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

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Children with a solitary functioning kidney (SFK) have an increased risk of kidney injury. The exact risk of and risk factors for kidney injury remain unknown, which impedes personalized care. Here, we recruited a nationwide multicenter cohort of 944 patients with SFK to get more insight into this by consenting patients born in 1993-2020 and diagnosed with congenital or acquired SFK before adulthood. The median follow-up was 12.8 years and four indications of kidney injury were studied: urine protein-creatinine ratios, blood pressure, estimated glomerular filtration rate and use of anti-hypertensive/proteinuric medication. For each indicator except medication use, separate cut-off values for any injury and severe injury were used. Survival analyses indicated that at 18 years of age, any or severe kidney injury were present in 75% and 39% of patients with congenital SFK, respectively. Risk factors for kidney injury included kidney agenesis as cause of the SFK, anomalies in the SFK, and high body mass index at last follow-up. Kidney agenesis and being overweight were specifically associated with proteinuria and high blood pressure, whereas anomalies in the SFK were associated with reduced estimated glomerular filtration rates. The high prevalence of kidney injury in patients with SFK emphasizes the need for long-term follow-up, in which lifestyle is an important topic to address. More research into the etiological role of risk factors will help to translate our findings into individualized care strategies. Thus, our study shows that a significant proportion of children with SFK will develop kidney injury over time.

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A solitary functioning kidney (SFK) is a common condition caused by congenital absence of one of the kidneys, a major malformation resulting in one nonfunctioning kidney, or unilateral nephrectomy. Previous work showed that an SFK in childhood predisposes to kidney injury (i.e., high blood pressure or chronic kidney disease) later in life. The exact prevalence of kidney injury is uncertain, however, with estimates ranging from 6% to 60% at 15 years of age.[1–4] Long-term studies are scarce, but the few studies with follow-up into adulthood showed considerable proportions of patients with kidney injury, ranging from 25% of patients with an estimated glomerular filtration rate (eGFR) <60 ml/min in one study[5] to 30% of patients reaching kidney failure in another study.[6] Although these studies likely included selected subgroups of more severely affected patients and may have overestimated the consequences of having an SFK from early in life, even mild to moderate kidney injury in childhood can lead to long-term complications, such as cardiovascular disease.[7,8] Therefore, kidney injury in children with SFK should be identified and treated as early as possible.

Although potential roles for genetic, perinatal, and lifestyle-related factors have been highlighted, it is still unknown why some patients with SFK develop kidney injury, whereas others do not.[1–3,5,6,9–13] Therefore, identification of risk factors for kidney injury in this population remains needed. We created the Solitary Functioning Kidney: Aetiology and Prognosis (SOFIA) study, a large nationwide cohort

of patients with SFK, to provide an improved estimate of the prevalence of kidney injury and to identify risk factors in children with an SFK.

METHODS

Patients

Patients were eligible for this study when diagnosed with an SFK (defined as <20% differential function on mercaptuacetyltriglycine (MAG-3) or dimercaptosuccinic acid (DMSA) scans or unilateral absence of kidney tissue on kidney ultrasound) before their 18th birthday and born between January 1, 1993, and December 31, 2020. Patients were derived from the AGORA (Aetiologic Research Into Genetic and Occupational/Environmental Risk Factors for Anomalies in Children) data and biobank[14,15] or informed about the study during clinical practice and/or using written information materials by pediatricians, pediatric nephrologists, and urologists from 36 hospitals in the Netherlands. After obtaining informed consent, electronic health records were searched for information regarding the cause of the SFK, exposure to potential risk factors for kidney injury, and follow-up data on the presence of kidney injury. Parents were asked to provide additional information on these topics using online questionnaires (available on request). Some patients (112 of 990 [11%]) had previously been included in the KIdney of MONofunctional Origin (KIMONO) study.[3] The study protocol was approved by the Regional Committee on Research Involving Human Subjects (registration number 2018-4524).

