

Albuminuria drives hyperlipidemia in patients with Alport syndrome

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ABSTRACT

Background and hypothesis. Hypercholesterolemia is a major driver of cardiovascular disease, a leading cause of premature mortality in patients with chronic kidney disease (CKD). Despite their typically young age, patients with Alport syndrome (AS), the second most prevalent genetic cause of CKD, may face a disproportionately high risk of hypercholesterolemia. This study investigates whether increased albuminuria precipitates hyperlipidemia in this population to a degree comparable with general CKD cohorts, while further delineating the risk factors underlying this development.

Methods. This was a multicenter, observational, non-interventional, and retrospective study.

Results. Among 459 patients with AS, 59.3% had hypercholesterolemia and 58.5% had elevated low-density lipoprotein cholesterol (LDL-C). Despite lower estimated glomerular filtration rate (eGFR) and higher albuminuria, patients receiving lipid-lowering therapy (LLT) had significantly lower total cholesterol levels compared to the untreated patients (193.6 ± 55.2 mg/dl vs. 208.2 ± 51.0 mg/dl; $P = .044$). Similarly, LDL-C levels were significantly lower in the treatment group (111.6 ± 51 mg/dl, $n = 59$) compared with the untreated group (124.3 ± 40.2 mg/dl, $n = 238$; $P = .041$). Multivariable regression analysis adjusted for age, sex body mass index (BMI), eGFR, and LLT revealed that albuminuria was a significant independent predictor of total cholesterol ($\beta = 0.315$; $P < .001$) and LDL-C levels ($\beta = 0.242$; $P < .001$). Male sex was associated with significantly higher LDL-C and lower high-density lipoprotein cholesterol (HDL-C) levels. Conversely, eGFR and BMI were not significant predictors of cholesterol levels. This association was also observed in the pediatric cohort ($n = 44$), where albuminuria was the only independent predictor of cholesterol ($\beta = 0.728$; $P < .001$).

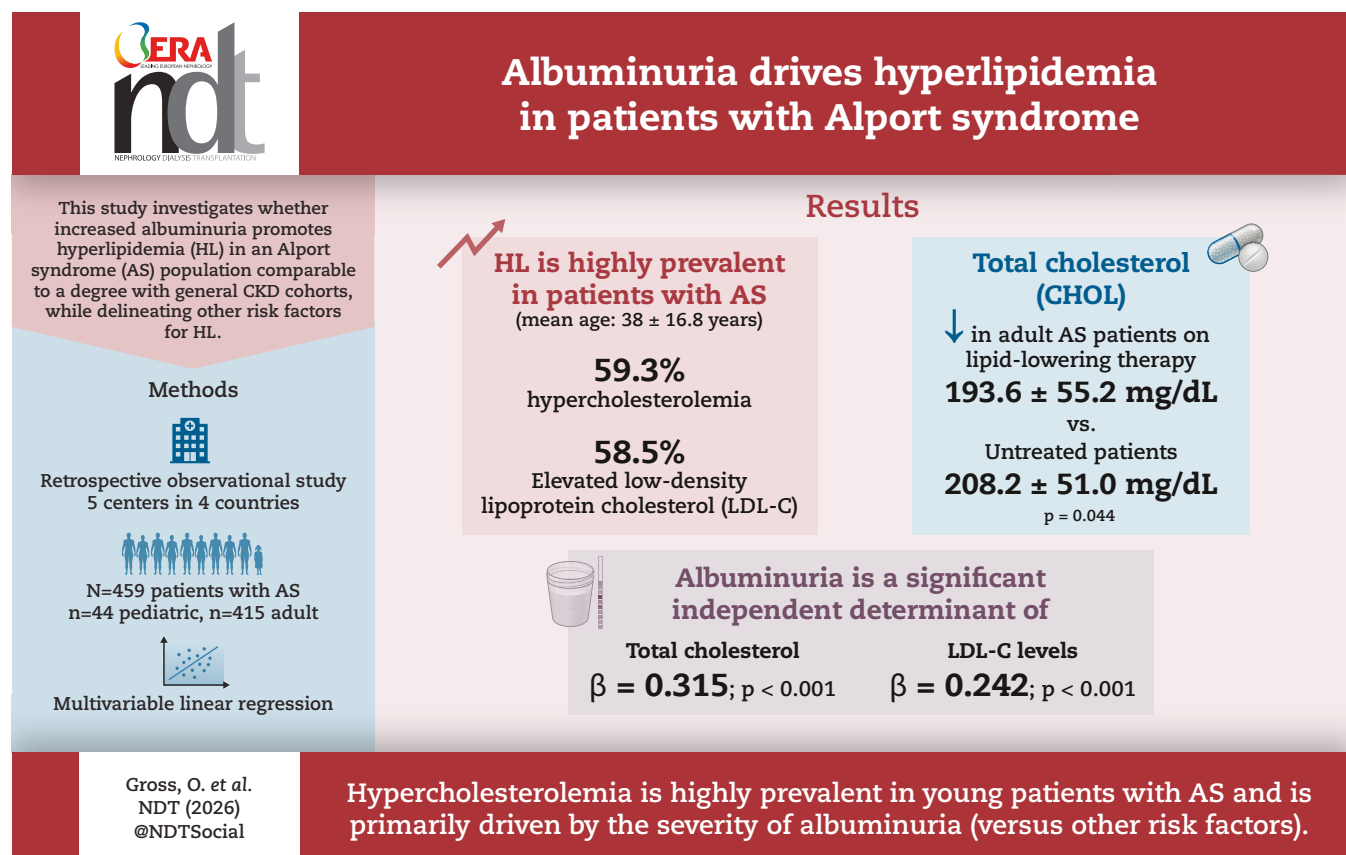
Conclusions. Hypercholesterolemia is highly prevalent in young patients with AS and is primarily driven by the severity of albuminuria, rather than other risk factors such as obesity or eGFR decline. These findings highlight a critical gap in current guidelines, support the implementation of early lipid screening and suggest that risk-adapted management may be necessary to prevent long-term cardiovascular complications.

Keywords: albuminuria, Alport syndrome, cardiovascular risk, dyslipidemia, lipid-lowering therapy

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GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What was known:

- Cardiovascular disease is a primary driver of premature mortality in CKD populations, with dyslipidemia typically influenced by age, proteinuria severity, and impaired GFR.
- Alport syndrome is a genetic cause of CKD, resulting from type IV collagen variants that lead to high proteinuria.
- Previous research regarding dyslipidemia in CKD has primarily focused on older cohorts, which may not be representative of the younger populations characteristic of hereditary conditions like AS.

This study adds:

- The study observed a 59.3% prevalence of hypercholesterolemia in AS patients at a mean age of 38, matching rates seen in general CKD populations aged ~64.
- Multivariable regression analysis suggests that albuminuria is a significant independent predictor of total cholesterol and LDL-C levels, while eGFR and BMI are not significant predictors.
- Despite lower eGFR and higher albuminuria, patients receiving lipid-lowering therapy had significantly lower total cholesterol levels compared to the untreated patients.

