

Epidemiology of Chronic Renal Failure in Children: Data From the Italkid Project

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ABSTRACT. *Objective.* The Italkid Project is a prospective, population-based registry that was started in 1990 with the aim of assessing the epidemiology of childhood chronic renal failure (CRF), describing the natural history of the disease, and identifying factors that influence its course. This article reports the epidemiologic results.

Methods. Prevalent and incident cases of CRF in children and adolescents were identified throughout Italy (total population base: 16.8 million children) by regularly asking all of the pediatric hospitals and adult nephrology units potentially involved in caring for children with kidney disease to report all cases that meet the inclusion criteria and then to update the clinical information regarding all previously reported patients on an annual basis. The inclusion criteria were 1) creatinine clearance (Ccr; according to Schwartz's formula) <75 mL/min/1.73m² bsa (predialysis) and 2) an age of <20 years at the time of registration.

Results. By December 31, 2000, 1197 patients (803 boys) had been registered. The mean incidence was 12.1 cases per million (range: 8.8–13.9), and the (point) prevalence was 74.7 per million of the age-related population. The mean age at registration was 6.9 ± 5.4 years, and the mean Ccr was 41.7 ± 20.5 mL/min/1.73 m². The leading causes of CRF were hypodysplasia associated with urinary tract malformations (53.6%) and isolated hypodysplasia (13.9%), whereas glomerular disease accounted for as few as 6.8%. Hypodysplasia associated with primary vesicoureteral reflux (VUR) alone was responsible for as many as 25.8% of the cases, thus being the leading single cause with a female-to-male ratio of 1:3.2. The diagnosis of VUR was established early in life at an overall median age of 3 months (range: 0–180). However, the diagnosis was made significantly later among girls, whose median age at diagnosis was 9 months (range: 0–156; 95% confidence interval: 21.2–49.3) as against 2 months among boys (range: 0–180; 95% confidence interval: 10.9–21.2). As many as 23.6% of the registered patients had at least 1 severe associated disease (excluding urological abnormalities). A steep decline in renal survival occurred during puberty and early postpuberty, leading almost 70% of the patients to end-stage renal failure by the age of 20 years. When the population was subdivided on the basis

of Ccr at the time of registration, the probability of kidney survival at 20 years of age was significantly different, being 63% in patients with mild renal failure (Ccr 51–75 mL/min), 30% in those with moderate renal failure (Ccr 25–50 mL/min), and 3% in those with severe renal failure (Ccr <25 mL/min). The incidence of renal replacement therapy was 7.3/y/100 patients, and the case-fatality rate on conservative treatment was 1.41%.

Conclusions. This study provides important and recent epidemiologic information concerning CRF in children and adolescents: a mean annual incidence of 12.1 new patients per million of the age-related population with a very high proportion (57.6%) of hypodysplastic renal diseases with or without urinary tract malformation. By the age of 20 years, the cumulative probability of end-stage renal disease in the population as a whole was 68%. The probability of kidney survival sharply declined during puberty and early postpuberty. This is the first prospective evaluation of the incidence and outcome of CRF in children, including those with mild and moderate renal impairment. *Pediatrics* 2003;111:e382–e387. URL: <http://www.pediatrics.org/cgi/content/full/111/4/e382>; kidney disease, renal failure, children, adolescents, epidemiology, vesicoureteral reflux.

ABBREVIATIONS. CRF, chronic renal failure; ESRD, end-stage renal disease; NCC, national coordinating center; Ccr, creatinine clearance; sCr, serum creatinine; marp, million of the age-related population; VUR, vesicoureteral reflux; RRT, renal replacement therapy.

The epidemiologic information concerning chronic renal failure (CRF) in children is scanty, particularly with regard to the less advanced stages of renal impairment that are potentially more susceptible to therapeutic interventions aimed at changing the course of the disease and avoiding end-stage renal disease (ESRD). The existing studies concentrate on the late and more severe stages of renal impairment^{1,2} or are not population-based in nature,³ and some methodologically well-designed childhood CRF registries have the major limitation of being restricted to small reference populations.^{4–6}

The lack of population-based information means that the epidemiology of childhood CRF is often based on renal replacement therapy data,⁷ but the vast majority of children with renal impairment (particularly congenital abnormalities) reach ESRD when they are far beyond pediatric age and are therefore not included.

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For providing current and reliable information concerning the epidemiology of CRF in children, a prospective population-based registry was established in Italy in 1990 (the Italkid Project) with the main aims of developing a standard protocol for the prospective surveillance of childhood CRF and describing the natural history of the disease and the factors that influence its course. This article describes the Italkid Project and reports the basic epidemiologic results of the first 10 years of registry activity.