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 cutoff values were used, reflecting any and severe kidney injury (Box 1). The last available record for each indicator of kidney injury was used to score the presence of the indicator and, if applicable, previous records were investigated to determine the starting age. Reference values for blood pressure were adopted from the American Academy of Pediatrics and the American Heart Association, with elevated blood pressure classified as any kidney injury and stage 1 or 2 hypertension classified as severe kidney injury (Box 1).[16–18] Serum creatinine measurements were used to calculate eGFR using the recent Chronic Kidney Disease in Children Under 25 (CKiD U25) age- and sex-dependent equation,[19] which showed high accuracy in children and young adults. When creatinine was measured before 2010, the original Schwartz formula was used, to take into account the transition from Jaffe to isotope dilution mass spectrometry traceable creatinine measurements in the Netherlands around 2010.[20]

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.[13] 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. Cause of the SFK was classified as congenital when a result of CAKUT, acquired when a clear non-congenital cause was present (e.g., Wilms tumor or thrombosis of the renal vein), and other/unknown when the cause could not be determined (e.g., dysplasia with recurrent UTIs). Length of the SFK was categorized using reference values based on Akhavan *et al.*, and age- and sex-specific references were used to classify BMI as normal or high.[21,22] Inclusion via an academic hospital was regarded as a potential confounder. Details on outcome and risk factor classifications as well as multiple imputation strategies are described in the Supplementary Methods.

Box 1 | 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.

Statistical analyses

Kaplan-Meier analysis was used to calculate survival without any kidney injury and without severe kidney injury. We assumed that all patients received follow-up until study closure, to account for shorter or less frequent follow-up of patients with favorable characteristics. Furthermore, follow-up after the age of 18 years was not used for the survival analyses, because data from follow-up at adult nephrologists or primary care physicians could not always be obtained. Patients were either censored at study closure or at 18 years of age, whichever came first, to account for selective loss to follow-up in patients with a low risk of kidney injury. Sensitivity analyses were performed in which patients were censored on the actual date of last follow-up or at 18 years of age.

Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals for each potential risk factor. Four outcomes were studied: any kidney injury (also including severe injury), severe kidney injury, eGFR <90 ml/min per 1.73 m^2, and 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. The cause of SFK, presence of CAKUT in the SFK, and SFK length were only considered as potential risk factors in children with congenital SFK. To avoid multicollinearity, separate models were created for SFK length within 90 days and at 1 year of age. We created log-log plots to check

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

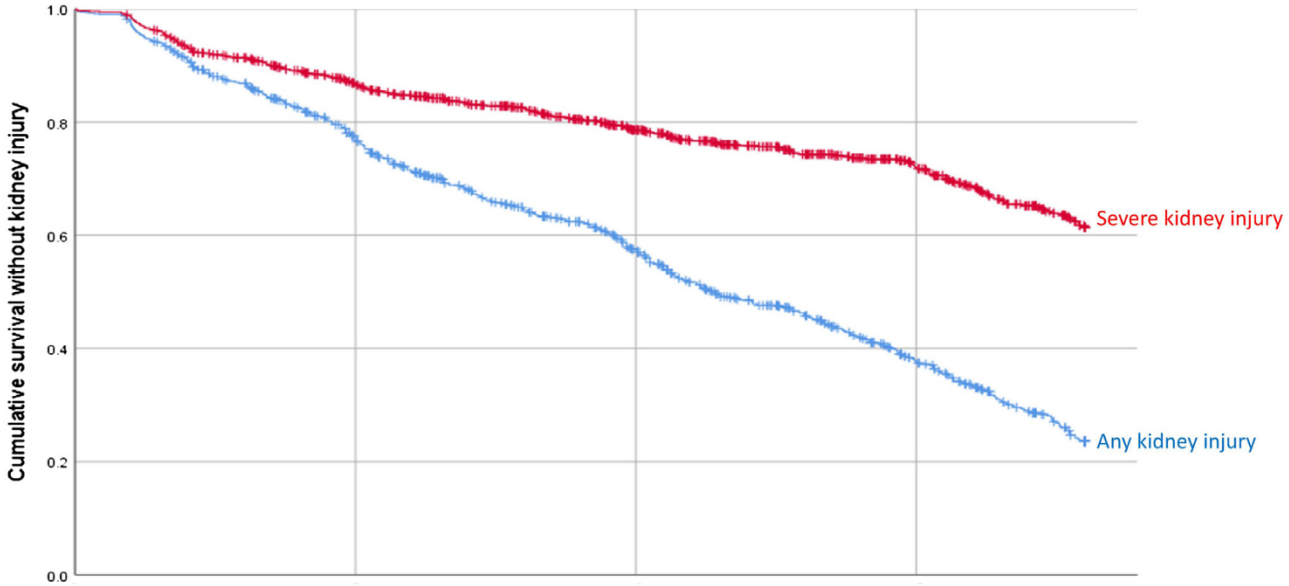
BMI, body mass index; CAKUT, congenital anomalies of the kidney and urinary tract; cSFK, congenital solitary functioning kidney; MCDK, multicystic dysplastic kidney; n/a, not applicable; p, percentile; PUV, posterior urethral valve; SFK, solitary functioning kidney; UKA, unilateral kidney agenesis; UTI, 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.