Potential impact:

- The data suggest that the implementation of early lipid screening for all AS patients, regardless of age, may be warranted to address current gaps in clinical guidelines.
- Despite the constraints inherent to its retrospective methodology, this study offers preliminary observations suggesting that lipid-lowering therapy may effectively reduce cholesterol levels in patients with Alport syndrome, which could potentially mitigate long-term cardiovascular complications.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of premature mortality in patients with chronic kidney disease (CKD) [1]. High or nephrotic-range proteinuria in patients with CKD leads to a highly atherogenic lipid profile, which is a major contributor to cardiovascular risk [2]. The key determinants of this dyslipidemia in CKD include age, the severity of proteinuria, impaired GFR, nutritional status, and coexisting conditions such as diabetes mellitus [3–5]. Patients with Alport syndrome (AS), the second most common genetic cause of CKD, frequently develop high proteinuria and even proteinuria in the nephrotic range. AS is caused by variants in genes encoding type IV collagen, an essential component of basement membranes in the kidney, eye, and cochlea [6]. Specifically, variants in the COL4A5 gene (X-linked AS) or the COL4A3/COL4A4 genes (autosomal recessive or dominant AS) lead to dysfunction of the glomerular basement membrane filtration barrier [7]. This results in kidney failure (KF), frequently accompanied by ocular lesions and progressive hearing loss [8–10]. Notably, the early and sustained renin-angiotensin system inhibition (RASi) has been shown to significantly slow the progression of CKD in patients with AS [11–13]. Prolonged dyslipidemia significantly elevates the risk of severe cardiovascular and thromboembolic events, encompassing accelerated atherosclerosis, myocardial infarction (MI), stroke, and thrombosis, but also increasingly appears to drive the pathogenesis of CKD via direct lipid-induced cellular injury [14]. The effectiveness of lipid-modifying agents, a cornerstone in the therapeutic strategy for patients with CKD, is modulated based on residual kidney function [15]. This underscores the critical need for the early, concurrent identification of both declining kidney function and hypercholesterolemia to optimize therapeutic strategies and improve long-term patient outcomes.

The prevalence of dyslipidemia in patients with CKD generally increases with disease progression, rising to nearly 70% in CKD stage 4 [16]. In general, these CKD cohorts are significantly older than cohorts of patients with AS due to the inherited nature of the latter condition and might not be representative of young patients with the rare disease AS. Therefore, this study investigated the hypothesis that patients with AS develop hypercholesterolemia as frequently as described in general CKD cohorts, despite their young age, due to increased albuminuria. Furthermore, this study examined the influence of various risk factors on the development of hypercholesterolemia.

MATERIALS AND METHODS

Study population

This was a multicenter, observational, non-interventional, and retrospective study and included a total of 532 patients from five centers (two German, one Belgian, one Lithuanian, and one Chinese) from 2012 to 2025. Presentation of the study design at the 2024 International Workshop on AS facilitated the recruitment of potential study sites. The primary inclusion criteria were a confirmed diagnosis of AS and the availability of at least one serum cholesterol measurement. A total of 73 patients were excluded due to unknown cholesterol levels or use of investigational study drugs that could influence cholesterol levels (Fig. 1). The study was conducted as part of the European Alport Syndrome Registry. The registry and data storage, in conformity with Good Clinical Practice guidelines and the Declaration of Helsinki, were approved by the Ethics Committee of the University Medi-

cal Center Goettingen (AZ 10/11/06; renewed version in 2014 and 2020; ClinicalTrials.gov identifier NCT02378805) and by the respective local ethics committees in accordance with local regulations. The patients provided written informed consent for the use of their data for research purposes.

Outcome measures

Hypercholesterolemia was defined as total serum cholesterol (CHOL) >200 mg/dl (>5.2 mmol/l) or current treatment with lipid-lowering therapy (LLT) [17]. Elevated low-density lipoprotein cholesterol (LDL-C) was defined as LDL-C serum level >115 mg/dl (>3.0 mmol/l) or current treatment with LLT [18]. Hypertriglyceridemia was defined as triglycerides (TG) >150 mg/dl (>1.7 mmol/l). In children, lipid status was examined according to previously published cutoff levels for normal serum lipids [19].

The baseline visit was defined as the day of cholesterol measurement. If more than one cholesterol measurement was available, the earliest measurement with the most complete dataset was used as baseline. Additional analyses included kidney function [estimated glomerular filtration rate (eGFR) in ml/min/1.73 m²], proteinuria in milligram/gram creatinine, body mass index (BMI) in kg/m² and blood pressure in mmHg. Estimated GFR was calculated using the serum creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation in adults and with the revised Schwartz formula in patients under 18 years old [20]. A cutoff value of 1000 mg/gram creatinine (mg/g) for the urine albumin-to-creatinine ratio (UACR), as recently described, was used to define two groups: (I) <1000 mg/g; and (II) ≥1000 mg/g [21].

Statistical methods

Statistical comparisons were not formally powered or prespecified. Continuous variables were presented as mean and standard deviation (SD) or as median and interquartile range, categorical variables as percentages. Data distribution was assessed for normality through histogram visualization. Comparison of means between groups was conducted with the unpaired Student's *t*-test in case of roughly normally distributed values. In case of non-normally distributed values or highly unequal sample sizes, the Mann-Whitney test was used. For categorical variables, the Chi-Square (χ^2) Test was used to determine differences in frequencies between the groups. Where the expected cell count in the Chi-Square test was less than five, Fisher's Exact Test was used. Pearson's or Spearman's correlation was performed to assess correlations as appropriate. The independent association between log-transformed albuminuria and total cholesterol or LDL-C was assessed using multiple linear regression, controlling for age, sex, BMI, eGFR, and LLT status. Probability values (*P* values) below .05 were considered statistically significant. Data analyses were performed with IBM SPSS Statistics (version 30 for macOS, IBM Corporation, Armonk, NY, USA). GraphPad Prism (version 10 for macOS, GraphPad Software, San Diego, CA, USA) was used to generate figures.

RESULTS

The total study cohort comprised 459 patients with AS, including 44 pediatric patients. The mean age was 38.3 ± 16.8 years, and 54% of the cohort were female. The mean BMI was 24.7 ± 5.6 kg/m² (*n* = 373). Kidney function was within the normal or near-normal range in most patients (mean eGFR: 80.9 ±

