Solitary Functioning Kidney and Kidney Injury- SOFIA Study.

Uncovering risk factors for kidney injury in children with a solitary functioning kidney

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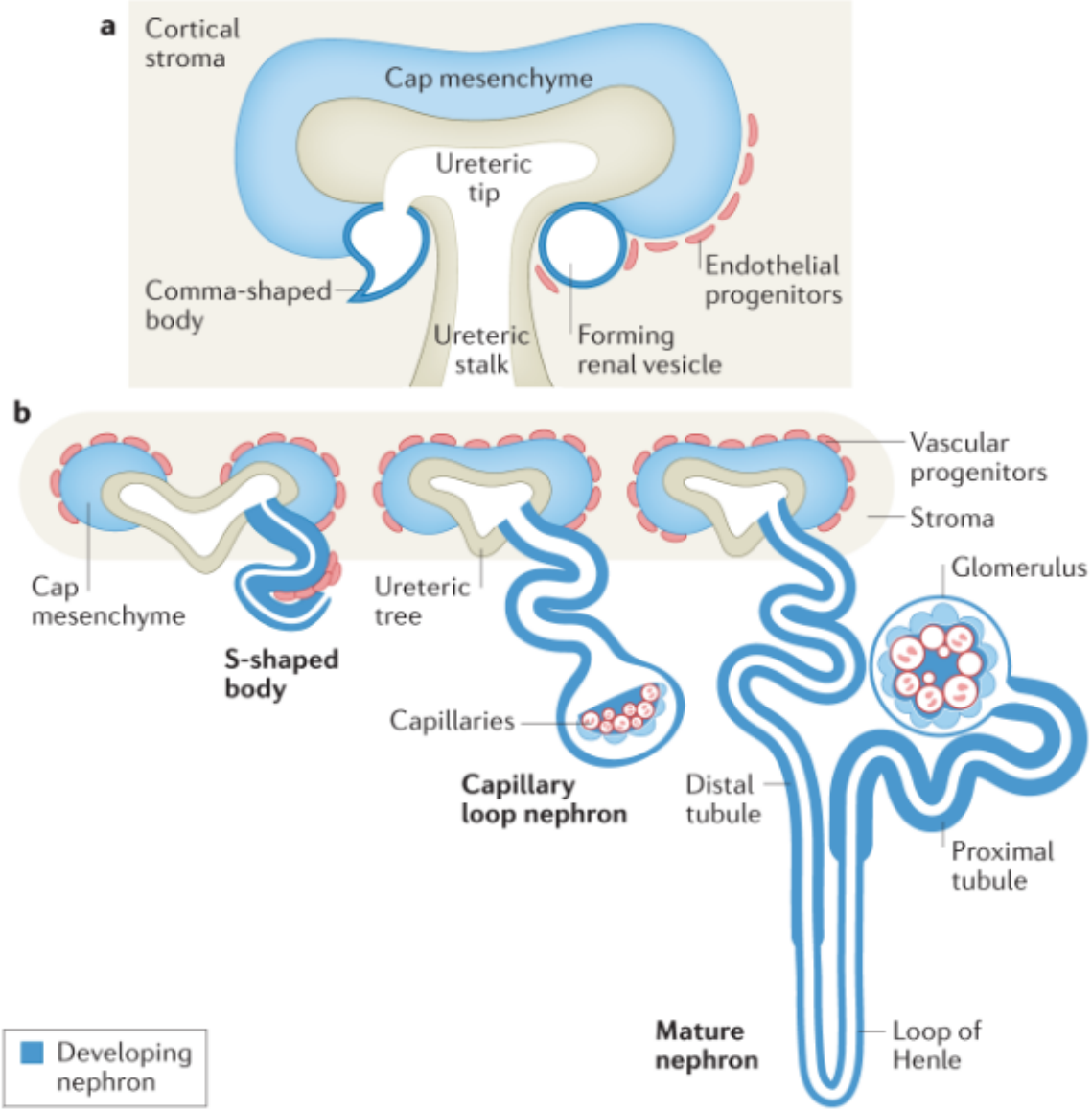
Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) are a major cause of morbidity in children and leading cause of End-Stage-Kidney-Disease (ESKD) in population <18 years. Development of the kidney occurs from 2 distinct embryological origins, i) the ureter-derived collecting duct, and ii) the mesenchymal blastema which will form the nephrons (glomerulus to the junction of connecting tubule to collecting tubules). The ureter-derived collecting duct is induced to branch, while the mesenchymal blastema is induced to enter the critical process of mesenchyme to epithelium conversion or transition (MET).