proportional hazards assumptions and investigated time-varying effects of sex and BMI by including interaction terms with time in our model. Analyses were stratified by cause of the SFK (congenital or acquired) and performed using SPSS version 25.0.

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%). A flowchart describing patient recruitment and number of patients lost to follow-up is included as Supplementary Figure S1. 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. Detailed clinical information is provided in Table 1.

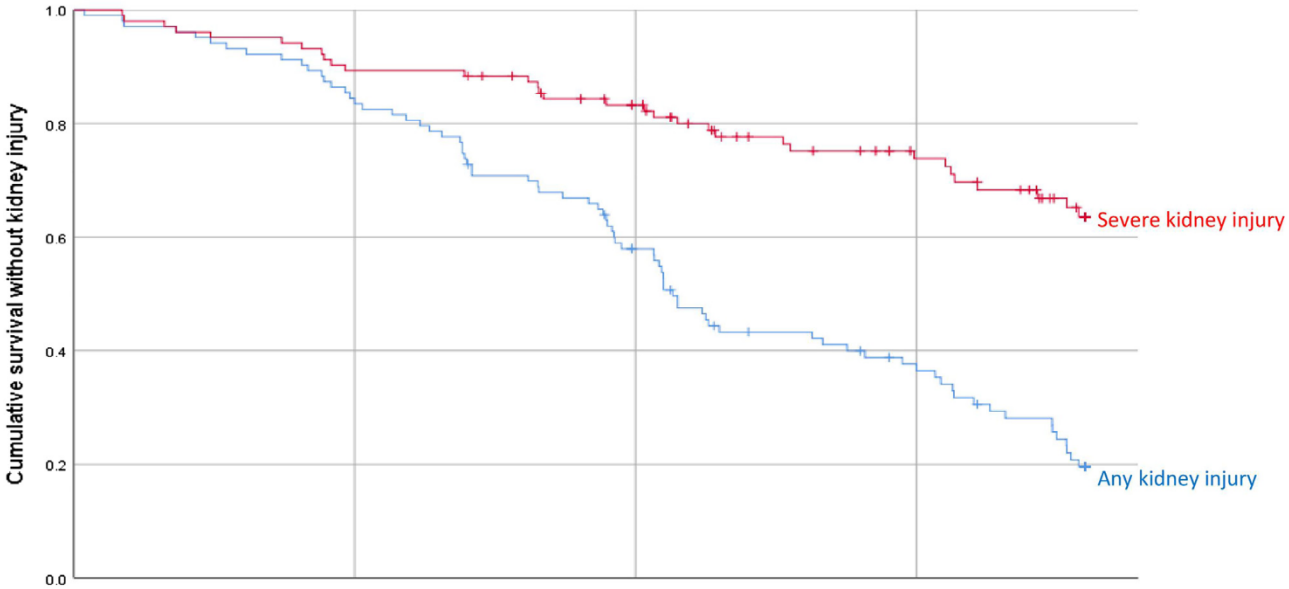
Patients had been followed up for a median duration of 12.8 years. The last age at follow-up was higher for patients with acquired or unknown cause of SFK compared with a congenital cause (median ages, 18.0, 17.1, and 11.3 years, respectively). At the end of follow-up, 553 patients (59%) showed ≥1 indicators of kidney injury and 255 patients (27%) had at least 1 indicator of severe injury. 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



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.

for severe injury. Another 50 patients (5%) had normal blood pressures at last measurement but used antihypertensive or antiproteinuric medication. An eGFR <90 ml/min per 1.73 m^2 was present in 290 patients (31%), of whom 26 (3%) had an eGFR <60 ml/min per 1.73 m^2 and 10 had received a kidney transplant (1%). In 152 (16%) and 15 (2%) patients,



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.