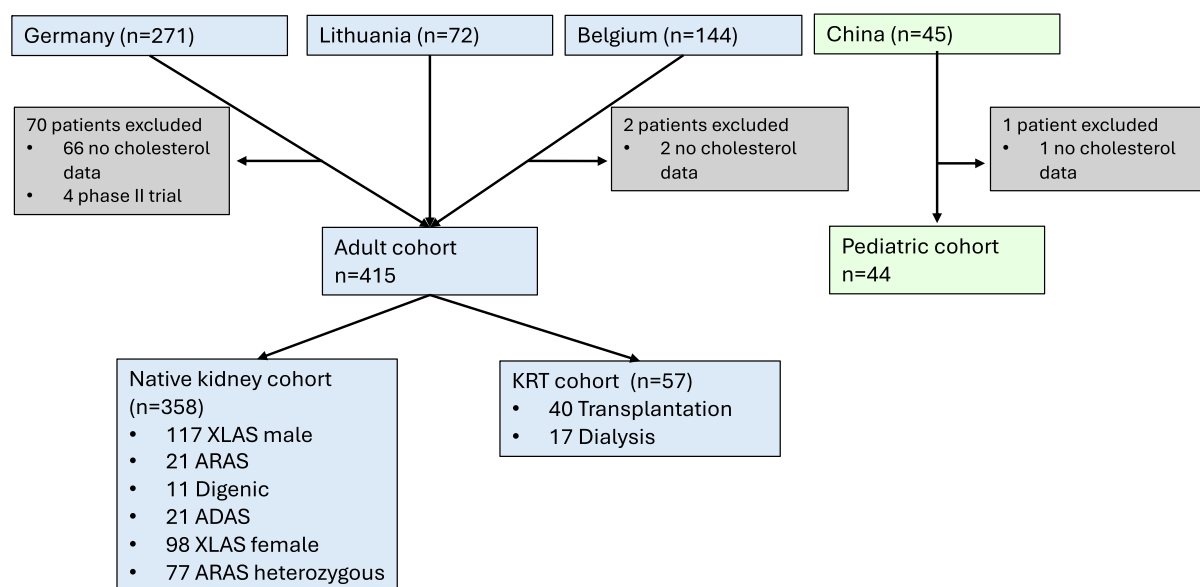


Figure 1: Flow Chart. Five hundred thirty-two patients were screened. A total of 459 patients were included in the analysis of this study.

Table 1: Demographic and clinical characteristics of the adult cohort.

	Total cohort (N = 415)	Native kidney cohort (n = 358)	KRT cohort (n = 57)	P-value
Age (years)	41.1 ± 15.1 (n = 415)	40.1 ± 15 (n = 358)	47.4 ± 14.4 (n = 57)	<.001
Sex (female)	238 (57.3) (n = 415)	214 (59.8) (n = 358)	24 (42.1) (n = 57)	.012
BMI (kg/m ²)	25.5 ± 5.2 (n = 331)	25.5 ± 5.4 (n = 278)	25.5 ± 4.5 (n = 53)	.958
Systolic/diastolic blood pressure (mmHg)	127 ± 18/80 ± 13 (n = 339)	126 ± 18/79 ± 13 (n = 288)	133 ± 17/85 ± 13 (n = 51)	.014/.02
Mode of inheritance	n = 401	n = 345	n = 56	
XLAS male	145 (36.2)	117 (33.9)	28 (50)	
ARAS	35 (8.7)	21 (6)	14 (25)	
Digenic	13 (3.2)	11 (3.2)	2 (3.6)	
ADAS	23 (5.7)	21 (6.1)	2 (3.6)	
XLAS female	107 (26.7)	98 (28.4)	9 (16.1)	
ARAS heterozygous	78 (19.5)	77 (22.3)	1 (1.8)	
eGFR (ml/min/1.73 m ²)		82.6 ± 34.6 (n = 354)		
UPCR (mg/g)	266 [92–1320] (n = 347)	250 [90–1196] (n = 337)	2660 [1906–6153] (n = 10)	<.001
UACR (mg/g)	148 [23–1074] (n = 339)	132 [22–989] (n = 331)	2022 [1184–4410] (n = 8)	.003
Lipid profile				
Hypercholesterolemia	243 (58.7) (n = 415)	213 (59.5) (n = 358)	30 (52.6) (n = 57)	.328
Total cholesterol (mg/dl)	202.1 ± 50.2 (n = 415)	205.2 ± 51.8 (n = 358)	182.5 ± 32.4 (n = 57)	<.001
LDL cholesterol (mg/dl)	118.7 ± 41.4 (n = 359)	121.7 ± 42.5 (n = 303)	102.7 ± 30 (n = 56)	<.001
HDL cholesterol (mg/dl)	61.4 ± 24.4 (n = 358)	62.2 ± 25.7 (n = 302)	57 ± 15.6 (n = 56)	.046
Triglycerides (mg/dl)	138.9 ± 98.8 (n = 363)	136.5 ± 96.4 (n = 306)	151.5 ± 111.1 (n = 57)	.343
Medication				
RAS inhibition	242 (59.9) (n = 404)	211(60.3) (n = 350)	31 (57.4) (n = 54)	.688
Lipid-lowering therapy	79 (19.5) (n = 405)	62 (17.7) (n = 351)	17 (31.5) (n = 54)	.017

Values are presented as mean ± standard deviation, median [interquartile range], or number (percentage). n indicates the number of available data for each specific variable. Abbreviations: KRT, kidney replacement therapy; BMI, body mass index; XLAS, X-linked Alport syndrome; ARAS, autosomal recessive Alport syndrome; ADAS, autosomal dominant Alport syndrome; eGFR, estimated glomerular filtration rate; UPCR, urinary protein-to-creatinine ratio; UACR, urinary albumin-to-creatinine ratio; LDL, low-density lipoprotein; HDL, high-density lipoprotein; RAS, renin-angiotensin system.

35.7 ml/min/1.73 m²; n = 409); however, 57 patients (12.4%) required kidney replacement therapy (KRT) defined as patients on dialysis and patients with kidney transplant. In the total cohort, the prevalence of hypercholesterolemia was 59.3%. Furthermore, 234 patients (58.5%, n = 400) were classified as having elevated LDL-C and 145 patients (36.3%, n = 400) presented with hypertriglyceridemia. LLT was recorded in 17.8% of patients (n = 449).

Adult cohort baseline characteristics

The adult cohort included 415 patients (Table 1), with a mean age of 41.1 ± 15.1 years and predominantly female patients (57.3%). Notably, the cohort included a significant proportion of heterozygous patients (46.2%). The mean BMI was 25.5 ± 5.2 kg/m² (n = 331), and mean blood pressure was slightly elevated (127 ± 18/80 ± 13 mmHg; n = 339). Mean eGFR was

