (6) were compared with MRI examinations performed at the end of the 10-year follow-up period. Total kidney volume (TKV) and renal cyst volumes were calculated using standard stereological methods and the modified ellipsoid formula. Dominant cyst growth was defined as the change in the volume of the largest renal cyst identified on serial T2-weighted MRI images obtained at baseline and follow-up periods. The Mayo Imaging Classification was used for assessment of disease progression and categorization of patients according to risk groups (7, 8).

Statistical analysis: Statistical analyses were performed using IBM SPSS Statistics for Windows, version 31.0 (IBM Corp., Armonk, NY, USA). Given the small sample size (n = 20) and non-normal distribution of most variables, as assessed by the Shapiro–Wilk test, non-parametric methods were applied. Continuous variables are presented as mean ± standard deviation or median (minimum–maximum), as appropriate, while categorical variables are summarized as frequencies (n) and percentages (%).

Comparisons between baseline and follow-up measurements were performed using the Wilcoxon signed-rank test. The SELE S128R polymorphism was analyzed by comparing AA and AC + CC genotype groups using the Mann–Whitney U test. Associations between continuous variables were assessed using Spearman’s rank correlation analysis, with correlation coefficients (r) and corresponding p values reported. The strength of correlations was interpreted according to standard thresholds used in biomedical research. A two-sided p value < 0.05 was considered statistically significant for all analyses.

Results

The demographic, radiological, and genetic characteristics of the study group are presented in Table 1. A total of 20 patients with autosomal dominant polycystic kidney disease (ADPKD) were included in the study. Of the participants, 12 were female (60.0%) and 8 were male (40.0%), with a mean baseline age of 48.60 ± 12.39 years. At the end of the 10-year follow-up, the mean age increased to 59.55 ± 12.28 years. In the baseline assessment, the most frequently observed Mayo Imaging Classification class was 1B, which was identified in 7 patients (35.0%). At the 10-year follow-up assessment, the most common class was 1C, observed in 8 patients (40.0%).

Table 1

Demographic characteristics, Mayo imaging classification, and E-selectin gene S128R polymorphism distribution in patients with autosomal dominant polycystic kidney disease (n = 20)

Variables	Category	n	%
Sex	Female	12	60.0
	Male	8	40.0
Age (years)	Baseline (mean $\pm$ SD)	48.60 $\pm$ 12.39	—
	Baseline (median, min–max)	45.50 (33.00–81.00)	—
	10-year follow-up (mean $\pm$ SD)	59.55 $\pm$ 12.28	—
	10-year follow-up (median, min–max)	56.00 (45.00–92.00)	—
Height (cm)	Mean $\pm$ SD	164.70 $\pm$ 7.31	—
	Median (min–max)	165.00 (153.00–179.00)	—
Mayo Imaging Class (Baseline)	1A	2	10.0
	1B	7	35.0
	1C	3	15.0
	1D	2	10.0
	1E	0	0.0
	Unclassified	6	30.0
Mayo Imaging Class (Follow-up)	1A	5	25.0
	1B	5	25.0
	1C	8	40.0
	1D	0	0.0
	1E	1	5.0
	Unclassified	1	5.0
E-selectin S128R polymorphism	AA (wild type)	13	65.0
	AC + CC (variant carriers)	7	35.0
Continuous variables are expressed as mean $\pm$ standard deviation or median (minimum–maximum), and categorical variables as number (n) and percentage (%).			

Significant changes in radiological parameters were observed during the 10-year follow-up period (Table 2). Total kidney volume (TKV) increased from 1119.23 ± 1130.21 mL at baseline to 1515.19 ± 1255.30 mL at the end of the 10-year follow-up ($p = 0.001$). Similarly, a significant increase was observed in height-adjusted total kidney volume (htTKV), which increased from 674.64 ± 660.99 mL/m at baseline to 914.69 ± 737.42 mL/m at follow-up ($p = 0.001$). When dominant cyst volumes were evaluated, an increasing trend was observed in right dominant cyst volume; however, this change did not reach statistical significance (from 53.78 ± 98.14 mL to 68.41 ± 83.60 mL; $p = 0.055$). In contrast, a significant increase was observed in left dominant cyst volume, with values increasing from 42.15 ± 50.57 mL to 102.32 ± 141.76 mL ($p = 0.013$). Regarding serum E-selectin levels, no significant difference was found between baseline and 10-year follow-up values (59.72 ± 27.12 ng/mL vs. 54.05 ± 29.25 ng/mL; $p = 0.551$) (Fig. 1).