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]

the reduced eGFR was the only indicator of any and severe kidney injury, respectively. Any and severe proteinuria were diagnosed in 68 (7%) and 20 (2%) patients, respectively. An overview of all combinations of injury is provided in Supplementary Table S1, and data regarding the missingness of outcomes are provided in Supplementary Table S2.

The proportion of patients without kidney injury decreased steadily with age (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. When restricting to severe injury, these percentages were 39% and 37%, respectively. Similar patterns were observed when including patients with UKA or MCDK only, or patients diagnosed antenatally only (Supplementary Figures S2 and S3). When censoring patients at the date of last follow-up instead of at the end of the study, estimated proportions of patients with kidney injury were 3% to 12% larger (Supplementary Figures S4 and S5).

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 (Table 2). For severe kidney injury, both MCDK and hypodysplasia decreased the risk compared with patients with UKA, whereas severe CAKUT in the SFK, SFK length below the 50th percentile (<p50) at 1 year of age, and especially high BMI were associated with increased risks. We found no indications for time-varying effects of sex and BMI. None of the potential risk factors was associated with kidney injury in the smaller population of patients with acquired SFK (Supplementary Table S3).

In Table 3, risk factors for specific forms of injury (i.e., eGFR <90 ml/min per 1.73 m^2 or hyperfiltration injury [proteinuria, high blood pressure, and/or medication use]) are reported. Female sex, severe CAKUT in the SFK, and smaller SFK length at 1 year were associated with reduced

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.
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]

eGFR, whereas birth weight above the 80th percentile (>p80), MCDK as cause of SFK, and high BMI were associated with hyperfiltration injury only. 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).

The percentage of missing values in our potential risk factors ranged from 0% to 54% (Supplementary Table S5). To assess the potential impact of selective missingness, sensitivity analyses were performed in which missing values were included in the reference category, assuming that abnormal values would have been recorded instead of left out. These analyses indicated that selective missingness did not influence the conclusions (Supplementary Table S6). Restricting analyses to patients with UKA or MCDK revealed similar results (Supplementary Tables S7 and S8).

DISCUSSION

In this cohort of 944 patients with SFK, we found that 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. These findings clearly indicate that SFK is a condition that warrants long-term follow-up.[23] Kidney agenesis, CAKUT in the SFK, and high BMI were associated with increased HRs for kidney injury in children with congenital SFK. We observed that CAKUT in the SFK and smaller SFK length showed strong associations with eGFR <90 ml/min per 1.73 m^2, whereas UKA and high BMI were associated with hyperfiltration injury.

In 2009, Sanna-Cherchi *et al.* were the first to report severe kidney injury in patients with SFK, with up to 30% of patients with SFK showing kidney failure by the age of 30 years.[6]

Others confirmed the possibility of severe outcomes and reported milder forms of kidney injury in 6% to 60% of patients.[1–3,5,6,9–12,24–26] These results were highly dependent on inclusion criteria, follow-up duration, and definition of kidney injury. The heterogeneity in these studies and results led to ongoing discussions on the implications of SFK.[27,28] Herein, we confirm that having an SFK from childhood results in kidney injury in the large majority of patients.

The most common outcome in our cohort was high blood pressure. The prevalence of severe high blood pressure (18%) was similar to that observed previously. In the KIMONO study, 26% of children with SFK had hypertension, diagnosed at a mean age of 5 years.[3] Alfandary *et al.* found that high blood pressure was more common in 17-year-old army recruits with SFK compared with controls (32% vs. 23%), whereas Xu *et al.* found hypertension in 32% of adult patients with UKA at a median age of 32 years.[4,5] In contrast, Marzuillo *et al.* identified only 2 patients with hypertension in their well-characterized cohort of 322 children with antenatally diagnosed SFK, who were followed up for a median duration of 7 years.[1] Similar definitions of hypertension were used, and none of these studies, including our own, used ambulatory blood pressure measurements systematically. Therefore, the low proportion of patients with hypertension in the Italian cohort is most likely caused by differences in study population and follow-up duration. Similar patterns were visible in the rates of proteinuria and reduced eGFR, which were also higher in our study than in the Italian cohort, but lower than in the KIMONO study and the Israeli cohort.[1,3,4]