METHODS

Organizational Structure of the Italkid Project

The Unit of Pediatric Nephrology, Dialysis and Transplantation in Milan acts as the national coordinating center (NCC) for the Italkid Project. It developed the study standards, processes the data, and coordinates their analysis with the assistance of the Scientific Committee.

Each of the 21 regions in Italy has a regional coordinating center and a regional principal investigator responsible for coordinating regional registry activities. At least 1 local investigator has been identified in each center potentially involved in caring for children with kidney diseases and is responsible for reporting all of the cases that meet the inclusion criteria at his or her unit and providing the relevant follow-up information.

Study Area and Population

A pilot registration study was started in 2 administratively and demographically well-defined regions in Italy (Lombardy and Piedmont) in 1990, and by 1995, the Registry had been extended to cover the entire country, which has a total population base of 16.8 million children and a general population of 56.6 million inhabitants.⁸ One of the first responsibilities of the regional coordinating centers was to identify and contact all of the units in the region that might have cared for children who meet the inclusion criteria. The first contact was made by means of a standard letter mailed to the head of the unit, which presented the objectives and methods of the initiative and included registration forms. All of the Italian centers potentially involved in caring for children and adolescents with renal diseases (pediatric, pediatric nephrology, pediatric urology, pediatric surgery, and adult nephrology units) were invited to report index cases.

Inclusion Criteria and Reporting Procedures

The index cases were defined using the following criteria: 1) creatinine clearance (Ccr) according to Schwartz's formula of $<75 \text{ mL/min/1.73 m}^2 \text{ bsa (predialysis)}$ ⁹; for children aged younger than 1 year, the registration forms included a table of age- and gender-specific limits for serum creatinine (sCr): mean sCr + 3 SD; and 2) age younger than 20 years at the time of registration (the age limit was 15 years until 1997).

New cases were reported using a standardized registration form containing the inclusion criteria, Schwartz's formula, and a predefined list of diagnoses to ensure a uniform diagnostic approach. The data required for each case included name, date of birth, gender, residence, primary renal diagnosis and associated diseases, and height and sCr at the time of registration. Once a patient had been registered, a named patient form was issued every year by the NCC and sent to the reporting center for completion to update the clinical and biochemical data. The follow-up form required the following information: weight, height, blood pressure, sCr, urea, calcium, inorganic phosphorus, bicarbonate, plasma parathyroid hormone, urinary proteins, urinary creatinine, and the prescribed treatment. The follow-up data referred to the last visit before December 31 of each year until the patient entered a renal replacement program. Between 1995 and 1997, a special survey was also made of the registered patients with a diagnosis of hypodysplasia associated with urological malformations to collect information regarding age at first diagnosis of the uropathy. This was done by adding an extra question to the follow-up form of index cases.

A total of 112 centers have so far reported cases that have been registered. The patients (if aged >18 years) or 1 parent were

required to give written informed consent to data collection, reporting, and storage.

Data Quality Control

The reported cases that did not meet the Ccr criteria at the first 2 subsequent determinations were not registered. A follow-up form requesting updated clinical and biochemical data were issued yearly by the NCC for each registered patient and contained patient identity data (name, date of birth, gender, diagnosis). This allowed the reporting center to check for any previous incorrect reporting, thus increasing the accuracy of the stored data and enhancing the likelihood that the follow-up data would be reported. During the first 10 years of registry activity, 110 (9.2%) patients were lost to follow-up. A fixed series of internal validity checks were made at the end of each year, and any inconsistencies were discussed with the reporting center.

In 1999, a survey aimed at verifying the accuracy of the epidemiologic data available in the Italkid Project database was undertaken using the capture-recapture method. A random sample of primary health care (family) pediatricians ($n = 100$, caring for a total of 80 000 children) were used as the independent information source and asked to report all of their patients with renal failure. Eighty-nine percent of the sampled physicians completed the questionnaire. The survey did not identify any patient other than those already identified by means of the primary information source.

A quality control survey involving a sample of 20% of the participating centers' laboratories (covering $>80\%$ of the registered patients) was conducted to ensure that the definition of CRF based on locally determined sCr levels was reliable. Three human serum samples taken from pools of sera in the normal, high, and very high sCr ranges were sent to the selected laboratories. At sCr levels of 0.86, 1.95, and 3.44 mg/dL, the observed coefficients of variation were respectively 13.0%, 7.6%, and 6.0%.