Table 2

Comparison of radiological parameters and serum E-selectin levels at baseline and after 10 years of follow-up in patients with autosomal dominant polycystic kidney disease (n = 20)

Variables	Initial evaluation (Mean $\pm$ SS / Median [Min–Max])	Final evaluation (Mean $\pm$ SS / Median [Min–Max])	p
Total kidney volume (mL)	$1119,23 \pm 1130,21 / 694,69$ (393,12–4702,40)	$1515,19 \pm 1255,30 / 1207,90$ (413,70–4863,90)	0,001*
htTKV (mL/m)	$674,64 \pm 660,99 / 433,15$ (236,60–2766,10)	$914,69 \pm 737,42 / 719,00$ (243,40–2861,20)	0,001*
Right dominant cyst volume (mL)	$53,78 \pm 98,14 / 34,07$ (3,16–388,00)	$68,41 \pm 83,60 / 35,01$ (1,99–285,86)	0,055
Left dominant cyst volume (mL)	$42,15 \pm 50,57 / 28,32$ (4,97–165,56)	$102,32 \pm 141,76 / 51,61$ (7,05–545,61)	0,013*
Serum E-selectin level (ng/mL)	$59,72 \pm 27,12 / 54,40$ (22,50–105,20)	$54,05 \pm 29,25 / 38,00$ (25,00–115,00)	0,551
<i>htTKV: height-adjusted total kidney volume; SS: standart sapma;</i>			
<i>Min–Maks: minimum–maximum.</i>			
The Wilcoxon signed-rank test was used to compare baseline and end-of-follow-up measurements.			

Laboratory parameters at baseline and at the 10-year follow-up are presented in Table 3. Renal function worsened during follow-up, with a significant increase in serum creatinine ($p = 0.022$) and a significant decline in eGFR ($p = 0.002$). Urea levels increased but did not reach statistical significance ($p = 0.093$). No significant changes were observed in electrolyte levels (sodium and potassium) or liver function

tests. Regarding mineral metabolism, serum phosphorus levels increased significantly ($p = 0.035$), whereas corrected calcium and parathyroid hormone levels remained unchanged. The urine albumin-to-creatinine ratio increased significantly ($p = 0.007$). Lipid profile, hematological parameters, and glucose levels did not show significant changes. Uric acid levels showed an increasing trend but did not reach statistical significance ($p = 0.053$) (Table 3).

Table 3

Comparison of laboratory parameters at baseline and 10-year follow-up in patients with autosomal dominant polycystic kidney disease (n = 20)

Variables	Baseline (Mean $\pm$ SD / Median [Min–Max])	Follow-up (Mean $\pm$ SD / Median [Min–Max])	p
Urea (mg/dL)	42.67 $\pm$ 27.78 / 33.00 (19.00–143.00)	55.35 $\pm$ 31.49 / 50.00 (22.00–150.00)	0.093
Creatinine (mg/dL)	1.26 $\pm$ 1.48 / 0.90 (0.60–7.40)	1.77 $\pm$ 1.78 / 1.11 (0.71–7.87)	0.022*
eGFR (MDRD) (mL/min/1.73 m ²)	80.46 $\pm$ 29.53 / 84.10 (5.80–122.30)	55.81 $\pm$ 25.18 / 59.15 (7.80–91.80)	0.002*
Sodium (mmol/L)	140.25 $\pm$ 3.37 / 141.00 (135.00–146.00)	141.05 $\pm$ 2.01 / 141.00 (137.00–145.00)	0.312
Potassium (mmol/L)	4.56 $\pm$ 0.46 / 4.50 (4.00–6.10)	4.58 $\pm$ 0.49 / 4.55 (3.96–5.99)	0.985
Parathyroid hormone (ng/L)	77.06 $\pm$ 92.85 / 50.25 (25.00–431.00)	113.15 $\pm$ 103.74 / 65.70 (9.10–382.00)	0.068
Corrected calcium (mg/dL)	9.44 $\pm$ 0.39 / 9.35 (8.50–10.00)	9.29 $\pm$ 0.57 / 9.37 (7.35–10.00)	0.177
Phosphorus (mg/dL)	3.31 $\pm$ 0.54 / 3.25 (2.30–4.60)	3.80 $\pm$ 0.89 / 3.80 (2.40–6.50)	0.035*
Albumin (g/dL)	4.55 $\pm$ 0.28 / 4.50 (4.00–5.20)	4.46 $\pm$ 0.27 / 4.50 (3.90–4.90)	0.361
Glucose (mg/dL)	106.70 $\pm$ 34.07 / 98.00 (79.00–239.00)	107.15 $\pm$ 30.29 / 98.50 (75.00–208.00)	0.562
AST (U/L)	21.37 $\pm$ 6.40 / 20.00 (14.00–37.00)	20.80 $\pm$ 6.44 / 19.00 (7.00–38.00)	0.343
ALT (U/L)	20.05 $\pm$ 6.27 / 20.00 (11.00–31.00)	20.25 $\pm$ 10.38 / 19.00 (8.00–54.00)	0.070
<i>Data are presented as mean $\pm$ standard deviation and median (minimum–maximum).</i>			
<i>Comparisons between baseline and follow-up were performed using the Wilcoxon signed-rank test.</i>			

