

Research Article

Chronic Kidney Disease in Adolescents after Surgery for Congenital Heart Disease

Mirela Bojan^a Laurence Pieroni^b Cristian Mirabile^c Marc Froissart^{d, e}
Damien Bonnet^{f, g}

^aDepartment of Anesthesiology, Congenital Cardiac Unit, Marie Lannelongue Hospital, Le Plessis-Robinson, France; ^bDepartment of Biochemistry, Lapeyronie Hospital, Montpellier, France; ^cDepartment of Critical Care, Congenital Cardiac Unit, Marie Lannelongue Hospital, Le Plessis-Robinson, France; ^dClinical Research Center, Lausanne University Hospital, Lausanne, Switzerland; ^eUniversity of Lausanne, Lausanne, Switzerland; ^fPediatric Cardiology, Necker-Enfants Malades Hospital, Paris, France; ^gParis Descartes University, Paris, France

Keywords

Chronic kidney disease · Congenital heart disease · Cardiac surgery

Abstract

Background: The onset of chronic kidney disease (CKD) is an important prognostic factor in young adults with congenital heart disease (CHD). Although it is likely that CKD is manifest early in CHD patients, the prevalence among adolescents is still unknown. The National Kidney Foundation's Kidney Disease Improving Global Outcomes guidelines 2012 recommend new equations for the estimated glomerular filtration rate (eGFR) and highlight the importance of albuminuria for CKD screening. The objective of the present study was to estimate the prevalence of CKD in CHD adolescents. **Methods:** This observational cross-sectional study included 115 patients aged 10–18 years attending the cardiologic outpatient clinic at our institution as a follow-up after cardiac surgery in infancy related to various CHDs. CKD assessment used the CKD criteria 2012, including eGFR equations based on serum creatinine and cystatin C, and measurement of albuminuria. **Results:** No patient had an eGFR $< 60 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$. However, 28.7% of all patients (95% CI 20.7–37.9) had eGFR between 60 and 89 $\text{mL min}^{-1} 1.73 \text{ m}^{-2}$ when estimated by the bedside Schwartz creatinine-based equation, and 17.4% (95% CI 11.2–24.1) had eGFR between 60 and 89 $\text{mL min}^{-1} 1.73 \text{ m}^{-2}$ when estimated by the Zappitelli equation, combining creatinine and cystatin C. Of all patients, 20.0% (95% CI 12.1–26.7) had orthostatic proteinuria, and none had persistent albuminuria. **Conclusions:** There was no evidence of CKD in the present population aged 10–18 years. The significance of an eGFR between 60 and 90 $\text{mL min}^{-1} 1.73 \text{ m}^{-2}$ is not concordant for this age range and requires further investigations.

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Mirela Bojan
Department of Anesthesiology, Congenital Cardiac Unit
Marie Lannelongue Hospital, 133, avenue de la Résistance
FR–92350 Le Plessis-Robinson (France)
m.bojan@hml.fr

Introduction

Renal impairment is an important prognostic factor in patients with chronic heart failure [1, 2] and is a stronger predictor of outcome compared to the left ventricular ejection in acute heart failure patients [3]. Altogether, the pathophysiology of congenital heart diseases (CHDs), exposure to nephrotoxins, and medical and surgical treatments impact on the kidney structure and function and place patients at risk to develop chronic kidney disease (CKD) [4]. Early studies focused on young adults with long-standing cyanotic CHD and reported evidence of glomerular [5–7] and tubular [8, 9] impairment. The study by Dimopoulos et al. [10] was a milestone in the field, reporting significantly impaired renal function in half of a large cohort of young adults with CHD and severely impaired renal function in almost 10%. When compared with the general population, the prevalence of significant renal impairment was 18-fold higher in noncyanotic adult CHD patients, up to 35-fold higher in cyanotic adult CHD patients [10] and significantly higher in patients with palliative surgery. There was an independent association of renal impairment with overall mortality on top of what the functional class and systemic ventricular function explained. The estimated progressive glomerular filtration reduction rate [10] enabled to speculate that evidence of renal impairment could be found at a younger age, an assumption supported by recent reports in patients with the Fontan palliation [11–13]. Nevertheless, the prevalence of CKD in adolescents with CHD is currently not known, and there are consequently no guidelines for clinicians in terms of renal assessment in the long-term follow-up of children with CHD. In this observational study, we estimate the prevalence of kidney impairment among a mixed population of adolescents having undergone reparative or palliative CHD surgery at our institution.