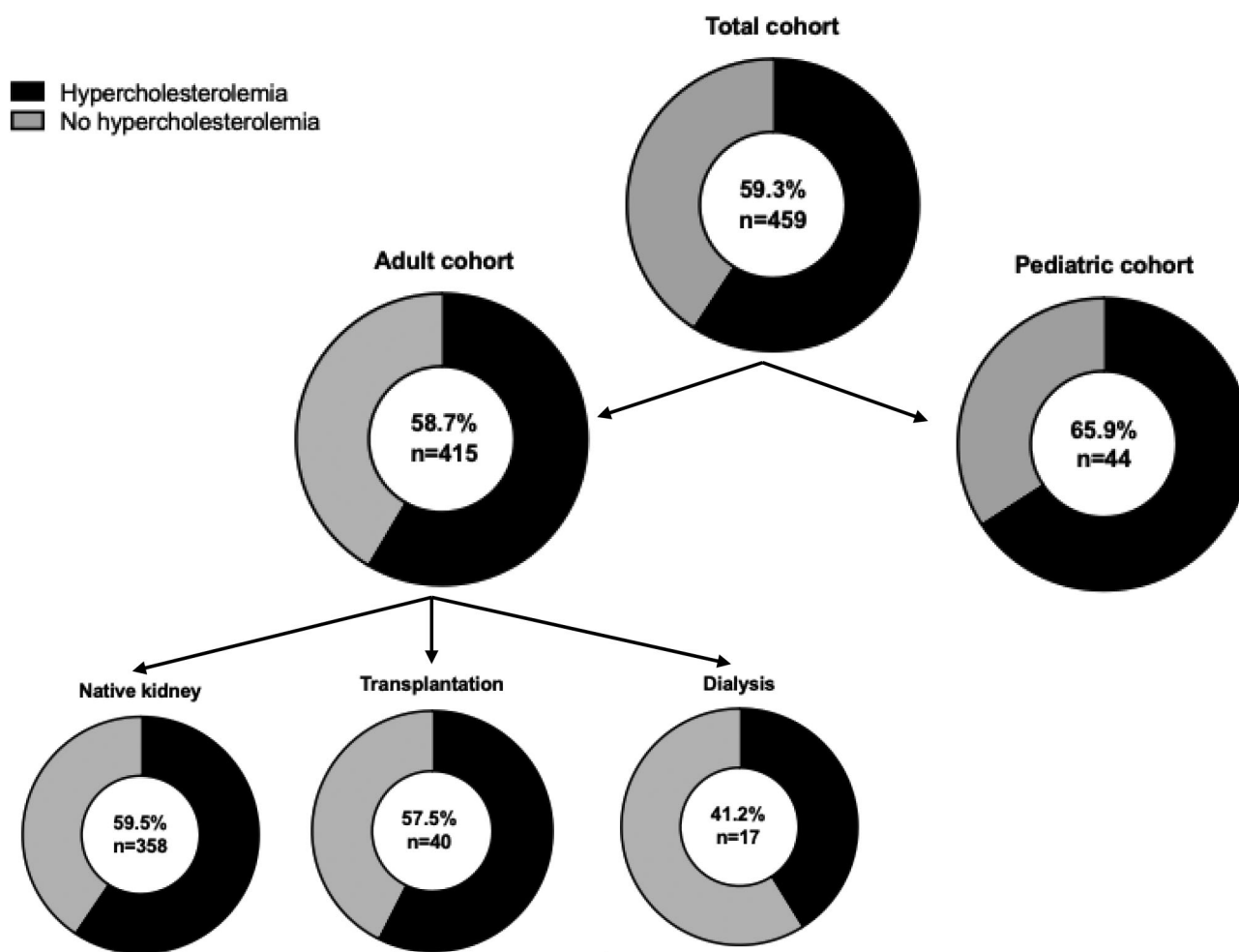


Figure 2: Prevalence of hypercholesterolemia across different stages of kidney function in patients with Alport syndrome. The donut charts illustrate the proportion of patients diagnosed with hypercholesterolemia (black segment) vs. no hypercholesterolemia (gray segment).

80.3 ± 36.3 ml/min/1.73 m² (n = 367) and median proteinuria (UPCR) was 266 mg/g [92–1320] (n = 347). Hypercholesterolemia was observed in 58.7% of the cohort (Fig. 2). Furthermore, 58.8% (n = 362) were classified as having elevated LDL-C and 33.9% (n = 363) as having hypertriglyceridemia. Mean CHOL (202.1 ± 50.2 mg/dl) and mean LDL-C (118.7 ± 41.4 mg/dl, n = 359) were slightly above the normal thresholds. Overall, 19.5% of patients (n = 405) received LLT, and 59.9% (n = 404) received RASi therapy. The adult cohort included 57 patients (13.7%) undergoing KRT. Specifically, 17 patients were on dialysis, and 40 patients had received a kidney transplant.

Comparison of native kidney and KRT cohorts

To account for KRT as a significant influencing factor, the overall cohort was divided into the native kidney cohort (n = 358) and patients with KRT (KRT cohort, n = 57), including 40 kidney transplant recipients and 17 patients receiving dialysis. Compared with the native kidney cohort, patients with KRT were significantly older (47.4 ± 14.4 years vs. 40.1 ± 15 years, P < .001) and had a lower proportion of female patients (42.1% vs. 59.8%, P = .012). BMI was similar between groups (25.5 ± 4.5 kg/m², n = 53 vs. 25.5 ± 5.4 kg/m², n = 278, P = .958). The prevalence of hypercholesterolemia was lower in the KRT cohort (52.6%) compared to the native kidney cohort (59.5%, P = .328) and lipid levels were consistently lower in the KRT group across CHOL

(182.5 ± 32.4 mg/dl vs. 205.2 ± 51.8 mg/dl, P < .001), LDL-C (102.7 ± 30 mg/dl, n = 56 vs. 121.7 ± 42.5 mg/dl, n = 303, P < .001) and high-density lipoprotein cholesterol (HDL-C, 57 ± 15.6 mg/dl, n = 56 vs. 62.2 ± 25.7 mg/dl, n = 302, P = .046). This was paralleled by a significantly higher rate of LLT in the KRT cohort (31.5%, n = 54) compared to the native kidney cohort (17.7%, n = 351, P = .017). Overall, univariate comparisons showed several significant differences in baseline characteristics and lipid parameters between the native kidney cohort and patients with KRT. Consequently, subsequent analyses of the drivers of dyslipidemia solely included the native kidney cohort.

Sex-specific analysis

To further evaluate influencing factors within the native kidney cohort, the cohort was divided into male and female patients (Table 2). Male patients (n = 144) were significantly younger than female patients (36.8 ± 15.1 vs. 42.4 ± 14.6 years, n = 214, P < .001), but had significantly lower eGFR (77.2 ± 38.9 ml/min/1.73 m², n = 143 vs. 86.3 ± 30.9 ml/min/1.73 m², n = 211, P = .02) and significantly higher albuminuria (1239.8 ± 1851.4 mg/g, n = 133 vs. 545.4 ± 1117.5 mg/g, n = 198, P < .001). No significant sex-specific differences were observed in either the proportion of hypercholesterolemia (males: 59.7% vs. females: 59.3%, P = .943) or mean CHOL levels (204.1 ± 54.2 vs. 205.9 ± 50.2 mg/dl, P = .355). Male patients had significantly higher LDL-C (129.1 ± 45.5 mg/dl,

Table 2: Sex specific analysis.