Others previously identified low birth weight, preterm birth, kidney agenesis, CAKUT in the SFK, recurrent UTI, smaller SFK size, and elevated BMI as risk factors for kidney injury.[1–6,9–12,29] In this study, we confirmed most associations, but not those with UTI or preterm birth. Both low and high birth weight may increase the risk of kidney injury in patients with SFK, but this should be interpreted with caution because effect sizes are relatively small and confidence intervals include 1. We 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.*[29] Because our multivariable model corrects for CAKUT in the SFK and extrarenal anomalies, these factors cannot explain the higher risk for patients with UKA. More likely, etiological differences play a role; agenesis is thought to result from a failed interaction between the ureteric bud and metanephric mesenchyme in early kidney development, whereas MCDK may arise later in development as a consequence of obstruction or abnormal branching of the ureteric bud.[30–32] As such, the SFK remaining after UKA is more likely to have developed suboptimally as well, resulting in a higher risk of injury. It is unclear why hypodysplasia also results in a lower risk; timing during nephrogenesis may play a role, although this warrants further investigation.

Whereas CAKUT in the SFK and smaller SFK size increased the HRs for reduced eGFR, UKA and elevated BMI increased the risk of hyperfiltration injury. We hypothesize that CAKUT in the SFK and smaller SFK size reflect a lower nephron number, leading to lower glomerular filtration rate from birth onwards. Being overweight might immediately increase glomerular filtration pressure, leading to proteinuria and hypertension, but may reduce the glomerular filtration rate after prolonged exposure only. Animal models proved that SFKs are capable of nephron hyperplasia prenatally, with nephron numbers ~70% of those in individuals born with 2 kidneys.[33] Therefore, increased SFK length soon after birth is considered to reflect increased nephron number, whereas absence of compensatory enlargement indicates failed compensatory mechanisms. This does not explain, however, why the HRs for SFK size after 1 year are larger compared with those for SFK size within 90 days. 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). This indicates that the increased HR was likely caused by underestimation of eGFR in girls 5 to 14 years old in the CKiD U25 equation.[19] To our knowledge, our study is the first that indicates differences in risk factors for a reduction in glomerular filtration rate and signs of hyperfiltration injury. Although we grouped hypertension and proteinuria as hyperfiltration injury, we cannot exclude other causes of these outcomes, and some misclassification will have occurred. Nonetheless, our findings illustrate that different pathophysiological mechanisms may play a role and that presence of different combinations of risk factors could lead to different kidney injury trajectories.

As we performed a retrospective study, several limitations should be considered. First, this design could have led to information bias because patients without kidney injury may have been discharged from follow-up earlier. To take this into account, we assumed that all patients received follow-up until study closure. Although this may have resulted in an underestimation of the prevalence of kidney injury, using the actual date of last follow-up likely results in an overestimation of the risk of kidney injury. Furthermore, the 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 excluding patients with congenital heart disease or patients with medication use as only outcome did not change results substantially (Supplementary Table S9). Missing information on risk factors, such as preterm birth, low birth weight, and occurrence of UTI, was a potential limitation, but our study benefitted from the parental questionnaires that were used to complete this information for most patients (~95%). We also performed multiple imputation for missing information to keep all patients in the multivariable analyses and repeated

our analyses in a database in which all missing values were included in the reference category. Reassuringly, our results proved robust even in this scenario.

A major strength of our study is its large cohort size, which is more than twice the size of the largest study on SFK reported so far.[3] This facilitated several secondary analyses and allowed more robust estimation of the long-term prevalence of kidney injury. Last, our broad inclusion criteria and multicenter design, with 7 academic and 29 nonacademic centers participating, prevented inclusion of severely affected patients only and improved generalizability, which was a substantial problem in previous studies.

Our results may have several implications for clinical practice. The high number of patients with kidney injury indicates that all children with an SFK require long-term follow-up.[23] 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.[17] Furthermore, extensive guidelines on prevention and treatment of childhood overweight and obesity are available, such as the staged treatment approach recommended by the American Academy of Pediatrics Expert Committee on Obesity.[34,35] 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.