Methods

The study was performed at the Necker-Enfants Malades University Hospital, Paris, after approval by the Ile de France II Regional ethics committee of the Paris Descartes University, France (reference 2008-147). As advised by the ethics committee, written consent was collected from all patients and parents. The study was registered on ClinicalTrials.gov under the reference NCT01845402 (registration on December 11, 2012) and was funded by Assistance Publique – Hôpitaux de Paris (grant AOR10087) and by the Association pour la Recherche en Cardiologie du Foetus à l'Adulte at the Necker-Enfants Malades Hospital, Paris, France.

The study was observational cross-sectional and enrolled patients having undergone surgery for CHD within the first 2 years of life and later followed up at our institution. According to the aim of detecting unrecognized CKD, only patients attending the cardiac outpatient clinic for follow-up and not requiring hospital admission for decompensated CHD were enrolled. Patients with renal abnormalities as part of inherited syndromes were excluded. No patient with Eisenmenger physiology was included.

After providing information and collecting written consent, a nurse measured the patients' height, weight, blood pressure and collected one blood and one urine sample for the purpose of the study. Serum creatinine concentration (SCr) and urine albumin-to-creatinine ratio were measured on the fresh samples. SCr was measured using the IDMS-calibrated Architect c16000 enzymatic assay (Abbott Diagnostics, Abbott Park, IL, USA) [14]. Serum cystatin C concentration (SCysC) was measured on another serum sample stored at -80°C using the Siemens immunonephelometric assay (N Latex Cystatin C, Siemens Healthcare Diagnostics) [15]. Diagnosis and classification of CKD followed the recommendations of the National Kidney Foundation's Kidney Disease Improving Global Outcomes (KDIGO) guidelines 2012 [16]: kidney damage was assessed by albuminuria, expressed as albumin-to-creatinine ratio, and impairment of kidney function by the estimated glomerular filtration rate (eGFR). Two eGFR equations were used, as recommended in the guidelines: the updated bedside Schwartz equation (eGFR_{CKiD}) [17], based on SCr measured by the enzymatic assay, and the Zappitelli equation [18], including SCr and ScysC:

$$\text{updates bedside Schwartz equation: } eGFR_{CKiD} = 0.413 \times \text{height}/SCr \quad (1)$$

$$\text{Zappitelli equation: } eGFR_{ZAP} = (507.76 \times e^{0.003 \times \text{height}})/SCysC^{0.635} \times SCr^{0.547} \quad (2)$$

where eGFR is expressed in $\text{mL min}^{-1} 1.73 \text{ m}^{-2}$, height in cm, SCr in mg dL^{-1} and SCysC in mg L^{-1} . The complete updated Schwartz equation [19] was not used here since its validation relies on a methodologically slightly differing turbidimetric method to measure SCysC. The use of pediatric equations even in the older patients was oriented by the recent literature [20].

Recently, new eGFR equations covering the full age range between young children and adults have been developed, the full age spectrum (FAS) equations, based on either SCr (eGFR FAS_{SCr}) or both SCr and SCysC (eGFR $FAS_{SCr-SCysC}$) [21, 22]. For the age range from 2 to 40 years, the FAS equations are:

$$eGFR_{FAS_{SCr}} = 107.3/(SCr/Q) \quad (3)$$

$$eGFR_{FAS_{SCr-SCysC}} = 107.3/[(SCr/Q) + (SCysC/0.82)] \quad (4)$$

where Q is the average age- and-sex-specific SCr value in healthy populations [22, 23], and 0.82 is the SCysC normalization factor used for children and adults up to 70 years old [22].

According to KDIGO criteria 2012, the CKD definition required an A2 (albumin-to-creatinine ratio: 3–30 mg mmol^{-1}) or A3 (albumin-to-creatinine ratio $>30 \text{ mg mmol}^{-1}$) albuminuria category, and/or a G3 eGFR category ($<60 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$) or higher. The protocol provided a second assessment in patients in whom the results showed evidence of CKD. In the case of isolated significant albuminuria, the patients were asked to send by mail a first-morning urine sample to exclude orthostatic proteinuria. In case of impossibility to contact a patient requiring a second assessment (unreachable through mail, e-mail or telephone), he or she was excluded from the analysis.