	Female (N = 214)	Male (N = 144)	P-value
Age (years)	42.4 ± 14.6 (n = 214)	36.8 ± 15.1 (n = 144)	<.001
BMI (kg/m ²)	25.4 ± 5.4 (n = 161)	25.6 ± 5.4 (n = 117)	.731
eGFR (ml/min/1.73m ²)	86.3 ± 30.9 (n = 211)	77.2 ± 38.9 (n = 143)	.02
UACR (mg/g)	545.4 ± 1117.5 (n = 198)	1239.8 ± 1851.4 (n = 133)	<.001
Total cholesterol (mg/dl)	205.9 ± 50.2 (n = 214)	204.1 ± 54.2 (n = 144)	.740
Triglycerides (mg/dl)	125.5 ± 84 (n = 179)	127.1 ± 110.1 (n = 127)	.023
LDL cholesterol (mg/dl)	116.2 ± 39.4 (n = 174)	129.1 ± 45.5 (n = 129)	.010
HDL cholesterol (mg/dl)	70.7 ± 28.3 (n = 174)	50.7 ± 15.5 (n = 128)	<.001
RAS inhibition (%)	101 (48.3) (n = 209)	110 (78) (n = 141)	<.001
Lipid-lowering therapy (%)	32 (15.2) (n = 210)	30 (21.3) (n = 141)	.146

Data are presented as mean ± standard deviation for continuous variables, and number (percentage) for categorical variables. n indicates the number of available data for each specific variable. Abbreviations: BMI, body mass index in kg/m²; eGFR, estimated glomerular filtration rate in ml/min/1.73m²; UACR, urinary albumin-to-creatinine ratio; LDL, low-density lipoprotein; HDL, high-density lipoprotein; RAS, renin-angiotensin system.

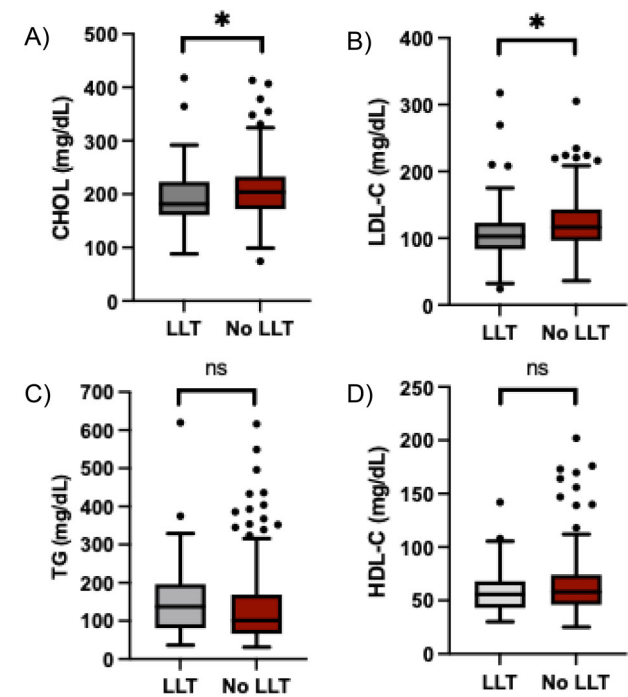


Figure 3: Comparison of lipid profiles in patients receiving lipid-lowering therapy (LLT, gray) vs. untreated patients (No LLT, red). Box plots illustrate serum concentrations of (A) total cholesterol (CHOL), (B) LDL cholesterol (LDL-C), (C) Triglycerides (TG), and (D) HDL cholesterol (HDL-C). Asterisk indicates a statistically significant difference ($P < .05$).

$n = 129$ vs. 116.2 ± 39.4 mg/dl, $n = 174$, $P = .01$) and significantly lower HDL-C (50.7 ± 15.5 mg/dl, $n = 128$ vs. 70.7 ± 28.3 mg/dl, $n = 174$, $P < .001$). The use of RASi was significantly higher in male patients (78%, $n = 141$ vs. 48.3%, $n = 209$, $P < .001$) and the use of LLT was also higher in males (21.3%, $n = 141$ vs. 15.2%, $n = 210$, $P = .146$). Notably, these sex-specific differences remained significant in the multivariable analysis after adjusting for LLT use (see section “Correlation of renal parameters and lipid profiles”).

Influence of lipid-lowering therapy on the lipid profile

To assess the impact of LLT on the lipid profile in patients with AS, patients receiving statins and/or ezetimibe ($n = 62$) were compared with those receiving no LLT ($n = 289$, Fig. 3). Patients without information on medication intake were ex-

cluded from this analysis ($n = 7$). Patients with LLT presented with significantly lower CHOL compared with the untreated patients (193.6 ± 55.2 mg/dl vs. 208.2 ± 51.0 mg/dl; $P = .044$). Similarly, LDL-C levels were significantly lower in the treatment group (111.6 ± 51 mg/dl, $n = 59$) compared with the untreated group (124.3 ± 40.2 mg/dl, $n = 238$; $P = .041$). No significant difference was observed in HDL cholesterol levels between treated (58.5 ± 20.0 mg/dl, $n = 59$) and untreated patients (63.5 ± 27.0 mg/dl, $n = 237$; $P = .184$). Patients receiving LLT were significantly older (53.4 ± 14.2 years, $n = 62$ vs. 37.1 ± 13.6 years, $n = 289$; $P < .001$) and had a higher BMI (27.3 ± 5.6 kg/m², $n = 53$ vs. 25.0 ± 5.3 kg/m², $n = 221$; $P = .006$). Furthermore, the treatment group had significantly impaired renal function, with a mean eGFR of 57.1 ± 30.9 ml/min/1.73 m² ($n = 61$) compared with 89.3 ± 31.5 ml/min/1.73 m² in the untreated group ($n = 286$, $P < .001$). The mean albuminuria was notably higher in treated patients (1236.5 ± 2172.7 mg/g, $n = 56$) compared with untreated patients (723.7 ± 1266.6 mg/g, $n = 271$, $P = .093$).

Correlation of kidney parameters and lipid profiles

Spearman’s rank correlation analysis showed that the strongest correlation with CHOL was observed for albuminuria ($\rho = 0.27$; $P = .002$). A significant positive correlation was also found between albuminuria and TG ($\rho = 0.297$; $P = .001$), however, LDL-C did not reach statistical significance ($\rho = 0.175$; $P = .054$). eGFR showed a significant positive association with HDL-C ($\rho = 0.311$; $P < .001$), as well as a significant negative association with TG ($\rho = -0.431$; $P < .001$). No statistically significant correlation was found between eGFR and LDL-C ($\rho = -0.028$; $P = .757$) or CHOL ($\rho = -0.058$; $P = .488$). Additionally, BMI showed a positive correlation with TG ($\rho = 0.527$; $P < .001$), but did not show a significant correlation with CHOL ($\rho = 0.158$; $P = .088$). Age also showed a significant positive correlation with CHOL ($\rho = 0.209$; $P = .012$). As expected, strong correlations were observed among the lipid parameters: CHOL was highly correlated with LDL-C ($\rho = 0.924$; $P < .001$) and TG ($\rho = 0.427$; $P < .001$).