Variables	Baseline (Mean $\pm$ SD / Median [Min–Max])	Follow-up (Mean $\pm$ SD / Median [Min–Max])	p
WBC ($\times 10^3/\mu\text{L}$)	6.51 $\pm$ 1.72 / 6.29 (4.28–11.10)	6.77 $\pm$ 1.91 / 6.46 (4.21–10.88)	0.653
Hemoglobin (g/dL)	13.24 $\pm$ 1.73 / 13.80 (10.20–16.00)	13.36 $\pm$ 2.11 / 13.20 (7.10–16.80)	0.722
Hematocrit (%)	41.07 $\pm$ 4.83 / 40.70 (31.70–49.80)	39.83 $\pm$ 6.13 / 39.50 (23.20–50.80)	0.246
Platelets ($\times 10^3/\mu\text{L}$)	236.92 $\pm$ 63.53 / 231.00 (133.20–372.00)	233.20 $\pm$ 65.19 / 236.00 (103.00–337.00)	0.687
Spot urine albumin/creatinine ratio (mg/g)	27.03 $\pm$ 32.24 / 9.85 (2.50–112.40)	58.38 $\pm$ 77.41 / 29.00 (6.00–319.00)	0.007*
Total cholesterol (mg/dL)	188.40 $\pm$ 49.70 / 173.00 (132.00–333.00)	190.55 $\pm$ 47.12 / 186.00 (119.00–303.00)	0.852
LDL cholesterol (mg/dL)	111.35 $\pm$ 41.65 / 107.00 (53.00–234.00)	107.05 $\pm$ 40.36 / 111.50 (47.00–199.00)	0.765
HDL cholesterol (mg/dL)	56.85 $\pm$ 15.48 / 53.50 (34.00–85.00)	55.45 $\pm$ 16.09 / 53.50 (33.00–91.00)	0.681
Triglycerides (mg/dL)	141.40 $\pm$ 81.67 / 137.00 (37.00–400.00)	145.05 $\pm$ 88.59 / 124.50 (54.00–394.00)	0.852
Uric acid (mg/dL)	4.85 $\pm$ 1.27 / 5.00 (2.50–6.40)	5.99 $\pm$ 2.05 / 5.75 (3.50–12.30)	0.053
<i>Data are presented as mean $\pm$ standard deviation and median (minimum–maximum).</i>			
<i>Comparisons between baseline and follow-up were performed using the Wilcoxon signed-rank test.</i>			

When analyzed according to SELE S128R genotype, within-group analyses showed significant increases in TKV, htTKV, and right/left dominant cyst volumes in the AA group ($p = 0.008$; $p = 0.008$; $p = 0.021$; $p = 0.008$, respectively). Moreover, we established significant increases in the creatinine and PTH ($p: 0.023$ and 0.021 , respectively), and significant decrease in the GFR ($p: 0.009$) in only AA genotype. However, no significant differences were observed between AA and AC + CC groups in demographic, radiological, or biochemical parameters at baseline or follow-up (all $p > 0.05$). In contrast, increases in TKV and htTKV in

the AC + CC group did not reach statistical significance (both $p = 0.068$). Serum E-selectin levels remained stable over time in both genotype groups (AA: $p = 0.441$; AC + CC: $p = 0.345$) (Table 4).

Table 4

Comparison of demographic characteristics, radiological findings, and serum E-selectin levels according to E-selectin gene S128R polymorphisms

Variables	Measurement	AA Genotype, n = 13) Mean $\pm$ SD / Median (Min–Max)	AC + CC Genotypes ,n = 7) Mean $\pm$ SD / Median (Min–Max)	p1
Age (years)	Baseline	47.85 $\pm$ 12.50/45.00 (33.00–81.00)	50.00 $\pm$ 13.03/46.00 (36.00–66.00)	0.812
	End of follow-up	58.92 $\pm$ 12.34/55.00 (45.00–92.00)	60.71 $\pm$ 13.06/57.00 (46.00–77.00)	0.843
	p2	0.001*	0.016*	
MRI-Measured Total Kidney Volume (mL)	Baseline	887.09 $\pm$ 542.59/674.49 (395.18–2137.26)	1537.06 $\pm$ 1795.33/865.34 (393.12–4702.40)	0.841
	End of follow-up	1428.38 $\pm$ 1104.73/1207.90 (443.00–4736.50)	1703.28 $\pm$ 1637.61/1338.30 (413.70–4863.90)	0.861
	p2	0.008*	0.068	
Height-adjusted Total Kidney Volume (htTKV) (mL/m)	Baseline	540.69 $\pm$ 318.42/425.50 (236.60–1257.20)	915.74 $\pm$ 1050.78/486.10 (248.80–2766.10)	0.841
	End of follow-up	867.42 $\pm$ 651.46/719.00 (280.00–2786.20)	1017.12 $\pm$ 959.52/789.05 (243.40–2861.20)	0.861
	p2	0.008*	0.068	
Right Dominant Cyst Volume (mL)	Baseline	30.63 $\pm$ 21.33/30.72 (5.87–60.85)	95.45 $\pm$ 164.37/37.42 (3.16–388.00)	0.841
	End of follow-up	65.98 $\pm$ 74.10/35.92 (6.28–271.12)	73.27 $\pm$ 107.90/34.43 (1.99–285.86)	0.640
	p2	0.021*	1.000	
Left Dominant Cyst Volume (mL)	Baseline	35.63 $\pm$ 43.26/20.22 (4.97–143.35)	53.90 $\pm$ 65.58/38.61 (6.05–165.56)	0.641
Data are presented as mean $\pm$ standard deviation or median (minimum–maximum). p1: Between-group comparisons (AA vs AC + CC) were performed using the Mann–Whitney U test. .p2: Within-group comparisons between baseline and follow-up were performed using the Wilcoxon signed-rank test.				