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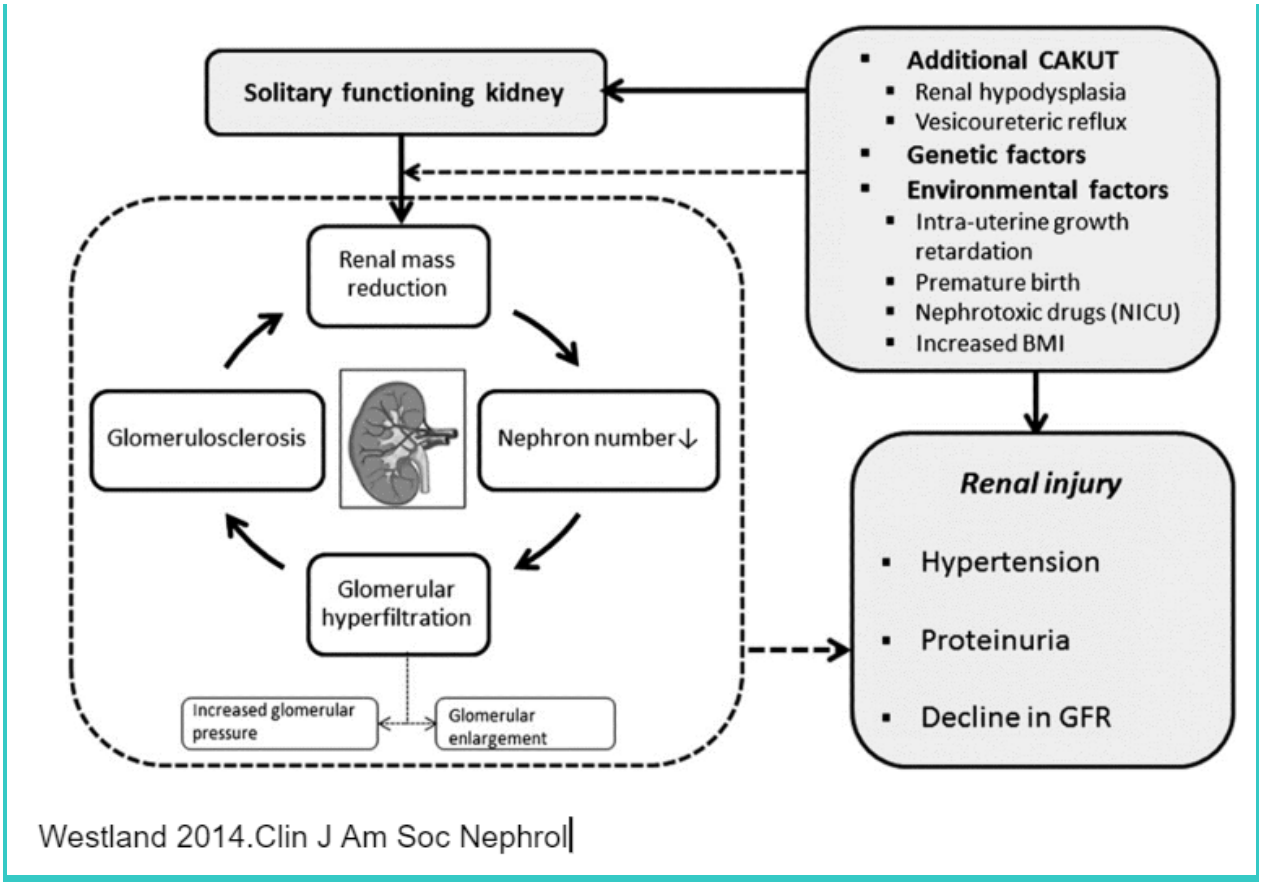
Solitary functioning kidney (SFK) can be due to congenital absence of one of the kidneys, or unilateral nephrectomy. Congenital SFK is third most common CAKUT, accounting for upto 19%. SFK in childhood predisposes to kidney injury (high blood pressure, proteinuria, or chronic kidney disease) later in life.



The exact prevalence of kidney injury however is uncertain, with estimates ranging from 6% to 60% at 15 years of age and about 25- 30% with long-term follow-up into adulthood. In addition, the risk of cardiovascular disease can increase in patients with kidney disease. However, it is unclear why some patients develop kidney injury and others don't. Solitary Functioning Kidney: Aetiology and Prognosis (SOFIA) study was undertaken in the Netherlands to provide an improved estimate of the prevalence of kidney injury and to identify risk factors in children with a SFK.

METHODS

INCLUSION CRITERIA

- Patients diagnosed with an SFK (defined as <20% differential function on mercaptoacetyltriglycine (MAG-3) or dimercaptosuccinic acid (DMSA) scans or unilateral absence of kidney tissue on kidney ultrasound) before their 18th birthday
- Born between January 1, 1993, and December 31, 2020
- AGORA (Aetiologic Research Into Genetic and Occupational/Environmental Risk Factors for Anomalies in Children) data and biobank or

- 36 hospitals in the Netherlands (patients informed by pediatricians, pediatric nephrologists, and urologists)

Outcome classification

Four indicators of kidney injury were considered: ***proteinuria, high blood pressure, reduced eGFR, and use of antihypertensive and/or antiproteinuric medication***. For all indicators except medication use, 2 cutoffs were used to define any and severe kidney injury and presence of the indicator was checked from the last available record for each indicator of kidney injury.