Statistical Analysis

The number of patients to be included was estimated at 400 in order to accurately identify a prevalence of 5 with a 2% precision. After the inclusion of the first 120 patients, the protocol stipulated an interim analysis. The present work shows the results of the per-protocol interim analysis, which resulted in the discontinuation of the study. Baseline and follow-up characteristics are shown using means and SDs, medians and ranges, numbers and proportions. All 95% CIs were estimated using bootstrapping with 2,000 resamples. The distribution of SCr, SCysC and eGFR for the study population was contrasted with the distribution of the same parameters for the general population. In order to do so, SCr, SCysC and eGFR results were dichotomized as 1st, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 90th percentiles following the distribution pattern in the published report from a subgroup of adolescents of the National Health and Nutrition Examination Survey (NHANES) [24]. Statistical analysis employed the basic package of the R software version 2.10.1 for Windows (www.r-project.org) and the “boot” package.

Results

Overall, 120 patients attending the cardiac outpatient clinic of the Necker-Enfants Malades University Hospital, Paris, were enrolled between April 1, 2013, and July 1, 2015. Two patients did not provide any urine sample, another 2 patients were lost during follow-up, and 1 patient had a known kidney malformation and was not eligible, leaving 115 patients for analysis. Patients’ characteristics at baseline, surgical details and follow-up parameters are shown in Table 1. Overall, 24 patients have had surgery for transposition of the great arteries, 23 for tetralogy of Fallot, 12 had reconstruction of the aortic arch and ventricular septal defect closure, 10 had complex CHD and underwent the Fontan palliation, 6 had reparative surgery for malposition of the great arteries and pulmonary stenosis, 6 had ventricular septal defect closure, 4 had total anomalous pulmonary venous connection repair, 4 had repair of abnormal left coronary artery from pulmonary artery, 2 had atrio-ventricular defect repair, and 19 had other CHDs which had required surgical repair with cardiopulmonary bypass. Another 5 patients underwent coarctation of the aorta repair within the first few weeks of age, which did not require cardiopulmonary bypass. One

Table 1. Baseline, surgical and follow-up characteristics of the study population

Variable	Mean ± SD
Age, years	14.3±2.1
Weight, kg	48.9±13.0
Height, cm	157.69±12.18
Body mass index weight category	
Underweight, <i>n</i> (%)	56 (0.47)
Healthy, <i>n</i> (%)	52 (0.45)
Overweight, <i>n</i> (%)	5 (0.04)
Obesity, <i>n</i> (%)	2 (0.02)
Males	55 (0.48)
Surgical repair requiring cardiopulmonary bypass, <i>n</i> (%)	110 (0.96)
Number of surgeries requiring cardiopulmonary bypass/patient	1.46±0.85
Reparative/palliative surgery during infancy	99/16
Number of angiographies during follow-up/patient (median, range)	1 [0–2]
Serum creatinine, mg dL ⁻¹	0.66±0.14
Serum cystatin C, mg L ⁻¹	0.78±0.09
Urine albumin-to-creatinine ratio (median, range), mg mmol ⁻¹	0.8 [0.5–1.9]
Systolic blood pressure, mm Hg	114.8±11.7
Diastolic blood pressure, mm Hg	64.8±7.7

Data are shown as means ± SD, numbers and percentages, or medians and interquartile ranges.

patient had reoperation for Fontan palliation within a year after inclusion and died postoperatively.