Variables	Measurement	AA Genotype, n = 13) Mean $\pm$ SD / Median (Min–Max)	AC + CC Genotypes ,n = 7) Mean $\pm$ SD / Median (Min–Max)	p1
	End of follow-up	130.85 $\pm$ 166.20/59.78 (16.65–545.61)	45.26 $\pm$ 41.17/33.26 (7.05–114.51)	0.134
	p2	0.008*	0.715	
E-selectin Level (ng/mL)	Baseline	68.48 $\pm$ 26.04/69.15 (22.50–105.20)	42.20 $\pm$ 21.76/36.10 (26.80–79.60)	0.086
	End of follow-up	53.33 $\pm$ 31.08/37.50 (25.00–115.00)	55.29 $\pm$ 28.15/38.00 (27.00–93.00)	0.767
	p2	0.441	0.345	
Serum Creatinine (mg/dL)	Baseline	0.87 $\pm$ 0.32/0.80 (0.60–1.70)	1.98 $\pm$ 2.40/1.20 (0.60–7.40)	0.081
	End of follow-up	1.65 $\pm$ 1.90/1.01 (0.86–7.87)	2.00 $\pm$ 1.65/1.30 (0.71–5.35)	0.311
	p2	0.023*	0.612	
Estimated Glomerular Filtration Rate (eGFR, MDRD) (mL/min/1.73 m²)	Baseline	87.50 $\pm$ 23.44/90.80 (45.00–122.30)	67.40 $\pm$ 36.81/64.30 (5.80–117.60)	0.241
	End of follow-up	58.03 $\pm$ 24.06/59.00 (7.80–88.80)	51.69 $\pm$ 28.63/59.30 (11.30–91.80)	0.699
	p2	0.009*	0.176	
Parathyroid Hormone (PTH)	Baseline	54.62 $\pm$ 30.89/48.50 (25.00–145.30)	121.95 $\pm$ 153.58/72.85 (27.50–431.00)	0.335
	End of follow-up	101.13 $\pm$ 95.31/62.20 (50.70–382.00)	133.74 $\pm$ 121.85/113.60 (9.10–325.00)	0.967
	p2	0.021*	0.917	
Data are presented as mean $\pm$ standard deviation or median (minimum–maximum). p1: Between-group comparisons (AA vs AC + CC) were performed using the Mann–Whitney U test. .p2: Within-group comparisons between baseline and follow-up were performed using the Wilcoxon signed-rank test.				

As shown in Table 5, baseline serum E-selectin levels were positively correlated with changes in creatinine ($r = 0.530$; $p = 0.042$) and parathyroid hormone ($r = 0.541$; $p = 0.046$). In contrast, no significant associations were observed between baseline E-selectin levels and SELE S128R polymorphism with 10-year changes in MRI-based TKV ($p = 0.502$ and $p = 0.465$), htTKV ($p = 0.689$ and $p = 0.465$), dominant cyst volumes (all $p > 0.05$), or changes in eGFR ($p = 0.550$ and $p = 0.171$). Among changes in E-selectin levels, only height showed a negative correlation ($r = -0.647$; $p = 0.012$), while no other significant associations were observed with demographic, radiological, or functional parameters. Furthermore, no significant associations were identified between SELE S128R polymorphism and any progression-related parameter (all $p > 0.05$).

Table 5

Associations between baseline E-selectin level, change in E-selectin, and S128R polymorphism with demographic, radiological, and functional progression parameters

Variables	Baseline E-selectin r (p)	Δ E-selectin r (p)	S128R polymorphism (AA vs AC + CC) p
Δ Total kidney volume (TKV)	0.227 (0.502)	0.000 (1.000)	0.465
Δ Height-adjusted TKV	0.136 (0.689)	0.091 (0.790)	0.465
Δ Right cyst volume	-0.409 (0.212)	0.473 (0.142)	0.663
Δ Left cyst volume	0.182 (0.593)	-0.127 (0.709)	0.089
Δ Creatinine	0.530 (0.042)*	-0.174 (0.551)	0.198
Δ eGFR	-0.168 (0.550)	-0.020 (0.946)	0.171
Δ Urea	0.284 (0.305)	0.117 (0.691)	0.335
Δ ACR (urine)	-0.111 (0.694)	0.389 (0.169)	0.732
Δ Parathyroid hormone	0.541 (0.046)*	-0.017 (0.957)	0.166
Δ Phosphorus	0.307 (0.265)	0.035 (0.905)	0.760
Δ Uric acid	-0.143 (0.611)	-0.073 (0.805)	0.420
Δ Hemoglobin	-0.247 (0.415)	0.077 (0.812)	0.811
Δ Hematocrit	-0.217 (0.476)	0.210 (0.512)	0.439
Δ Albumin	-0.332 (0.247)	0.215 (0.481)	0.136
Age (baseline)	0.322 (0.242)	0.046 (0.875)	0.819
Age (follow-up)	0.346 (0.206)	0.015 (0.958)	0.849
Height	0.337 (0.220)	-0.647 (0.012)*	0.644
Sex	0.189 (0.500)	-0.286 (0.321)	0.274

Data are presented as Spearman correlation coefficients (r) with p-values for continuous variables.