Definitions of kidney injury

Variable	Cutoff value for any injury	Cutoff value for severe injury
Proteinuria	uPCR >20 mg/mmol and/or uACR >3 mg/mmol (≥2 yr); uACR >10 mg/mmol (<2 yr)	uPCR >50 mg/mmol and/or uACR >30 mg/mmol
High blood pressure	Office BP: SBP and/or DBP ≥p90 for age and sex or ≥120/80 mm Hg (whichever is lower) ABPM: 24-h SBP and/or DBP ≥p90 for age and sex	Office BP: SBP and/or DBP ≥p95 for age and sex or ≥130/80 mm Hg (whichever is lower) ABPM: 24-h SBP and/or DBP ≥p95 for age and sex
Reduced eGFR	<90 ml/min per 1.73 m^2 (≥2 yr)	<60 ml/min per 1.73 m^2 (≥1 yr)
Medication	Prescription of any of the following medication classes: ACE inhibitors, ARBs, calcium antagonists, or thiazide diuretics	

ABPM, ambulatory blood pressure measurement; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; p, percentile; SBP, systolic blood pressure; uACR, urine albumin-creatinine ratio; uPCR, urine protein-creatinine ratio.

Risk factors

Potential risk factors for kidney injury were predefined on the basis of existing literature and knowledge of the pathophysiological mechanisms leading to kidney injury. These included:

- ❖ Female sex
- ❖ Birth weight percentile
- ❖ Preterm birth (gestational age <37 weeks)
- ❖ Cause of the SFK
- ❖ Presence of extrarenal congenital anomalies

- ❖ Right sided SFK
- ❖ Congenital anomalies of the kidney and urinary tract (CAKUT) in the SFK
- ❖ Urinary tract infections (UTIs) in the first year of life
- ❖ SFK length within 90 days and at 1 year of age, and
- ❖ High body mass index (BMI) at last follow-up.

Statistical analyses

Kaplan-Meier analysis was used to calculate survival without any kidney injury and without severe kidney injury assuming that all patients received follow-up until study closure or age of 18 years.

Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals for each potential risk factor:

- Any kidney injury (also including severe injury)
- Severe kidney injury
- eGFR <90 ml/min per 1.73 m2
- Hyperfiltration injury (any proteinuria or high blood pressure and/or medication use).

Crude HRs were derived from the original database, and adjusted HRs were estimated using a model containing the factor of interest and all other potential risk factors after multiple imputation of missing values.

Results

In total, 990 SFK patients provided informed consent. Clinical information could be obtained for 944 patients (95%), and questionnaires were completed by parents of 883 patients with SFK (89%).

Clinical characteristics of the 944 patients with SFK

Of patients with clinical information, 60% were men and 76% had a congenital SFK. Among the congenital causes (n= 715), an antenatal diagnosis was recorded in 76%, and multicystic dysplastic kidney (MCDK; n=308) and unilateral kidney agenesis (UKA; n= 150) were most common.

Table 1 | Clinical characteristics of the 944 patients with SFK

Factor	Congenital (n = 715)	Acquired (n = 103)	Unknown cause (n = 126)
Academic center	463 (65)	89 (86)	79 (63)
Female sex	254 (36)	54 (52)	65 (52)
Birth weight			
<p20	126 (24)	21 (23)	26 (24)
p20–p40	112 (17)	13 (14)	15 (14)
p40–p60	109 (16)	12 (13)	22 (20)
p60–p80	135 (20)	18 (20)	18 (16)
>p80	161 (24)	27 (30)	29 (26)
Preterm birth	102 (15)	12 (13)	11 (9.9)
Extrarenal congenital anomaly[a]	158 (22)	10 (10)	23 (18)
Genital anomaly (boys)	55 (12)	1 (1)	6 (9.8)
Genital anomaly (girls)	25 (9.8)	0 (0)	3 (4.6)
Congenital heart defect	42 (5.9)	2 (1.9)	7 (5.6)
Anorectal malformation	32 (4.5)	0 (0)	2 (1.6)
Syndrome or association	30 (4.2)	4 (3.9)	3 (2.4)
Other congenital anomaly	65 (9.1)	4 (3.9)	7 (5.6)
Right-sided SFK	367 (51)	59 (57)	70 (56)
Any CAKUT in SFK	284 (46)	6 (21)	9 (60)
Severe CAKUT in SFK[b]	133 (21)	2 (7.1)	6 (40)
UTI in first year of life	189 (28)	15 (16)	17 (15)
BMI at last follow-up			
Normal weight	378 (86)	77 (83)	91 (87)
Overweight/obese	61 (14)	16 (17)	14 (13)
Antenatal diagnosis	542 (76)	n/a	n/a
Cause of cSFK			
UKA	150 (21)	n/a	n/a
MCDK	308 (43)	n/a	n/a
Hypodysplasia	68 (10)	n/a	n/a
Unilateral obstruction	52 (7.3)	n/a	n/a
PUV	39 (5.5)	n/a	n/a
VUR	56 (7.8)	n/a	n/a
Other/unknown	42 (5.9)	n/a	n/a
Length of SFK (first 90 d)			
<p50	46 (14)	n/a	n/a
p50–p75	36 (11)	n/a	n/a
p75–p95	109 (33)	n/a	n/a
>p95	137 (42)	n/a	n/a
Length of SFK (first year)			
<p50	48 (12)	n/a	n/a
p50–p75	37 (9.0)	n/a	n/a
p75–p95	94 (23)	n/a	n/a
>p95	234 (57)	n/a	n/a

BMI, body mass index; CAKUT, congenital anomalies of the kidney and urinary tract; cSFK, congenital solitary functioning kidney; MCDK, multicystic dysplastic kidney; n/a, not applicable; p, percentile; PUV, posterior urethral valve; SFK, solitary functioning kidney; UKA, unilateral kidney agenesis; UTI, urinary tract infection; VUR, vesicoureteral reflux. Data are given as n (%). Percentages calculated for subjects with nonmissing values.