Statistical Methods

Morbidity rates were based on the data from the 2 regions (Lombardy and Piedmont) in which the surveillance system has been active since 1990. The incidence rate was calculated as the incidence per calendar year and per million individuals at risk. The given incidence refers to the mean figure of the last 5 years after a stable incidence had been reached. The prevalence rate is the point prevalence on December 31, 2000, per million individuals at risk.

The estimated number of people "at risk" for the morbidity analysis was derived from the 1991 Census⁸ of individuals who were younger than 20 years and residing in the study area, which was geographically defined to correspond with administrative and census boundaries. Renal survival was analyzed using Kaplan-Meier life tables.

RESULTS

During the first 10 years, 1197 patients have been registered. The mean incidence during the last 5 years (1995–2000) was 12.1 cases per year per million of the age-related population (marp; range: 8.8–13.9). The point prevalence as of January 1, 2001 was 74.7 per marp. The male/female ratio was 2.03 for the population as a whole and 1.72 when the patients with posterior urethral valves were excluded. The mean age at registration was 6.9 ± 5.4 years, and the mean Ccr at registration was $41.7 \pm 20.5 \text{ mL/min/1.73 m}^2$.

Table 1 shows the primary renal disease responsible for CRF in the overall population and in the patients who reached ESRD during the follow-up. Hypodysplasia with or without urological malformations accounted for as many as 57.6% of all cases, whereas glomerular disease was a much less important cause (6.8%). Table 2 shows the urinary tract malformations associated with hypodysplasia. Hypodysplasia associated with primary vesicoureteral

TABLE 1. Primary Cause of CRF in Children*

	All Registered Patients		Patients Reaching ESRD	
	No.	%	No.	%
Hypodysplasia				
With identified uropathy	522	43.6	71	27.1
Without urinary tract malformations	167	13.9	33	12.5
Neurogenic bladder	44	3.7	8	3.0
Chronic glomerulonephritis†	31	2.6	16	6.1
Focal glomerulosclerosis	21	1.8	12	4.6
Congenital nephrotic syndrome	13	1.1	5	1.9
Membranous nephropathy	3	0.3	2	0.8
Systemic lupus erythematosus	13	1.1	5	1.9
Hemolytic uremic syndrome	43	3.6	9	3.4
Polycystic kidney disease	60	5.0	9	3.4
Nephronophthysis	41	3.4	21	8.0
Alport's syndrome	18	1.5	9	3.4
Cystinosis	22	1.8	9	3.4
Hereditary nephropathies‡	45	3.8	13	4.9
Cortical necrosis (perinatal)	49	4.1	8	3.0
Medications	14	1.2	2	0.8
Idiopathic interstitial nephritis	24	2.0	9	3.4
Wilms' tumour	4	0.3	3	1.1
Miscellaneous non-hereditary diseases	23	1.9	8	3.0
Unknown	40	3.3	11	4.3

* Including monolateral renal agenesis (65), nephrectomy (30), and multicystic kidney (25).

† Including unlisted systemic immunological diseases.

‡ Other than those individually listed.

TABLE 2. Urinary Tract Malformations Associated With Hypodysplasia in Children With CRF*

Urinary Malformation	No.	%
Vesicoureteral reflux	309	59.2
Posterior urethral valves	124	23.8
Urethral hypoplasia/atresia	12	2.3
Ureteropelvic junction stenosis	19	3.6
Obstructive megaureter	18	3.5
Ureterocele	9	1.7
Duplication of collection system	8	1.5
Other complex uropathies†	23	4.4

* Including monolateral renal agenesis (38), nephrectomy (19), and multicystic kidney (15).

† Including prune-belly syndrome (6).

reflux (VUR) alone accounted for as many as 25.8% of the cases and proved to be the first single cause of childhood and adolescent CRF. The female-to-male ratio of the patients with VUR was 1:3.2.

In the population as a whole, 5.4% of the patients were affected by monolateral renal agenesis, but it was more frequent in the 2 diagnostic groups of isolated hypodysplasia (12.7%) and hypodysplasia with VUR (9.8%); the prevalence of this condition in the patients with posterior urethral valves was only 0.8%.

The special survey conducted in 1995–1997 to collect information regarding age at VUR diagnosis provided data relating to 187 patients (144 boys and 43 girls). Figure 1 shows the cumulative percentage of such patients by age and gender. The diagnosis was established early in life at an overall median age of 3 months (range: 0–180). However, the diagnosis was made significantly later among girls, whose median age at diagnosis was 9 months (range: 0–156; 95% confidence interval: 21.2–49.3) as against 2 months among boys (range: 0–180; 95% confidence interval: 10.9–21.2).