To assess the correlation of albuminuria and lipid metabolism without the confounding effects of pharmacological intervention, a subanalysis was performed excluding patients currently receiving LLT or with no information on medication intake. In these patients, the significant positive correlation between albuminuria and hypercholesterolemia was stronger ($\rho = 0.32$; $P < .01$, Fig. 4). The analysis further showed a significant positive correlation between albuminuria and LDL-C ($\rho = 0.256$; $P < .001$) and a significant negative correlation with HDL-C ($\rho =$

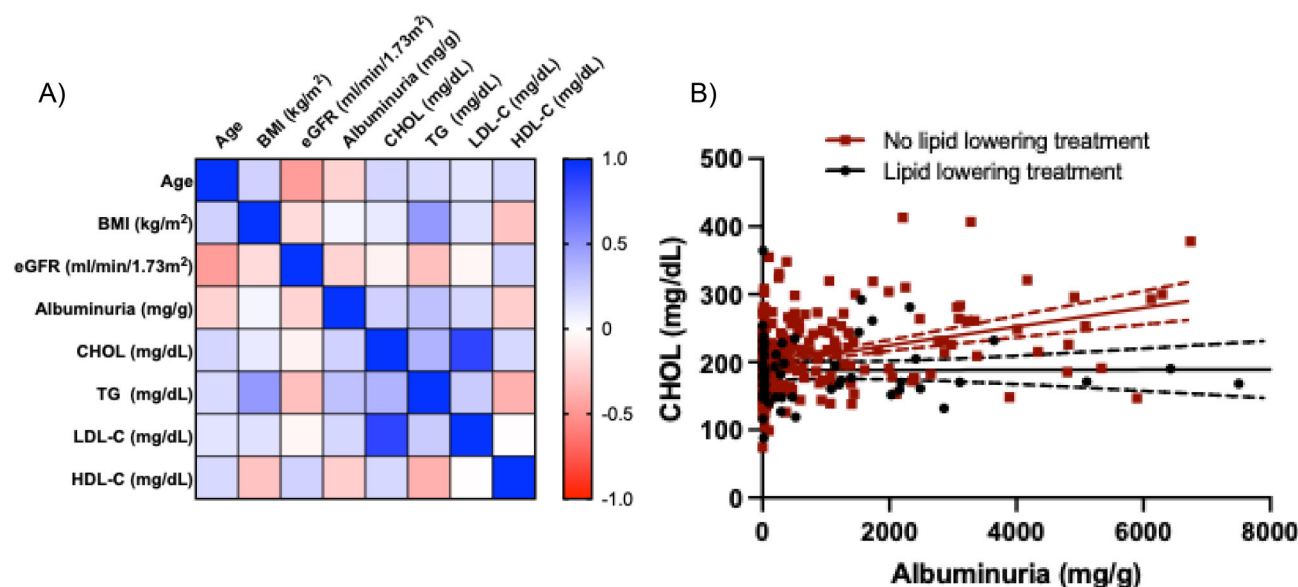


Figure 4: (A) Spearman correlation of the adult native kidney cohort ($n = 358$). The heatmap illustrates the Spearman rank correlations between kidney function markers (eGFR, Albuminuria), demographics (age, BMI), and lipid profile. The color scale represents the correlation coefficient, ranging from dark red (strong negative correlation, -1.0) to dark blue (strong positive correlation, $+1.0$). (B) Scatter plot of albuminuria and total cholesterol (CHOL) stratified into patients receiving lipid-lowering therapy (black, $n = 62$) and those without lipid-lowering therapy (red, $n = 289$). The highest albuminuria value (11,955 mg/g) is not displayed in Fig. 4B to avoid compressing the distribution of the remaining data.

Table 3: Baseline characteristics, stratified by status of UACR.

	UACR ≥ 1000 mg/g	UACR <1000 mg/g	P-value
Age (years)	35.8 $\pm$ 15.1 ($n = 83$)	41.1 $\pm$ 15.1 ($n = 248$)	.006
BMI (kg/m ²)	25.8 $\pm$ 5.5 ($n = 56$)	25.3 $\pm$ 5.3 ($n = 207$)	.489
Systolic BP (mmHg)	131.9 $\pm$ 17.3 ($n = 63$)	124.5 $\pm$ 18.1 ($n = 212$)	.005
Diastolic BP (mmHg)	84.2 $\pm$ 13.1 ($n = 63$)	77.7 $\pm$ 12.3 ($n = 212$)	$<.001$
eGFR (ml/min/1.73 m ²)	66.8 $\pm$ 39.6 ($n = 83$)	89.3 $\pm$ 29.7 ($n = 247$)	$<.001$
Total cholesterol (mg/dl)	223.7 $\pm$ 60.4 ($n = 83$)	196.5 $\pm$ 45.4 ($n = 248$)	$<.001$
Triglycerides (mg/dl)	168.2 $\pm$ 116 ($n = 64$)	125.8 $\pm$ 87.3 ($n = 222$)	.008
LDL cholesterol (mg/dl)	134.5 $\pm$ 46 ($n = 66$)	116 $\pm$ 38.1 ($n = 219$)	.001
HDL cholesterol (mg/dl)	52.1 $\pm$ 16.3 ($n = 67$)	65.1 $\pm$ 26 ($n = 217$)	$<.001$
RAS inhibition (%)	67 (82.7) ($n = 81$)	131 (53.3) ($n = 246$)	$<.001$
Lipid-lowering therapy (%)	21 (25.6) ($n = 82$)	35 (14.2) ($n = 245$)	.027

Data are presented as mean $\pm$ standard deviation for continuous variables, and number (percentage) for categorical variables. n indicates the number of available data for each specific variable. Abbreviations: UACR, urinary albumin-to-creatinine ratio; BMI, body mass index in kg/m²; systolic BP, systolic blood pressure; diastolic BP, diastolic blood pressure; eGFR, estimated glomerular filtration rate in ml/min/1.73 m²; LDL, low-density lipoprotein; HDL, high-density lipoprotein; RAS, renin-angiotensin system.

-0.258 ; $P < .001$). To determine the independent predictive value of albuminuria on CHOL, controlling for other identified risk factors, a multiple linear regression analysis was performed. The model, including albuminuria, age, BMI, eGFR, sex, and LLT as independent predictors, demonstrated that log-transformed albuminuria ($\beta = 0.315$; $P < .001$), age ($\beta = 0.359$; $P < .001$), and LLT ($\beta = -0.251$; $P < .001$) were independent and significant predictors of CHOL levels, while sex, BMI, and eGFR did not reach statistical significance in predicting CHOL levels ($P > .05$ for all). Another multiple linear regression analysis determined the independent predictors of LDL-C, using the same set of covariates, age ($\beta = 0.314$; $P < .001$), female sex ($\beta = -0.192$; $P = .003$), LLT ($\beta = -0.3$; $P < .001$), and albuminuria ($\beta = 0.242$; $P < .001$) independently and significantly predicted LDL-C levels. BMI ($\beta = 0.077$) and eGFR ($\beta = 0.097$) were not significant predictors in this model ($P > .05$ for both).

Comparison of patients with severe and less severe albuminuria

Table 3 presents the baseline characteristics of the study cohort, stratified by UACR status into a severe albuminuria group (≥ 1000 mg/g, $n = 83$) and a less severe albuminuria group (<1000 mg/g, $n = 248$). Patients in the severe albuminuria group were significantly younger (35.8 ± 15.1 vs. 41.1 ± 15.1 years, $P = .006$) but had impaired eGFR (66.8 ± 39.6 , $n = 83$ vs. 89.3 ± 29.7 , $n = 247$, $P < .001$) and an adverse lipid profile across all measured parameters. Mean CHOL was significantly higher (223.7 vs. 196.5 mg/dl, $P < .001$), alongside higher LDL-C (134.5 ± 46 , $n = 66$ vs. 116 ± 38.1 , $n = 219$, $P = .001$) and TG (168.2 ± 116 , $n = 64$ vs. 125.8 ± 87.3 , $n = 222$, $P = .008$) and lower HDL-C (52.1 ± 16.3 , $n = 67$ vs. 65.1 ± 26 , $n = 217$, $P < .001$), despite a significantly more frequent use of LLT (25.6%, $n = 82$ vs. 14.2%, $n = 245$, $P = .027$).