[a]Numbers do not add up to 100% because some patients had >1 extrarenal anomaly.

[b]Severe CAKUT was defined as grade 3 or 4 hydronephrosis, grade 3–5 VUR, parenchymal abnormalities or defects, and/or dysplasia on any ultrasound, voiding cystourethrography, or nuclear scan.

Duration of follow up

Patients had been followed up for a median duration of **12.8 years**. The last age at follow-up was higher for patients with acquired or unknown cause of SFK compared with a congenital cause (median ages, 18.0, 17.1, and 11.3 years, respectively).

Indicators of kidney injury

At the end of follow-up, 553 patients (59%) showed ⩾1 indicators of kidney injury and 255 patients (27%) had at least 1 indicator of severe injury.

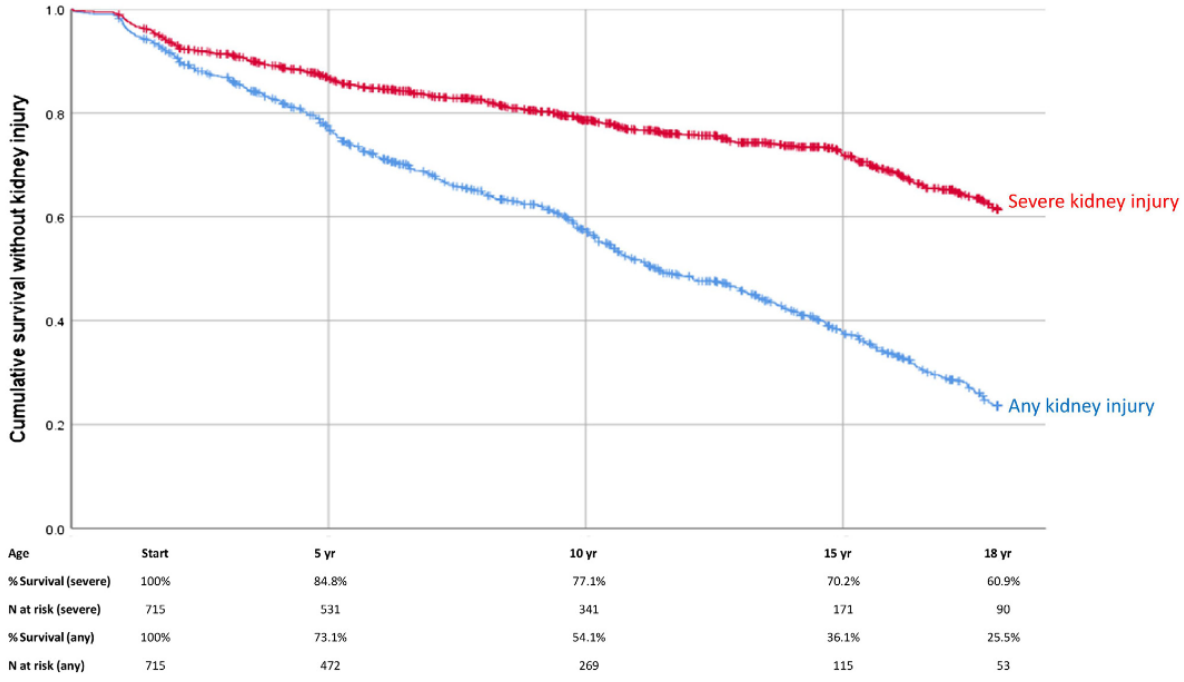
i) High blood pressure was most common, with 323 patients (34%) having their last blood pressure measurement above the threshold for any kidney injury and 172 patients (18%) above the threshold for severe injury.

ii) Another 50 patients (5%) had normal blood pressures at last measurement but used **antihypertensive or antiproteinuric medication.**

iii) CKD: An eGFR <90 ml/min per 1.73 m2 was present in 290 patients (31%), of whom 26 (3%) had an eGFR <60 ml/min per 1.73 m2 and 10 had received a kidney transplant (1%). In 152 (16%) and 15 (2%) patients, the reduced eGFR was the only indicator of any and severe kidney injury, respectively.