The baseline, surgical and follow-up characteristics of the study population are shown in Table 1. The percentile distribution of SCr, SCysC and eGFR in the present cohort using the 4 eGFR equations and comparatively in the NHANES [24] are shown in Table 2. None of our patients had eGFR <60 mL min⁻¹ 1.73 m⁻² with any formula. The number of patients with eGFR between 60 and 89 mL min⁻¹ 1.73 m⁻² was 33 (29.6%; 95% CI 20.7–37.9) when assessed with eGFR_{CKiD}. When assessed with eGFR_{ZAP}, 20 patients had eGFR between 60 and 89 mL min⁻¹ 1.73 m⁻² (17.4%; 95% CI 11.2–24.1). When assessed with the new eGFR FAS_{SCr} and eGFR FAS_{SCr-SCysC} formulas, the number of patients who had eGFR between 60 and 89 mL min⁻¹ 1.73 m⁻² was 19 (16.5%; 95% CI 10.3–23.3) and 8 (6.9%; 95% CI 2.7–12.5), respectively. All the other patients had eGFR ≥90 mL min⁻¹ 1.73 m⁻². A 12-year-old boy with Fontan palliation was found with glomerular hyperfiltration (eGFR_{ZAP} = 156 mL min⁻¹ 1.73 m⁻²) but no albuminuria. All of the patients with missing SCysC measurements had eGFR_{CKiD} >90 mL min⁻¹ 1.73 m⁻². Based on GFR categories, no patient had evidence of CKD.

In total, 23 (20%) of all patients were found with significant albuminuria at the first assessment: 22 patients had A2 albuminuria category and 1 patient had A3 (albumin-to-creatinine ratio of 33.6 mg mmol⁻¹). None of these patients had significant albuminuria when analyses were repeated on a first-morning urine sample: all of these cases were categorized as orthostatic proteinuria. As such, the overall prevalence of orthostatic proteinuria in the present population was 20.0% (95% CI 12.1–26.7), i.e. it was 14.5% (95% CI 7.4–23.5) in males and 25.0% (95% CI 14.6–37.5) in females. Based on albuminuria categories, no patient had evidence of CKD. The distribution of the CKD risk categories when following the KDIGO criteria [16] is shown in Figure 1 (eGFR was assessed using both eGFR_{CKiD} and eGFR_{ZAP}).

No association was found between eGFR and the number of surgeries with cardiopulmonary bypass, the type of surgery (whether reparative or palliative) and the number of

Table 2. Percentile distribution (1st to 99th) of creatinine, cystatin C and eGFR in adolescents aged 12–17 years, enrolled in the National Health and Nutrition Examination Survey (NHANES) 1999–2002 and in the present population

	1st	5th	10th	25th	50th	75th	90th	95th	99th
<i>NHANES cohort</i>									
Serum creatinine concentration, mL dL ⁻¹	0.5	0.5	0.6	0.6	0.7	0.8	0.9	1	1.1
Serum cystatin C concentration, mg L ⁻¹	0.57	0.65	0.68	0.75	0.83	0.91	1.01	1.06	1.21
eGFR, mL min ⁻¹ 1.73 m ⁻²									
eGFR according to the bedside Schwartz equation	62.9	71.1	75.6	84.4	96.6	108.8	122.1	131.6	149.1
eGFR according to the Zappitelli equation	69.0	74.8	78.5	87.2	97.6	110.0	119.1	126.8	140.2
<i>Present cohort</i>									
Serum creatinine concentration, mL dL ⁻¹	0.41	0.47	0.51	0.56	0.62	0.76	0.85	0.94	0.96
Serum cystatin C concentration, mg L ⁻¹	0.58	0.64	0.67	0.71	0.77	0.84	0.91	0.94	0.98
eGFR, mL min ⁻¹ 1.73 m ⁻²									
eGFR according to the bedside Schwartz equation	73.2	77.3	82.5	87.4	99.4	113.0	125.8	129.6	146.9
eGFR according to the Zappitelli equation	79.5	83.1	86.5	96.5	105.1	115.3	124.1	130.0	142.7
eGFR FAS _{SCr}	76.1	80.3	85.0	93.5	102.4	117.1	130.0	139.7	148.7
eGFR FAS _{SCr-SCysC}	85.2	88.6	92.9	101.8	108.6	116.3	124.9	128.3	136.9

In the NHANES cohort [26], creatinine concentration measurement used the Jaffe reaction, with a correction equation applied to standardize according to the enzymatic assay between 1999 and 2000. Cystatin C concentration measurement used the immunonephelometric assay. Both creatinine and cystatin C concentrations measured in the present population were below the concentrations reported in a general population of adolescents in the NHANES cohort [26], and the GFR estimations using all formulas in the present population were higher. eGFR, estimated glomerular filtration rate; eGFR FAS_{SCr}, serum creatinine-based full age spectrum eGFR; eGFR FAS_{SCr-SCysC}, serum creatinine- and serum cystatin C-based full age spectrum eGFR.