S128R polymorphism was analyzed as a categorical variable (AA vs AC + CC) using the Mann–Whitney U test, and only p-values are reported. Δ indicates change between follow-up and baseline values.

According to Table 6, no significant correlations were found between Δ TKV or Δ htTKV and age, sex, height, baseline creatinine, baseline eGFR, or other biochemical parameters (all $p > 0.05$). Similarly, changes in E-selectin, creatinine, eGFR, urea, parathyroid hormone, phosphorus, uric acid, hemoglobin, hematocrit, and albumin were not associated with changes in TKV or htTKV. For cyst volume changes, most variables showed no significant association, except for a negative correlation between Δ ACR and left dominant cyst volume change ($r = -0.632$; $p = 0.021$). Additionally, SELE S128R polymorphism showed no significant association with any progression-related imaging parameter, including TKV, htTKV, or cyst volume changes (all $p > 0.05$).

Table 6
Associations between radiological progression markers and demographic, clinical, and biochemical variables

Variables	Δ TKV r (p)	Δ htTKV r (p)	Δ Right cyst r (p)	Δ Left cyst r (p)	S128R p
Age	-0.193 (0.528)	-0.204 (0.504)	-0.295 (0.328)	-0.140 (0.647)	0.819
Height	0.061 (0.842)	0.033 (0.914)	-0.045 (0.885)	0.223 (0.464)	0.644
Sex	0.165 (0.590)	0.165 (0.590)	0.041 (0.894)	0.000 (1.000)	0.274
Baseline creatinine	0.241 (0.428)	0.216 (0.479)	0.003 (0.993)	0.279 (0.355)	0.198
Baseline eGFR	-0.192 (0.529)	-0.159 (0.603)	0.060 (0.845)	-0.313 (0.297)	0.171
Δ E-selectin	0.000 (1.000)	0.091 (0.790)	0.473 (0.142)	-0.127 (0.709)	0.345
Δ Creatinine	0.377 (0.204)	0.366 (0.219)	-0.162 (0.596)	0.127 (0.680)	0.198
Δ eGFR	-0.286 (0.344)	-0.319 (0.289)	-0.044 (0.887)	-0.110 (0.721)	0.171
Δ Urea	0.366 (0.219)	0.410 (0.164)	0.179 (0.559)	0.171 (0.577)	0.335
Δ ACR	-0.280 (0.354)	-0.236 (0.437)	-0.121 (0.694)	-0.632 (0.021*)	0.732
Δ PTH	0.394 (0.260)	0.370 (0.293)	-0.030 (0.934)	0.176 (0.627)	0.166
Δ Phosphorus	-0.386 (0.193)	-0.369 (0.214)	-0.259 (0.393)	-0.044 (0.886)	0.760
Δ Uric acid	-0.182 (0.553)	-0.206 (0.499)	-0.168 (0.584)	-0.462 (0.112)	0.420
Δ Hemoglobin	-0.182 (0.572)	-0.126 (0.697)	-0.056 (0.863)	-0.371 (0.236)	0.811
Δ Hematocrit	0.060 (0.854)	0.130 (0.688)	0.168 (0.601)	-0.196 (0.541)	0.439
Δ Albumin	-0.226 (0.480)	-0.226 (0.480)	0.280 (0.379)	0.237 (0.459)	0.136

Data are presented as Spearman correlation coefficients (r) with p-values. S128R polymorphism was analyzed as a categorical variable (AA vs AC + CC) using the Mann–Whitney U test, and only p-values are reported. Δ indicates change from baseline to follow-up.

Clinical outcomes were evaluated using data from the baseline cohort of 76 patients. Clinical outcomes of all patients in the baseline cohort according to **SELE** S128R genotype are presented in Table 7.

Table 7
Clinical outcomes according to SELE S128R genotype in the baseline cohort (n = 76)

RRT Status	AA n (%)	AC n (%)	CC n (%)	Total n (%)
No RRT	28 (51.9)	11 (73.3)	5 (71.4)	44 (57.9)
Hemodialysis (HD)	8 (14.8)	2 (13.3)	0 (0.0)	10 (13.2)
Peritoneal dialysis (PD)	1 (1.9)	0 (0.0)	0 (0.0)	1 (1.3)
Kidney transplantation (KT)	2 (3.7)	0 (0.0)	0 (0.0)	2 (2.6)
Lost to follow-up	7 (13.0)	1 (6.7)	1 (14.3)	9 (11.8)
Death	8 (14.8)	1 (6.7)	1 (14.3)	10 (13.2)
Total	54 (100)	15 (100)	7 (100)	76 (100)
RRT, renal replacement therapy; HD, hemodialysis; PD, peritoneal dialysis; KT, kidney transplantation. Data are presented as n (%). Percentages were calculated within each genotype group.				