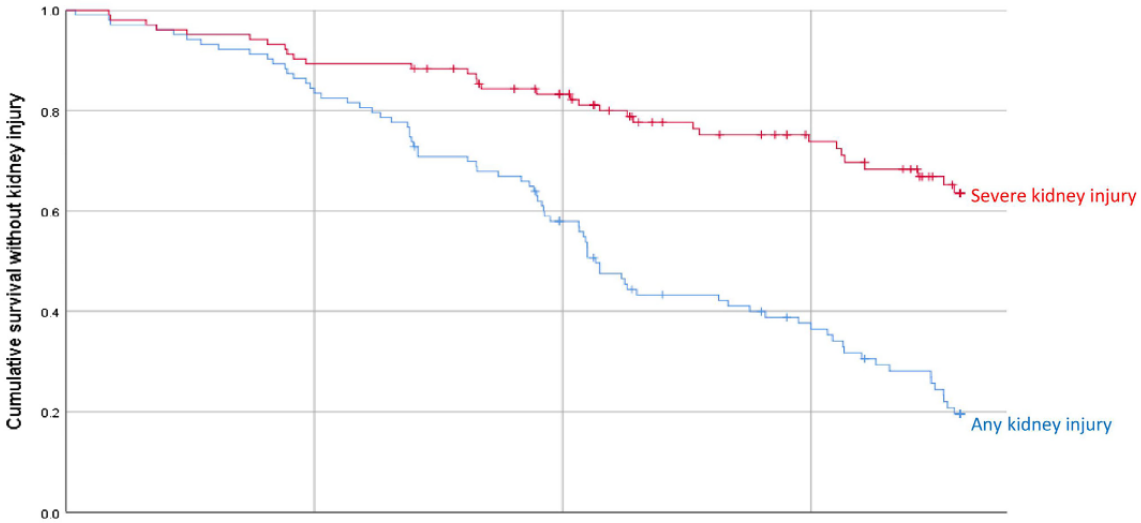
iv) Any and severe **proteinuria** were diagnosed in 68 (7%) and 20 (2%) patients, respectively.

The proportion of patients without kidney injury decreased steadily with age in SFK and was similar between congenital and acquired SFK (Figures 1 and 2). At 18 years of age, 75% of patients with congenital SFK and 80% of patients with acquired SFK had >1 indicators of kidney injury.



Age	Start	5 yr	10 yr	15 yr	18 yr
% Survival (severe)	100%	84.8%	77.1%	70.2%	60.9%
N at risk (severe)	715	531	341	171	90
% Survival (any)	100%	73.1%	54.1%	36.1%	25.5%
N at risk (any)	715	472	269	115	53

Figure 1 | Cumulative survival without any kidney injury (blue line) or without severe kidney injury (red line) among children with congenital solitary functioning kidney.



Age	Start	5 yr	10 yr	15 yr	18 yr
% Survival (severe)	100%	89.3%	83.3%	73.8%	63.5%
N at risk (severe)	103	92	78	54	38
% Survival (any)	100%	83.5%	58.0%	37.5%	19.6%
N at risk (any)	103	86	56	31	16

Figure 2| Cumulative survival without any kidney injury (blue line) or without severe kidney injury (red line) among children with acquired solitary functioning kidney.

Analysis of the potential risk factors in patients with congenital SFK revealed that female sex, severe CAKUT in the SFK, and high BMI at last follow-up were associated with an increased risk of any kidney injury. For severe kidney injury, both multicystic dysplastic kidney (MCDK) and hypodysplasia decreased the risk compared with patients with Unilateral Kidney Agenesis (UKA), whereas severe CAKUT in the SFK, SFK length below the 50th percentile at 1 year of age, and high BMI were associated with increased risks. Further, female sex, severe CAKUT in the SFK, and smaller SFK length at 1 year were associated with reduced eGFR, whereas birth weight above the 80th percentile (>p80), MCDK as cause of SFK, and high BMI were associated with hyperfiltration injury only.

Table 2 | cHRs and aHRs for potential risk factors for any and severe kidney injury in children with cSFK