Table 4: Pediatric cohort.

	Total cohort (N = 44)
Age (years)	12 ± 4 (n = 44)
Sex (female)	10 (22.7) (n = 44)
BMI (kg/m ²)	18.6 ± 4.2 (n = 42)
Systolic/diastolic blood pressure (mmHg)	105 ± 10.8/65.3 ± 9 (n = 26)
Mode of inheritance	
XLAS male	35 (79.5)
ARAS	9 (20.5)
eGFR (ml/min/1.73 m ²)	86.5 ± 29.8 (n = 42)
UACR (mg/g)	1137 [284–2438] (n = 41)
Total cholesterol (mg/dl)	225.4 ± 75.9 (n = 44)
LDL cholesterol (mg/dl)	138.1 ± 56.8 (n = 38)
HDL cholesterol (mg/dl)	55.4 ± 18.2 (n = 26)
Triglycerides (mg/dl)	164.1 ± 95.5 (n = 37)
RAS inhibition (%)	37 (84.1) (n = 44)
Lipid-lowering therapy (%)	1 (2.3) (n = 44)

Values are presented as mean ± standard deviation, median [interquartile range], or number (percentage). *n* indicates the number of available data for each specific variable. Abbreviations: BMI, body mass index; XLAS, X-linked Alport syndrome; ARAS, autosomal recessive Alport syndrome; UACR, urinary albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; RAS, renin-angiotensin system.

Pediatric cohort

The pediatric cohort included 44 children with a mean age of 12 ± 4 years (Table 4). Mean BMI was 18.6 ± 4.2 kg/m² (*n* = 42) and mean blood pressure was 105 ± 10.8/65.3 ± 9 mmHg (*n* = 26). Mean eGFR was 86.5 ± 29.8 ml/min/1.73 m² (*n* = 42), with overt UACR (2004.5 ± 2781.8 mg/g, *n* = 41). All children were either male with XLAS (79.5%) or patients with ARAS (20.5%). A high percentage (84.1%) of the patients were on RASi, while only one child (2.3%) received LLT. The proportion of children with hypercholesterolemia was 65.9%. 59.5% of the patients in the pediatric cohort had hypertriglyceridemia (*n* = 37) and 55.3% were classified as having elevated LDL-C (*n* = 38). Spearman's rank correlation analysis showed a strong positive correlation between CHOL and albuminuria ($\rho = 0.742$, $P < .001$), TG and albuminuria ($\rho = 0.736$, $P < .001$), and LDL-C and albuminuria ($\rho = 0.636$, $P < .001$), while there was no significant correlation between CHOL and eGFR, age or BMI (Fig. 5). As observed in the adult cohort, there was also a significant negative correlation between eGFR and TG ($\rho = -0.454$, $P = .006$). In a multiple linear regression analysis, including albuminuria, age, BMI, eGFR, and sex as independent predictors, log-transformed albuminuria ($\beta = 0.728$; $P < .001$) was the only independent and significant predictor of CHOL levels, while sex, age, BMI, and eGFR did not reach statistical significance ($P > .05$ for all).

DISCUSSION

This study investigated the hypothesis that patients with AS develop hypercholesterolemia as frequently as described in general CKD cohorts, despite their young age, due to increased albuminuria.

This study found a prevalence of 59.3% across patients at various stages of CKD.

The National Health and Nutrition Examination Survey (NHANES) examined the prevalence of dyslipidemia in patients with CKD, which increased from 45.5% in CKD stage 1 to 67.8% in CKD stage 4 [16]. Notably, the hypercholesterolemia prevalence

in this study reached 59.3%—consistent with NHANES findings—but occurred at a significantly earlier life stage, with a mean age of 38 years compared to approximately 64 years in the reference population [16].

This study also showed a correlation between albuminuria and elevated lipids, which is likely driven by the urinary loss of albumin and liporegulatory proteins, which reduces oncotic pressure and impairs clearance, thereby stimulating compensatory hepatic lipoprotein synthesis [22]. Notably, this association was absent in patients receiving LLT and patients with LLT presented with significantly lower CHOL and LDL-C levels compared with the untreated patients, indicating that LLT may effectively uncouple the secondary dyslipidemia from proteinuria [23]. After adjusting for age, BMI, eGFR, sex, and LLT, albuminuria ($\beta = 0.315$; $P < .001$), age ($\beta = 0.359$; $P < .001$), and LLT ($\beta = -0.251$; $P < .001$) were independent and significant predictors of CHOL levels, while sex, BMI, and eGFR did not reach statistical significance ($P > .05$ for all). This finding was even stronger in the pediatric cohort, in which albuminuria was the only independent and significant predictor of CHOL levels ($\beta = 0.728$; $P < .001$). This might be attributable to a combination of factors: the lack of pharmacological interference by LLT and the absence of cumulative age-related confounders, which might allow a more direct observation of the pathophysiology in the pediatric group.

Interestingly, this study identified a consistent sex-specific difference: male patients exhibited significantly higher LDL-C and lower HDL-C levels, and male sex was found to be an independent predictor of LDL-C levels. Taken together, although the univariate correlations were modest, the multivariable model demonstrated that albuminuria and age were similarly strong independent predictors of CHOL levels, thereby underscoring the clinical importance of albuminuria as a primary driver of dyslipidemia in AS.

Prolonged dyslipidemia in patients with overt proteinuria significantly elevates the risk of severe cardiovascular events. Beyond cardiovascular risk, dyslipidemia may directly contribute to CKD progression via renal lipotoxicity, in which the accumulation of lipids incites cellular organelle dysfunction, fibrosis, mesangial cell proliferation, and podocyte apoptosis [24–27]. Notably, in a mouse model of AS, the HMG-CoA reductase inhibitor cerivastatin slightly prolonged time to KF and slowed disease progression by reducing renal fibrosis and inflammatory cell infiltration [28].

The KDIGO guidelines for dyslipidemia treatment in non-dialysis-dependent CKD patients differ by age [29]. For patients aged ≥50 years with eGFR < 60 ml/min/1.73 m², a statin or statin/ezetimibe combination is recommended. For adults aged <50 years, statins are only recommended if the patient has established coronary heart disease, diabetes, prior ischemic stroke, or an estimated >10% ten-year risk of coronary death or non-fatal MI, estimated using a validated risk prediction tool. The European Society of Cardiology guidelines classify non-dialysis-dependent CKD stages 3–5 as high or very high risk for CVD, recommending statin or statin/ezetimibe combination therapy [18]. For stage 1–2 CKD, intervention strategies rely on total risk estimation (e.g. using SCORE2) in conjunction with untreated LDL-C levels. Notably, 250 patients in this study (54.5%) were under the age of 40 and thus fell below the validated age threshold for SCORE2 risk estimation, highlighting a significant gap in current risk stratification tools for this population.