Discussion

In this 10-year prospective longitudinal study, the association of baseline serum E-selectin levels and SELE S128R polymorphism with long-term disease progression was evaluated in patients with autosomal dominant polycystic kidney disease (ADPKD). During follow-up, the increase in creatinine levels, decline in eGFR, increase in phosphorus levels, trend toward increased PTH levels, and increase in microalbuminuria in the total patient group demonstrated significant renal functional deterioration in ADPKD.

One of the most noteworthy findings of the study was the more pronounced decline in renal function over time in patients with the AA genotype. In these patients, a significant increase in serum creatinine and parathyroid hormone (PTH) levels, together with a significant decrease in estimated glomerular filtration rate (eGFR), was observed. This finding suggests that the SELE S128R polymorphism may have genotype-specific effects during ADPKD progression and that the AA genotype may be particularly associated with long-term deterioration in renal function.

At the end of the follow-up period, MRI-based total kidney volume (TKV) and height-adjusted total kidney volume (htTKV) significantly increased, accompanied by an increase in left dominant cyst volume. The observed increase in TKV and htTKV is consistent with the natural course of ADPKD. Particularly, the increase in htTKV is important as it demonstrates that true kidney enlargement continues independently of body size differences among patients. The fact that the increase in dominant cyst volume was

significant only on the left side suggests that cystic growth may have a heterogeneous distribution within the kidney and that local factors may contribute to cyst progression.

MRI-based volumetric measurements and the Mayo Imaging Classification are currently among the most reliable tools for prognostic evaluation in ADPKD (8). In our study, the shift from class 1B toward class 1C in the Mayo Imaging Classification during follow-up supported that patients progressed toward a higher-risk structural category over time and that disease progression continued (7). The CRISP and HALT-PKD studies demonstrated that increases in kidney volume begin years before decline in glomerular filtration rate and represent one of the strongest predictors of long-term renal functional loss (1, 8). Similarly, in our study, a decrease in GFR, increases in TKV and htTKV, and a shift from Mayo Imaging Classification 1B to 1C were observed during the 10-year follow-up period.

E-selectin is an adhesion molecule expressed during endothelial cell activation and plays an important role in the regulation of leukocyte adhesion and inflammatory responses (1). Therefore, it is considered to contribute to endothelial dysfunction and chronic inflammatory processes in ADPKD. The S128R (rs5361) polymorphism in the SELE gene has been described as a genetic variant that may alter E-selectin function and has been associated with endothelial dysfunction in various cardiovascular and inflammatory diseases (10–11). In our study, the significant increases in TKV, htTKV, and renal cyst volumes observed over the follow-up period in patients with the AA genotype suggest that genetic mechanisms associated with endothelial activation may contribute to disease progression. It should be considered that the statistical power for evaluating this association was limited due to the small sample size of the AC + CC group in within-group analyses.

In contrast, the lack of significant changes in serum E-selectin levels during follow-up and the absence of differences between genotype groups suggest that circulating E-selectin levels alone may not be a sufficient marker reflecting long-term ADPKD progression. Disease progression is shaped by multiple molecular mechanisms, including inflammatory pathways, cAMP signaling, mTOR activation, and cellular metabolic alterations (12). Therefore, the absence of a direct association between serum E-selectin levels and renal progression may reflect the multifactorial nature of ADPKD. However, the association of the AA genotype with increases in TKV, htTKV, cyst volumes, and renal functional decline suggests that SELE genetic variation may influence disease susceptibility.

Furthermore, the lack of association between serum E-selectin levels and disease progression suggests that circulating E-selectin levels alone may not be sufficient to predict long-term ADPKD progression. The more pronounced increases in TKV, htTKV, and cyst volumes, together with renal functional decline in patients with the AA genotype, suggest that this genotype may be associated with more pronounced disease progression parameters. This finding further supports that kidney volume remains a major structural marker of disease progression (13–14).

Data regarding the clinical effects of the SELE S128R polymorphism in ADPKD are limited, and existing studies are mostly based on small sample sizes and short-term investigations (6). Although endothelial dysfunction and inflammation play important roles in the pathogenesis of ADPKD (3, 4), evidence directly

evaluating the impact of SELE gene variants on disease progression remains insufficient, and current knowledge is largely based on indirect findings obtained from cardiovascular and inflammatory diseases (15, 16). In this context, our study contributes to the literature by being one of the rare longitudinal studies evaluating SELE S128R polymorphism and serum E-selectin levels together with imaging-based and biochemical progression parameters over a 10-year follow-up period. However, larger-scale studies including functional analyses are required to determine the clinical significance of this polymorphism in terms of kidney volume progression and endothelial activation in ADPKD.