As many as 23.6% of the children had a severe disease associated with renal insufficiency. The most prevalent comorbidities were those involving the central nervous system (4.2%) and metabolic disorders (3.1%).

During the first 10 years of the surveillance system, a total of 263 patients (162 boys) started renal replacement therapy (RRT). The relative distribution of primary renal diseases is substantially different when the analysis is restricted to the patients who reached ESRD (Table 1): the relative percentage of glomerular diseases increases from 6.8% (overall population) to 15.2%, and that of hypodysplasia consequently decreases from 57.6% to 39.5%.

The incidence of RRT was 7.3/y/100 patients. In the population as a whole, the risk of developing ESRD by the age of 20 years was 68% (Fig 2). The probability of kidney survival does not decrease linearly with age, as there is a sharp decline during puberty and early postpuberty. When the population was subdivided on the basis of Ccr levels at the time of registration, the probability of kidney survival at 20 years of age was significantly different, being 63% in the patients with mild renal failure (Ccr 51–75 mL/min), 30% in those with moderate renal failure (Ccr 25–50 mL/min), and 3% in those with severe renal failure (Ccr <25 mL/min). Sixteen children died on conservative treatment, leading to a case-fatality rate of 1.41%.

DISCUSSION

This study provides the first prospective evaluation of the incidence of CRF in children and adolescents, including those with less severe degrees of renal impairment (Ccr <75 mL/min/1.73m²). Previous studies attempting to describe the epidemiology of renal insufficiency in children have provided mor-

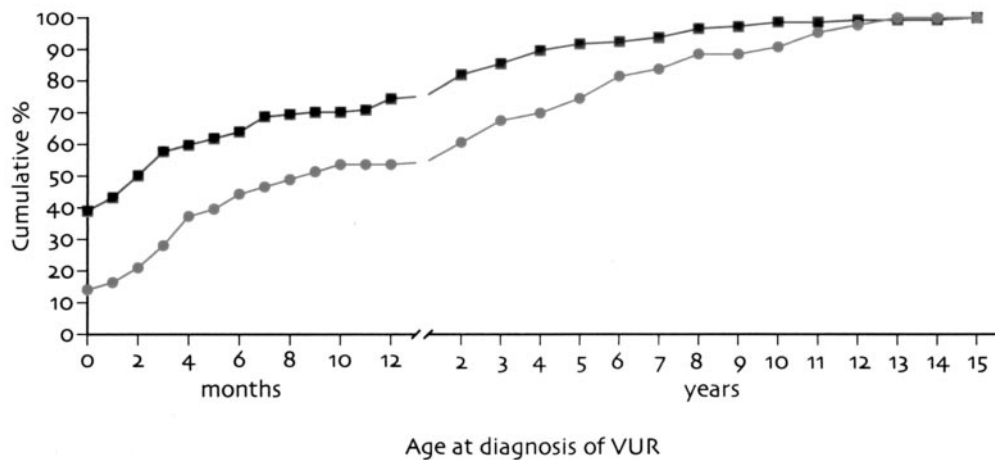


Fig 1. Age at diagnosis of urinary tract malformations in children with CRF as a result of hypodysplasia and VUR by gender. Boys ($n = 144$; —■—); girls ($n = 43$; —●—).

bidity figures but, as they were sometimes more like multicenter investigations than population-based registry studies³ or concentrated on more severe degrees of renal insufficiency,^{1,2} have offered an incomplete picture.

These methodological differences alone may explain why the incidence rate estimated in our study (12.1 per marp) is higher than that reported in the few other areas of the world where it has been studied. We believe that the extensive case definition used by the Italkid Project probably makes our figures closer to the true morbidity rate than any of the previously reported figures. The incidence rate in Lorraine (France) was estimated as 10.5 per marp, but the case definition included only patients with severe renal impairment,⁵ and the same is true for the investigations undertaken in Sweden, where the incidence rate of CRF with Ccr levels of <30 mL/min/ 1.73 m² was estimated as being 7.7 per marp.^{4,6} Unfortunately, methodological differences in case definitions and disease classifications make it difficult to compare studies of the epidemiology of CRF in young populations in different geographical areas. A consensus conference on the basic methodological approach to renal registry keeping is critically needed and should be included among the priorities in the agenda of the international pediatric nephrology scientific community.