Fig. 1. The distribution of the chronic kidney disease risk categories when following the recommendations of the National Kidney Foundation’s Kidney Disease Improving Global Outcomes (KDIGO) guidelines 2012 [16]. Kidney damage was assessed by albuminuria, expressed as albumin-to-creatinine ratio, and impairment of kidney function by the estimated glomerular filtration rate (eGFR). eGFR was assessed using both eGFR_{CKiD} and eGFR_{ZAP}.

KDIGO criteria 2012		Albuminuria (mg mmol ⁻¹ creatinine)			
		A1 (<3)	A2 (3–30)	A3 (>30)	Total
Glomerular filtration rate (mL min ⁻¹ 1.73 m ⁻²)	G1 (>90)	82–95	0	0	82–95 (71.3–82.6%)
	G2 (60–90)	20–33	0	0	20–33 (17.4–28.7%)
	G3 (45–60)	0	0	0	0
	Total	115 (100%)	0	0	115

■ Low risk ■ Moderately increased risk ■ High risk ■ Very high risk

Color version available online

angiographies during follow-up. We elected not to present data on ventricular ejection fraction because of the inherent difficulties and limitations of such a measure in patients with a variety of systemic ventricles.

Discussion

In the present population aged 10–18 years, having undergone congenital cardiac disease surgery during infancy, we did not identify clear evidence of CKD. However, no patient with Eisenmenger syndrome was analyzed. According to eGFR formulas that have been used,

7.1–29.6% of the cohort had an eGFR $<90 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$. Overall, 20.0% of the patients had orthostatic proteinuria, and none had persistent albuminuria.

Few publications reported renal outcomes in children having undergone CHD surgery. The study by Dimopoulos et al. [10] reported results from a mixed cohort and focused on adults with grown-up congenital diseases: GFR was mildly decreased ($60\text{--}90 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$) in 41% of patients and moderately to severely decreased ($<60 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$) in 9%. Interestingly, the estimated GFR reduction for a 10-year increase in age was $8.3 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$. If the progression of GFR was constant over decades, knowing that the mean age was 36 years in the study by Dimopoulos et al. [10], one would expect to find evidence of CKD in at least 9% of a population of CHD patients on average 16 years old.

Recent studies reported a prevalence of CKD reaching 18% in various populations having undergone cardiac surgery during infancy [12, 13, 25, 26]. Beyond differences in age, there were differences in the definition of CKD among the studies. For the 131 children included in the TRIBE-AKI collaboration cohort, Greenberg et al. [25] reported 18% prevalence of eGFR $<90 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ and/or microalbuminuria at the 5-year follow-up (median 7.7 years of age). Using Canadian administrative health care databases, Parikh et al. [26] reported a 1% prevalence of end-stage kidney disease in patients having undergone surgery within 10 years of birth and for a median 5.9 years of follow-up. Following the Fontan palliation, eGFR was found to be $<80 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ in 8% of patients within 1 year of palliation [12], and this was $<90 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ in 10% of patients reaching the age of 13 years [13]. In the present population on average 14.3 ± 2.1 years old, about 7–30% of the patients had eGFR $<90 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$, and none had eGFR $<60 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$. The use of the new CKD eGFR threshold, i.e. $<60 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$, is likely to explain the difference observed between our findings and previous reports.