This study has several limitations. In the initial cohort consisting of 76 patients, 56 patients were excluded due to loss to follow-up, initiation of renal replacement therapy, kidney transplantation, or death, and analyses were performed in 20 patients. The small sample size may have limited statistical power, particularly in comparisons between genotype subgroups. In addition, the lack of correction for multiple comparisons increases the risk of Type I error. Treatment changes during follow-up were not systematically recorded, and their potential effects on disease progression cannot be completely excluded.

At the molecular level, E-selectin contributes to endothelial activation and leukocyte adhesion through inflammatory pathways (17). Although endothelial activation and increased adhesion molecule expression have been implicated in ADPKD pathogenesis (18, 19), our findings suggest that serum E-selectin levels alone may not adequately reflect long-term disease progression. In contrast, the association of the SELE S128R polymorphism, particularly the AA genotype, with structural and functional progression parameters suggests a potential genetic contribution to disease susceptibility. Further studies with larger cohorts and functional analyses are required to confirm these findings.

Declarations

Authors of the manuscript declare that there is no conflict of interest with regard to this manuscript.

No financial support was received from a person or a company.

Author Contribution

B.E, A.E.A and F.K wrote the main manuscript and conducted the follow-up of the patients. B.E , F.K prepared the tables and figures. T.S conducted the MR examinations and measurements of cyst volume. H.A conducted the genetical analysis. All authors reviewed the manuscript. B.E and A.E.A submitted the documents.

References

1. Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. *Lancet*. 2007;369(9569):1287–301. 10.1016/S0140-6736(07)60601-1.

2. Cornec-Le Gall E, Alam A, Perrone RD. Autosomal dominant polycystic kidney disease. *Lancet*. 2019;393(10174):919–935. 10.1016/S0140-6736(18)32782-X. PMID: 30819594.
3. Nowak KL, Chonchol M. Vascular dysfunction in autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2018;13(1):149–152. 10.2215/CJN.05850518. PMID: 30228110.
4. Blankenberg S, Barbaux S, Tiret L. Adhesion molecules and atherosclerosis. *Atherosclerosis*. 2003;170(2):191–203. 10.1016/S0021-9150(03)00097-5.
5. Ding G, Wang J, Liu K, Huang B, Deng W, He T. Association of E-selectin gene rs5361 polymorphism with ischemic stroke susceptibility: a systematic review and meta-analysis. *Int J Neurosci*. 2021;131(5):511–517. doi:10.1080/00207454.2020.1750385. PMID: 32241219.
6. Esen B, Sayin T, Akbaş H, Sağlam Gökmen E, Atay AE, Pilten Güzel S, et al. The role of serum E-selectin level and E-selectin gene S128R polymorphism on the enlargement of renal cyst in patients with polycystic kidney disease: Genetic background of renal cyst growth. *Clin Nephrol*. 2020;93(1):34–41. 10.5414/CN109750.
7. Irazabal MV, Rangel LJ, Bergstralh EJ, Torres VE, Harris PC, Kim K, et al. Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. *Kidney Int*. 2015;88(1):15–22. 10.1038/ki.2015.104.
8. Grantham JJ, Torres VE, Chapman AB, Tighiouart H, Bae KT, King BF, et al. Volume progression in polycystic kidney disease. *N Engl J Med*. 2006;354(20):2122–30. 10.1056/NEJMoa054341.
9. Dahl NK, August P, Besse W, Chebib FT, Chonchol M, Cowley BD Jr et al. KDOQI US commentary on the KDIGO 2025 clinical practice guideline for the evaluation, management and treatment of autosomal dominant polycystic kidney disease (ADPKD). *Am J Kidney Dis*. 2026;87(4):447–507. 10.1053/j.ajkd.2025.11.006. PMID: 41864657.
10. Sandoval-Pinto E, Padilla-Gutierrez JR, Valdes-Alvarado E, García-González IJ, Valdez-Haro A, Muñoz-Valle JF et al. Assessment of the E-selectin rs5361 (561A > C) polymorphism and soluble protein concentration in acute coronary syndrome: association with circulating levels. *Mediators Inflamm*. 2014;2014:158367. 10.1155/2014/158367. PMID: 25147432 PMCID: PMC4132325.
11. Blann AD, Amiral J, McCollum CN. Circulating endothelial cell/leucocyte adhesion molecules in ischaemic heart disease. *Br J Haematol*. 1996;95(2):263–265. 10.1046/j.1365-2141.1996.d01-1921.x PMID: 8904879.
12. Menezes LF, Germino GG. The pathobiology of polycystic kidney disease from a metabolic viewpoint. *Nat Rev Nephrol*. 2019;15(12):735–49. 10.1038/s41581-019-0183-y.
13. Chapman AB, Bost JE, Torres VE, Guay-Woodford LM, Bae KT, Landsittel DP, et al. Kidney volume and functional outcomes in autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2012;7(3):479–86. 10.2215/CJN.09500911.
14. Chebib FT, Torres VE. Autosomal dominant polycystic kidney disease: core curriculum 2016. *Am J Kidney Dis*. 2016;67(5):792–810. 10.1053/j.ajkd.2015.07.037.
15. Jilma B, Marsik C, Kovar F, Wagner OF, Jilma-Stohlawetz P, Endler G. The single nucleotide polymorphism Ser128Arg in the E-selectin gene is associated with enhanced coagulation during

human endotoxemia. *Blood*. 2005;105(6):2380–3. 10.1182/blood-2004-09-3752.