Factor	No kidney injury (n = 320)	Any kidney injury (n = 395)	cHR	aHR[a]	95% CI[a]	Severe kidney injury (n = 187)	cHR	aHR[a]	95% CI[a]
Academic center	189 (59)	274 (69)	1.0	1.0	0.8–1.3	133 (71)	1.2	1.2	0.8–1.7
Female sex	103 (32)	151 (38)	**1.3**	**1.3**	**1.1–1.7**	62 (33)	1.1	1.2	0.8–1.6
Birth weight percentile									
<p20	71 (23)	91 (24)	1.1	1.1	0.7–1.5	44 (24)	1.3	1.2	0.7–2.0
p20–p40	51 (17)	61 (16)	1.2	1.1	0.8–1.7	30 (17)	1.2	1.2	0.7–2.1
p40–p60	55 (18)	54 (14)	1.0	1.0	ref	23 (13)	1.0	1.0	ref
p60–p80	63 (21)	72 (19)	1.2	1.2	0.8–1.7	37 (20)	1.3	1.3	0.7–2.2
>p80	64 (21)	97 (26)	1.3	1.3	0.9–1.8	48 (26)	1.6	1.5	0.9–2.6
Prematurity	43 (14)	59 (16)	1.0	0.9	0.6–1.2	32 (18)	1.1	0.9	0.6–1.3
Cause of cSFK									
UKA	62 (19)	88 (22)	1.0	1.0	ref	49 (26)	1.0	1.0	ref
MCDK	149 (47)	159 (40)	0.8	0.8	0.6–1.1	67 (36)	0.7	**0.6**	**0.4–0.9**
Hypodysplasia	34 (11)	34 (8.6)	0.8	0.7	0.4–1.0	16 (8.6)	0.7	**0.5**	**0.3–1.0**
Unilateral obstruction	21 (6.6)	31 (7.8)	0.9	0.8	0.5–1.2	14 (7.5)	0.8	0.6	0.3–1.2
PUV	32 (3.8)	27 (6.8)	0.9	0.8	0.5–1.4	15 (8.0)	1.1	0.9	0.4–1.9
VUR	22 (6.9)	34 (8.6)	0.9	0.8	0.5–1.2	15 (8.0)	0.8	0.7	0.3–1.3
Other/unknown	20 (6.3)	22 (5.6)	0.7	0.6	0.4–1.1	11 (5.9)	0.7	0.7	0.3–1.6
Any extrarenal anomaly	59 (18)	99 (25)	1.0	0.9	0.7–1.2	41 (22)	0.9	0.8	0.5–1.2
Right-sided SFK	160 (50)	207 (52)	1.0	1.0	0.8–1.2	93 (50)	1.0	1.0	0.7–1.4
Severe CAKUT in SFK[b]	40 (14)	93 (27)	**1.3**	**1.3**	**1.0–1.7**	50 (31)	**1.6**	**1.5**	**1.0–2.3**
UTI in first year	71 (23)	118 (32)	1.1	1.1	0.8–1.4	60 (34)	1.3	1.0	0.7–1.5
SFK length (90 d)[c]									
<p50	15 (8.5)	31 (20)	1.5	1.3	0.6–2.9	14 (23)	**2.0**	2.0	0.5–8.0
p50–p75	16 (9.1)	20 (13)	0.9	0.9	0.6–1.5	6 (9.7)	0.8	0.9	0.3–2.2
p75–p95	67 (38)	42 (28)	0.7	0.8	0.5–1.3	16 (26)	0.7	0.8	0.4–1.7
>p95	78 (44)	59 (39)	1.0	1.0	ref	26 (42)	1.0	1.0	ref
SFK length (1 yr)[c]									
<p50	17 (8.1)	31 (15)	1.3	1.4	0.9–2.3	18 (21)	**1.8**	2.3	1.0–5.3
p50–p75	16 (7.7)	21 (10)	1.1	1.1	0.7–1.7	4 (4.6)	0.6	0.7	0.3–1.9
p75–p95	52 (25)	42 (21)	0.9	1.0	0.7–1.5	14 (16)	0.7	0.9	0.5–1.6
>p95	124 (59)	110 (54)	1.0	1.0	ref	51 (59)	1.0	1.0	ref
High BMI at last follow-up	10 (6.3)	51 (18)	**1.8**	**1.6**	**1.0–2.6**	31 (25)	**2.9**	**2.4**	**1.2–4.8**

aHR, adjusted hazard ratio, BMI, body mass index; CAKUT, congenital anomalies of the kidney and urinary tract; cHR, crude hazard ratio; CI, confidence interval; cSFK, congenital solitary functioning kidney; MCDK, multicystic dysplastic kidney; p, percentile; PUV, posterior urethral valve; ref, reference; SFK, solitary functioning kidney; UKA, unilateral kidney agenesis; UTI, urinary tract infection; VUR, vesicoureteral reflux.

Data are given as n (%), unless otherwise indicated. Bold values indicate associations with a 95% CI not including 1.0.

[a]On the basis of a multivariable model including SFK length at 1 year of age, except for hazard ratio of SFK length (90 days).

[b]Severe CAKUT was defined as grade 3 or 4 hydronephrosis, grade 3–5 VUR, parenchymal abnormalities or defects, and/or dysplasia on any ultrasound, voiding cystourethrography, or nuclear scan.

[c]The length of the SFK was compared with reference values based on Akhavan *et al.*[21]

Table 3 | cHRs and aHRs for potential risk factors for impaired eGFR (<90 ml/min per 1.73 m^2) and hyperfiltration injury (proteinuria, high blood pressure, or antihypertensive medication use) in children with cSFK