In conclusion, this study shows that a large proportion of children with SFK will develop kidney injury, for which we identified distinct risk factors that can be used in clinical management. Patients with SFK should be followed up into adulthood, and special attention should be given to overweight as preventable risk factor. Further studies should validate our findings regarding different risk factor patterns for different outcomes and help translation of our findings into individualized care strategies.

APPENDIX

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DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Methods.

Table S1. Combinations of signs of any and severe kidney injury in 944 patients with solitary functioning kidney.

Table S2. Number of missing values for signs of kidney injury, stratified by cause of the solitary functioning kidney.

Table S3. Crude and adjusted hazard ratios for potential risk factors for any and severe kidney injury in children with acquired solitary functioning kidney.

Table S4. Crude and adjusted hazard ratios for potential risk factors for impaired estimated glomerular filtration rate (eGFR; $<$90 ml/min per 1.73 m^2) and hyperfiltration injury (proteinuria, high blood pressure, or antihypertensive medication use) in children with acquired solitary functioning kidney.

Table S5. Number of missing values for potential risk factors for kidney injury, stratified by cause of the solitary functioning kidney.

Table S6. Adjusted hazard ratios for potential risk factors for all outcomes in children with congenital solitary functioning kidney, with missing values classified in the reference category

Table S7. Crude and adjusted hazard ratios for potential risk factors for any and severe kidney injury in children with unilateral kidney agenesis or multicystic kidney dysplasia.

Table S8. Crude and adjusted hazard ratios for potential risk factors for impaired estimated glomerular filtration rate (eGFR; $<$90 ml/min per 1.73 m^2) and hyperfiltration injury (proteinuria, high blood pressure, or antihypertensive medication use) in children with unilateral kidney agenesis or multicystic kidney dysplasia.

Table S9. Cumulative survival without signs of kidney injury at the age of 18 years after exclusion of patients using medication other than renin-angiotensin-aldosterone system inhibitors, patients with congenital heart disease, and patients in whom medication use was the only sign of kidney injury.

Table S10. Comparison of reference values for solitary functioning kidney (SFK) length in the first year of life by Akhavan *et al*[S2] and smoothed reference values for this study.

Figure S1. Flowchart of patient recruitment and number of patients lost to follow-up. Hospitals with active recruitment were hospitals in which patients were approached with information letters via regular post because eligible patients with solitary functioning kidney could be identified from electronic patient records. In hospitals with passive recruitment, information materials were spread among eligible patients by health care providers during regular patient care, but no active case identification was possible. Of the 944 patients from whom clinical information could be obtained, 166 (18%) were followed up until their 17th birthday. Of the 778 patients who did not reach this age before the end of the study, 118 (13% of the total cohort of 944 patients) did not visit the hospital in the last 3 years before study closure and could be classified as lost to follow-up.

Figure S2. Cumulative survival without any kidney injury (blue line) or without severe kidney injury (red line) among children with unilateral kidney agenesis or multicystic kidney dysplasia.

Figure S3. Cumulative survival without any kidney injury (blue line) or without severe kidney injury (red line) among children with antenatally detected congenital solitary functioning kidney.

Figure S4. Sensitivity analysis comparing cumulative survival without kidney injury estimated using the original censoring approach (at study closure or 18th birthday, whichever came first) and an alternative censoring approach (date of last follow-up visit or 18th birthday, whichever came first) in patients with congenital solitary functioning kidney. Original data are depicted in light red (any injury) and light blue (severe injury), and alternative data are depicted in dark red (any injury) and dark blue (severe injury).

Figure S5. Sensitivity analysis comparing cumulative survival without kidney injury estimated using the original censoring approach (at study closure or 18th birthday, whichever came first) and an alternative censoring approach (date of last follow-up visit or 18th birthday, whichever came first) in patients with acquired solitary functioning kidney. Original data are depicted in light red (any injury) and light blue (severe injury), and alternative data are depicted in dark red (any injury) and dark blue (severe injury).

Figure S6. Comparison of reference values for solitary functioning kidney (SFK) length in the first year of life by Akhavan *et al*.[S2] (upper panel) and smoothed reference values for this study (lower panel).

Supplementary References.

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