16. Wu Z, Lou Y, Lu L, Liu Y, Chen Q, Huang B, et al. Heterogeneous effect of two selectin gene polymorphisms on coronary artery disease risk: a meta-analysis. *PLoS ONE*. 2014;9(2):e88152. 10.1371/journal.pone.0088152. . PMID:24498435.
17. Pober JS, Sessa WC. Evolving functions of endothelial cells in inflammation. *Nat Rev Immunol*. 2007;7(10):803–15. 10.1038/nri2171.
18. Bevilacqua MP, Nelson RM. Endothelial-leukocyte adhesion molecules in inflammation and metastasis. *Cancer Metastasis Rev*. 1993;12(1):1–15. 10.1007/BF01305229. PMID: 8236092.
19. Miller MA, Kerry SM, Dong Y, Sagnella GA, Cook DG, Cappuccio FP. Circulating soluble E-selectin levels and the Ser128Arg polymorphism in individuals from different ethnic groups. *Nutr Metab Cardiovasc Dis*. 2005;15(1):65–70. 10.1016/j.numecd.2004.05.002.

Figures

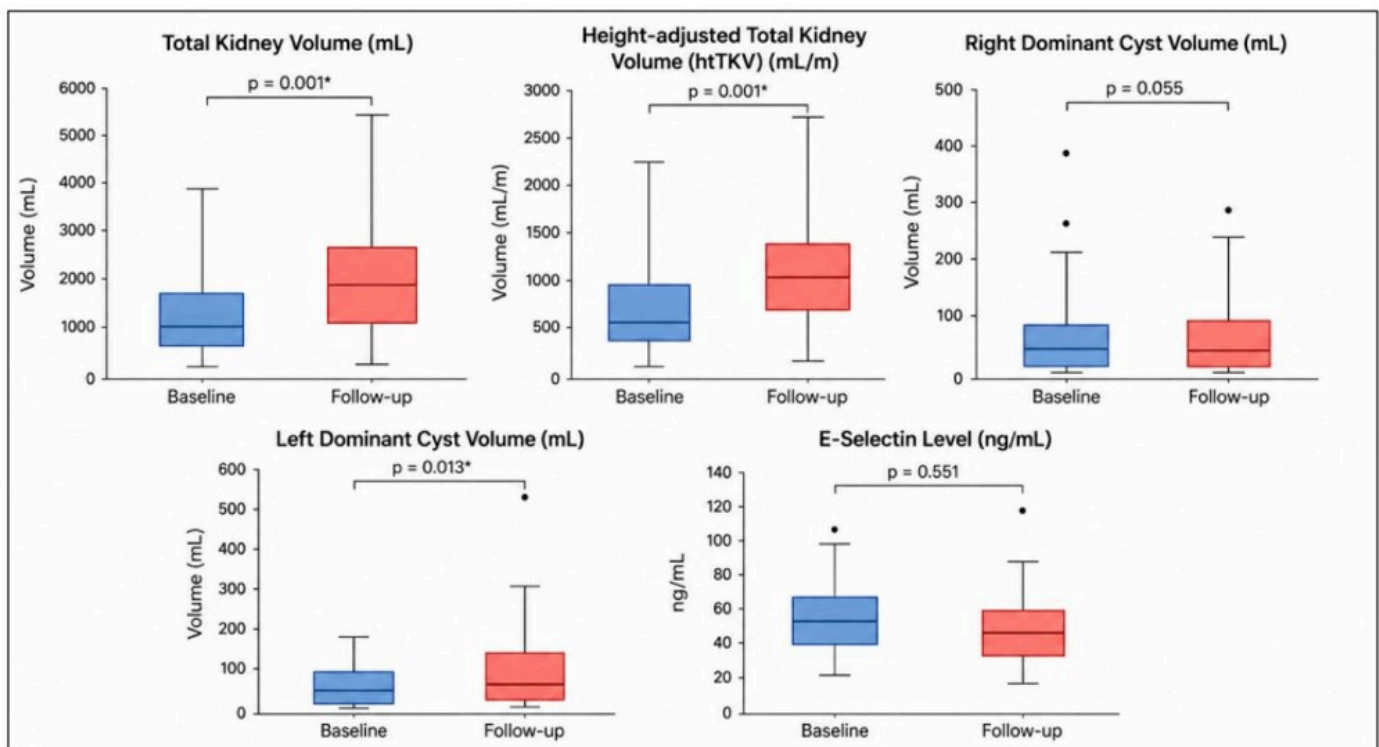


Figure 1

Comparison of Baseline and End-of-Follow-up Radiological Parameters and E-Selectin Levels in Patients with Autosomal Dominant Polycystic Kidney Disease