Factor	eGFR ≥90 ml/ min per 1.73 m^2 (n = 341)	eGFR <90 ml/ min per 1.73 m^2 (n = 194)	cHR	aHR[a]	95% CI[a]	No hyperfiltration injury (n = 414)	Hyperfiltration injury (n = 286)	cHR	aHR[a]	95% CI[a]
Academic center	241 (71)	144 (74)	1.0	1.0	0.7–1.4	260 (63)	196 (69)	0.9	1.0	0.7–1.3
Female sex	104 (31)	92 (47)	**2.0**	**2.3**	**1.6–3.1**	152 (37)	97 (34)	1.0	1.0	0.7–1.3
Birth weight percentile										
<p20	75 (23)	52 (28)	1.3	1.4	0.8–2.3	94 (24)	63 (23)	1.1	1.0	0.7–1.6
p20–p40	51 (16)	32 (17)	1.3	1.4	0.8–2.5	66 (17)	44 (16)	1.2	1.1	0.7–1.7
p40–p60	55 (17)	28 (15)	1.0	1.0	ref	70 (18)	37 (14)	1.0	1.0	ref
p60–p80	61 (19)	34 (19)	1.1	1.2	0.7–2.1	80 (20)	54 (20)	1.2	1.2	0.8–1.9
>p80	81 (25)	38 (21)	1.0	1.2	0.7–2.0	82 (21)	77 (28)	1.5	1.5	1.0–2.2
Prematurity	51 (16)	33 (18)	1.0	0.9	0.6–1.3	60 (15)	40 (14)	0.8	0.8	0.6–1.2
Cause of cSFK										
UKA	75 (22)	34 (18)	1.0	1.0	ref	76 (18)	70 (25)	1.0	1.0	ref
MCDK	148 (43)	72 (37)	1.1	1.2	0.8–1.9	191 (46)	110 (39)	**0.7**	**0.6**	**0.5–0.9**
Hypodysplasia	40 (12)	14 (7.2)	0.9	0.8	0.4–1.5	39 (9.4)	28 (9.8)	0.8	0.7	0.4–1.2
Unilateral obstruction	21 (6.2)	16 (8.2)	1.4	1.2	0.6–2.3	30 (7.2)	22 (7.7)	0.7	0.6	0.4–1.0
PUV	18 (5.3)	20 (10)	1.5	1.6	0.8–3.4	20 (4.8)	19 (6.6)	0.7	0.7	0.4–1.4
VUR	22 (6.5)	24 (12)	1.5	1.4	0.8–2.7	32 (7.7)	23 (8.0)	0.7	0.7	0.4–1.1
Other/unknown	17 (5.0)	14 (7.2)	1.5	1.2	0.6–2.4	26 (6.3)	14 (4.9)	**0.5**	0.5	0.3–1.0
Any extrarenal anomaly	81 (24)	56 (29)	1.0	1.0	0.7–1.5	86 (21)	67 (23)	0.9	0.8	0.6–1.1
Right-sided SFK	164 (48)	109 (56)	1.2	1.1	0.8–1.4	220 (53)	142 (50)	0.9	0.8	0.7–1.1
Severe CAKUT in SFK[b]	55 (19)	62 (38)	**1.8**	**1.6**	**1.1–2.3**	66 (18)	65 (26)	1.1	1.1	0.8–1.6
UTI in first year	89 (28)	78 (43)	**1.5**	1.3	0.9–1.9	108 (28)	78 (29)	0.9	0.9	0.6–1.2
SFK length (90 d)[c]										
<p50	20 (13)	18 (32)	**3.8**	2.0	0.8–5.1	25 (12)	20 (17)	0.9	1.1	0.4–2.9
p50–p75	15 (9.4)	11 (19)	**2.6**	1.7	0.7–4.0	22 (11)	14 (12)	0.6	0.7	0.4–1.4
p75–p95	59 (37)	17 (30)	1.6	1.3	0.6–3.1	76 (37)	31 (27)	0.6	0.7	0.4–1.1
>p95	66 (41)	11 (19)	1.0	1.0	ref	85 (41)	50 (44)	1.0	1.0	ref
SFK length (1 yr)[c]										
<p50	19 (9.3)	18 (22)	**2.9**	**2.7**	**1.3–5.6**	24 (9.5)	24 (16)	1.1	1.3	0.7–2.3
p50–p75	16 (7.8)	13 (16)	**2.6**	**2.5**	**1.2–5.5**	24 (9.5)	13 (8.4)	0.7	0.7	0.3–1.4
p75–p95	43 (21)	22 (27)	**2.0**	**2.1**	**1.1–4.0**	65 (26)	27 (17)	0.7	0.8	0.5–1.2
>p95	126 (62)	29 (35)	1.0	1.0	ref	140 (55)	91 (59)	1.0	1.0	ref
High BMI at last follow-up	27 (12)	29 (17)	1.4	1.2	0.8–2.0	26 (10)	35 (19)	**1.5**	**1.6**	**1.0–2.7**

aHR, adjusted hazard ratio; BMI, body mass index; CAKUT, congenital anomalies of the kidney and urinary tract; cHR, crude hazard ratio; CI, confidence interval; cSFK, congenital solitary functioning kidney; eGFR, estimated glomerular filtration rate; MCDK, multicystic dysplastic kidney; p, percentile; PUV, posterior urethral valve; ref, reference; SFK, solitary functioning kidney; UKA, unilateral kidney agenesis; UTI, urinary tract infection; VUR, vesicoureteral reflux.
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[a]On the basis of a multivariable model including SFK length at 1 year of age, except for hazard ratio of SFK length (90 days).
[b]Severe CAKUT was defined as grade 3 or 4 hydronephrosis, grade 3–5 VUR, parenchymal abnormalities or defects, and/or dysplasia on any ultrasound, voiding cystourethrography, or nuclear scan.
[c]The length of the SFK was compared with reference values based on Akhavan *et al.*[21]

None of the potential risk factors was clearly associated with reduced eGFR or hyperfiltration injury in the smaller population of patients with acquired SFK Supplementary Table S4).