Given the high prevalence of hypercholesterolemia observed, early screening is warranted to facilitate long-term risk stratification, the implementation of early lifestyle modifications,

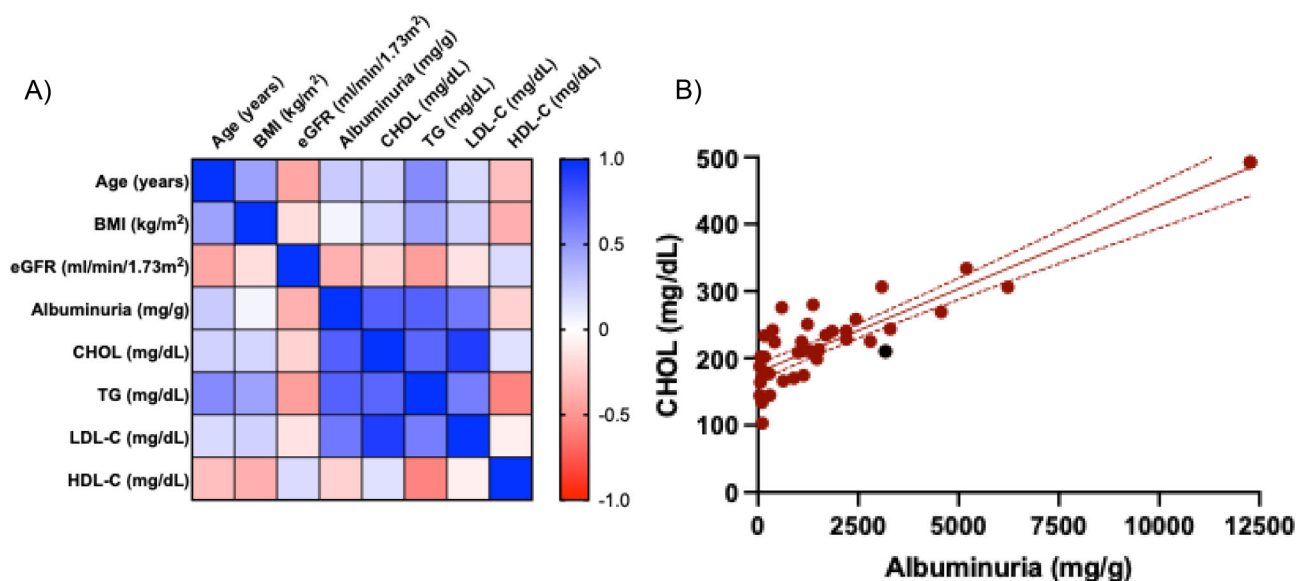


Figure 5: (A) Spearman correlation of the pediatric cohort ($n = 44$). The heatmap illustrates the pairwise Spearman rank correlations between kidney function markers (eGFR, Albuminuria), demographics (age, BMI), and lipid profile. The color scale represents the correlation coefficient, ranging from dark red (strong negative correlation, -1.0) to dark blue (strong positive correlation, $+1.0$). (B) Scatter plot of albuminuria and total cholesterol (CHOL). One patient (black dot) received lipid-lowering therapy.

and—where clinically appropriate—the initiation of pharmacological interventions. While older recommendations included statins as an adjunctive treatment for dyslipidemia in adult patients with AS to mitigate cardiovascular risk, current guidelines on AS do not specifically address cholesterol management and, therefore, physicians must currently base treatment decisions on an individual patient's risk profile and a thorough risk-benefit assessment [30–32]. In addition, lifestyle modifications, such as the achievement and maintenance of a normal body weight, consumption of a healthy diet, engagement in regular physical activity, and smoking cessation, can lower cardiovascular risk [33–36]. These interventions are anticipated to concurrently be beneficial for the course of kidney function in AS [37]. Additionally, future studies should also investigate how new therapies that lower albuminuria affect the lipid status in patients with AS, as this could potentially be a dual therapeutic benefit [38].

Several limitations should be considered when interpreting the findings of this study:

A primary limitation is the non-interventional, retrospective design, which limits the ability to draw conclusions regarding the clinical impact of hypercholesterolemia on the long-term progression of AS or the development of cardiovascular events. Furthermore, the retrospective methodology resulted in incomplete or non-standardized baseline data in some patients. Specifically, detailed information on potential confounders, such as specific dietary intake and physical activity levels, which are known to influence hypercholesterolemia, was also limited. In addition, medication adherence was not formally assessed, representing a potential source of unmeasured bias in the analysis of treatment efficacy [39–41]. While the study was multicenter, the cohort was drawn from specialized nephrology centers. This may introduce a degree of selection bias and thus limit the generalizability of our findings to the broader, undiagnosed, or less-monitored patients with AS. Furthermore, this study's definition of hypercholesterolemia included patients on LLT. While many of these patients were treated for overt dyslipidemia—

at young ages and early CKD stages—it is possible that for a subset of patients, LLT was initiated for primary prevention, which may have a potential impact on the reported prevalence rates. Finally, this study did not include a direct control group of CKD patients with etiologies other than AS from the participating centers. Instead, data from the NHANES study were utilized for comparison; however, differences in study design (prospective vs. retrospective) and geography (USA vs. Europe and China) necessitate caution when directly comparing prevalence rates. Due to these limitations, our findings should be interpreted cautiously. Future prospective studies are warranted to validate these results and definitively address the clinical significance of hypercholesterolemia in AS. Nevertheless, this study is the first to identify a significant correlation between cholesterol levels and the degree of albuminuria in patients with AS and largely normal or only mildly reduced eGFR, providing novel clinical insights for cardiovascular risk stratification in this population.

CONCLUSIONS

This study shows that patients with AS exhibit a high prevalence of hypercholesterolemia at a significantly younger age than comparable CKD cohorts. This lipid dysregulation was independently associated with the degree of albuminuria, suggesting a direct mechanistic link between glomerular protein loss and lipid dysregulation. Despite lower eGFR and higher albuminuria, patients with LLT had significantly lower CHOL and LDL-C levels compared with the untreated patients. Consequently, early lipid screening in patients with AS is recommended to facilitate long-term risk stratification, the implementation of early lifestyle modifications, and—where clinically appropriate—the initiation of pharmacological interventions. Future prospective studies are needed to determine whether LLT can mitigate both cardiovascular risk and CKD progression in this specific group.

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AUTHORS' CONTRIBUTIONS

J.B. wrote the first draft of the article and contributed to data analysis, data interpretation, content and design of all figures, discussion of the results and manuscript. OG contributed as principal investigator of the study, assessed the final data and critically revised the manuscript. A.J., A.C.-K., V.G., Y.Z., I.B., and J.W. contributed to data collection, data interpretation, and discussion of the results and the manuscript. F.W., J.D., J.H., M.C., K.C., and M.W. contributed to data interpretation and discussion of the results and the manuscript. All authors edited and approved the final version of the article.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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