The international pediatric nephrology community has embraced the recently updated adult KDIGO staging system [27] in children over the age of 2 years. Accordingly, an eGFR between 60 and $90 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ does not imply a decrease in kidney function and is not evidence of CKD. Indeed, when applied to the NHANES cohort, the above-mentioned eGFR formulas resulted in a proportion of adolescents with eGFR $<90 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ of over 25% [24, 28]. None of the participants with eGFR <10 th percentile ($75.6 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ for the bedside Schwartz equation and $78.5 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ for the Zappitelli equation) had an increased prevalence of comorbid conditions consistent with CKD in the NHANES cohort [24, 28]. Given the rarity of CKD in the general pediatric population, and as morbidities that commonly associate with CKD were not more prevalent among those with lower eGFRs, it can be safely assumed that most had a normal kidney function. On the other hand, the prevalence of eGFR $<90 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ in the present population is similar to that reported previously [12, 13, 25]. The large percentage of underweight patients and a very low percentage of overweight and obese patients in the present cohort could have biased the interpretation of SCr-based eGFR by overestimating GFR, when compared with the NHANES cohort [24] (47% underweight patients here vs. 3.3% in NHANES, 4 vs. 14.9% overweight and 2 vs. 17% obese, respectively). However, the conclusions were similar when using SCysC-based eGFR equations, not influenced by the body mass.

Children with eGFR $<60 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ are likely to have either structural abnormalities or advanced renal damage, and it is unlikely that isolated reduction in GFR would occur as in older adults [27]. Because of acknowledged associations with a higher risk of all-cause mortality in the general population [29], an eGFR $<60 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ for >3 months was chosen in the KDIGO guidelines 2012 to indicate CKD in children older than 2 years. However, when eGFR is $60 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$, this level is almost half of the normal GFR in children, thought to be of approximately $110 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ [30], and is less than half of that in young adults, of approximately $125 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$. When reporting results from the Groeninge Hospital cohort, Pottel et al. [31] concluded that eGFR values below 75 mL min^{-1}

1.73 m⁻² were abnormal in children and adolescents. Therefore, recent studies in children and adolescents with CHD continue to report CKD on the basis of a decrease in eGFR below 90 mL min⁻¹ 1.73 m⁻² [12, 13]. Further research is needed to clarify whether adolescents with eGFR between 60 and 90 mL min⁻¹ 1.73 m⁻² require a specific renal follow-up.

The KDIGO guidelines 2012 highlight the importance of albuminuria in the definition and staging of CKD [27]. Albuminuria is the earliest marker of glomerular disease and has been shown to be the most important independent predictor of decline in GFR in children with CKD older than 2 years [32]. Wong et al. [33] demonstrated that an average 10% decline in GFR was independently associated with a 14% increase in proteinuria in children. According to the KDIGO guidelines 2012, an albumin-to-creatinine ratio >3 mg mmol⁻¹ is a sign of kidney damage and defines CKD if persistent for more than 3 months [27]. The interpretation of what was known as microalbuminuria (albumin-to-creatinine ratio of 3–30 mg mmol⁻¹) is, nevertheless, delicate, since healthy individuals may express such an albumin excretion rate [34]. The estimated prevalence of orthostatic proteinuria in the present population was 20.0% (95% CI 12.1–26.7), 14.5% (95% CI 7.4–23.5) in males and 25.0% (95% CI 14.6–37.5) in females. This prevalence was higher than the prevalence of microalbuminuria reported in the healthy subgroup of the NHANES cohort [34], which was 6.2% in males and 13.4% in females. However, no evidence to date relates orthostatic proteinuria to kidney damage, and we could not identify evidence of CKD based on albuminuria in the present population.

Limitations

Over a decade, both SCr measurement technique and eGFR formulas as well as interpretation of the eGFR values changed, which makes it difficult to compare our findings with the previous literature. SCr and SCysC values were obtained at a single time point, and we were not able to comment on the risk of CKD over time in this cohort. Patients with Eisenmenger syndrome, known to have a high prevalence of CKD during adulthood, have not been included. Due to the limited size population of patients, no CKD risk factor was identified.

Conclusions

There was no evidence of CKD in this observational cross-sectional study of patients aged 10–18 years, having undergone congenital cardiac disease surgery during infancy. The population did not include patients with Eisenmenger syndrome. The significance of an eGFR between 60 and 90 mL min⁻¹ 1.73 m⁻², found in 7.1–29.6% of the cohort (according to the eGFR formula that has been used), is, nevertheless, not concordant for this age range and requires further investigations.

Acknowledgments

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Statement of Ethics

The study was conducted after having been approved by the Ile de France II Regional ethics committee of the Paris Descartes University, France (approval reference 2008-147). Written consent to participate in the study was collected from all patients and parents.

Disclosure Statement

The authors have no conflict of interest to declare.

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