DISCUSSION

In the current study cohort of 944 patients with SFK, the indicators of severe kidney injury were present in 39% of patients with congenital SFK and 37% of patients with acquired SFK at the age of 18 years. Any indicators of injury were present in 75% and 80% of patients, respectively. Kidney agenesis, CAKUT in the SFK, and high BMI were associated with increased HRs for kidney injury in children with congenital SFK. The authors noted that CAKUT in the SFK and smaller SFK length showed strong associations with eGFR <90 ml/min per 1.73 m2, whereas UKA and high BMI were

associated with hyperfiltration injury. These findings highlight that patients with SFK warrant long-term follow-up.

This is slightly higher than Sanna-Cherchi *et al.* who were the first to report severe kidney injury in patients with SFK in 2009, with up to 30% of patients showing kidney failure by the age of 30 years. Depending on inclusion criteria, follow-up duration, and definition of kidney injury, the possibility of severe outcomes and milder forms of kidney injury was reported in 6% to 60% of patients .

The most common outcome in this study was high blood pressure. The prevalence of severe high blood pressure (18%) was similar to that observed previously in KIMONO study (26%), Alfandary *et al* (32%), and Xu *et al* (32%).

This study confirmed most associations, such as low birth weight, kidney agenesis, CAKUT in the SFK, smaller SFK size, and elevated BMI as risk factors for kidney injury, but not those with UTI or preterm birth. Also, this study identified an almost 2-fold lower risk of severe kidney injury in patients with MCDK or hypodysplasia compared with UKA (adjusted HRs, 0.6 and 0.5, respectively), which is in line with earlier findings by Matsell *et al.* Possible reason could be that agenesis is thought to result from a failed interaction between the ureteric bud and metanephric mesenchyme in early kidney development and theer fore SFK remaining after UKA is more likely to have developed suboptimally as well, resulting in a higher risk of injury, whereas MCDK may arise later in development as a consequence of obstruction or abnormal branching of the ureteric bud.

Animal models proved that SFKs are capable of nephron **hyperplasia** prenatally, with nephron numbers ~70% of those in individuals born with 2 kidneys. Perhaps children with an SFK failing to show compensatory enlargement between 90 days and 1 year of age more often have a structurally abnormal SFK than children whose SFK size increases to larger than the 95th percentile (>p95) in this period.

The association between reduced eGFR and female sex was not observed when using the revised Schwartz formula for eGFR (adjusted HRs, 2.3 and 1.1 for CKiD U25 and revised Schwartz formulas, respectively).

Strengths of the study

- One of the strengths of this study is its large cohort size, which is more than twice the size of the largest study on SFK reported so far.
- Further the broad inclusion criteria and the multi-centre design should increase the generalisability of study results.
- This study used a nationwide cohort with standardized definitions of outcomes

Limitations of the study

- ❖ Multicenter study may have resulted in variation among centers in the execution of measurements, especially for blood pressure and creatinine.
- ❖ Data regarding the indication for antihypertensive or antiproteinuric medication were not available but authors noted that excluding patients with congenital heart disease or patients with medication use as only outcome did not change results substantially
- ❖ Missing information on risk factors (preterm birth, low birth weight, and occurrence of UTI, was another potential limitation), but the information was available for most patients (95%) through parental questionnaires. And, multiple imputation analysis reported similar results.
- ❖ The retrospective design induced information bias as patients without kidney injury may have been discharged from follow-up earlier. To take this into account, the authors assumed that all patients received follow-up until study closure (underestimation of the prevalence of kidney injury,however, using the actual date of last follow-up likely results in an overestimation).

IMPLICATIONS FOR CLINICAL PRACTICE

- ★ The high number of patients with kidney injury in this study indicates that all children with an SFK require long-term follow-up.
- ★ If not already present, kidney injury may well become manifest in early adulthood, warranting adequate transition and continued follow-up, of which patients, parents, and health care providers should be aware. Follow-up of patients with SFK without severe injury may best be delivered by primary care physicians and should focus on early identification of proteinuria, hypertension, or a reduced eGFR. If kidney injury is discovered, local referral practices should ensure that patients are seen by the most appropriate medical specialist.
- ★ The identification of high BMI as a factor that is strongly associated with kidney injury highlights the importance of lifestyle management in patients with SFK and can be implemented in clinical practice directly. Improvements in lifestyle, such as following a healthy diet and adhering to physical activity guidelines, have been shown effective for the prevention and treatment of hypertension in children.
- ★ Given the shared embryological origin, men with external GU birth defects (undescended testis) also may have congenital anomalies of the kidney and urinary tract. Fertility also is reduced in patients with significant renal anomalies, CKD, and ESKD because of reduced sperm quality.
- ★ Last, further research into the underlying mechanisms of kidney injury in children with SFK may help to understand the pathophysiology, develop preventative strategies, and ultimately reduce the rates of kidney injury.

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