An additional consequence of the different methods is that the relative percentages of the causes of CRF in children and adolescents are strikingly different depending on the information source. It has previously been reported that glomerular diseases account for $>20\%$ of pediatric patients with ESRD,⁷ as against the $<7\%$ found in the present study of patients with preterminal renal failure. This discrepancy is probably attributable to the low rate of progression of hypodysplasia, which means that patients may reach ESRD when they are far beyond pediatric age. This can be clearly seen by comparing the relative percentages of the overall causes of CRF with those referring to patients who reached ESRD (Table 1): the relative percentage of glomerular disease increases from 6.8% in the overall population to

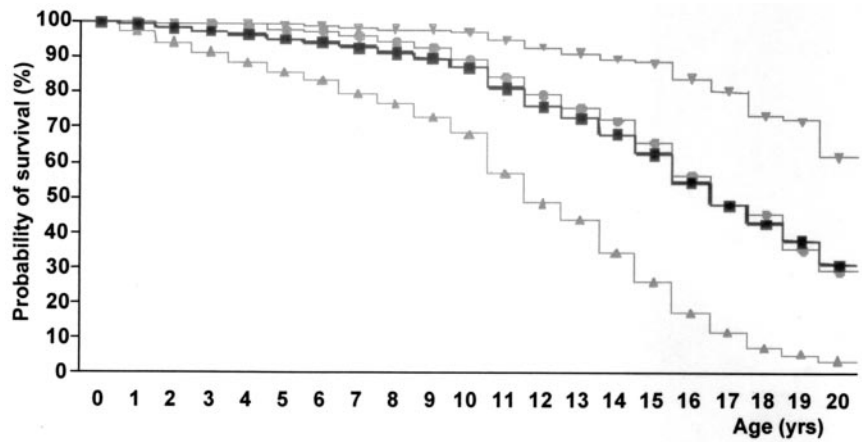
15.2%, and that of hypodysplasia consequently decreases to from 57.6% to 39.5%. It therefore seems to be very important that registries of children with renal impairment continue the follow-up into young adulthood (with the necessary cooperation of adult nephrologists) to ensure the availability of complete information concerning final outcomes. We expect that the Italkid Project (which prolongs the follow-up until the beginning of RRT or death) will ultimately provide important information concerning the final outcome of patients who develop renal insufficiency during the first 2 decades of life.

Hypodysplasia associated with VUR is confirmed as being the most important single cause of childhood CRF (25.8%). On the basis of the very early age of VUR diagnosis in this population already affected by CRF (a median of 3 months; Fig 1), and as is increasingly being accepted,^{10–12} it can be speculated that renal insufficiency is more likely to be congenital than acquired as a result of recurrent urinary tract infections and scarring.

Furthermore, it is widely known that the female-to-male ratio (4:1) in the population of VUR patients without CRF¹³ is the opposite of that observed in our study (1:3.2), thus making it unlikely that patients with VUR and CRF simply come from the universe of patients with VUR as a result of recurrent urinary tract infections. For these reasons, we have here preferred to refer to hypodysplasia associated with VUR rather than reflux nephropathy, which suggests a cause-effect relationship between the reflux and the kidney disease. That isolated hypodysplasia and hypodysplasia associated with VUR share an uncommonly high prevalence of associated monolateral renal agenesis (not found in any other diagnostic group) supports the hypothesis that the 2 conditions may be related to similar developmental factors (congenital anomalies of the kidney and urinary tract).^{14,15}

The observation that almost 70% of CRF patients reach ESRD by 20 years of age is potentially relevant to health care planning. It is not surprising that the probability of kidney survival decreases with the decrease of Ccr levels at the beginning of follow-up

Fig 2. Estimated kidney survival in children with CRF by age. Overall population ($n = 1197$; —■—); patients with baseline creatinine clearance <25 mL/min ($n = 315$; —▲—); 25–50 mL/min ($n = 419$; —●—); 51–75 mL/min ($n = 463$; —▼—).



(almost 0% in the group of patients with a baseline Ccr of <25 mL/min). However, regardless of the initial level of renal insufficiency, puberty seems to be a critical age for patients with renal impairment insofar as a number of adolescent subjects show signs of rapid progression, documented by a sharp decrease in estimated kidney survival (Fig 2). It can be speculated that this pattern of progression, which has also been observed in other chronic human diseases,¹⁶ may be attributable to an adolescence-specific pathophysiological mechanism, possibly related to sex hormone and/or the imbalance between residual nephron mass and rapidly growing body size. This unexplored area certainly deserves additional investigation by pediatric nephrologists.

The case-fatality rate in this population was very low (1.41%). However, this needs to be completed with the mortality rate early after the beginning of RRT, which cannot be provided by registries of pre-terminal renal failure or chronic dialysis. It is in fact likely that RRT is started immediately when the clinical condition of patients with severe renal impairment worsens, and so the subsequent mortality is likely to be classified as mortality on RRT or not classified at all.

CONCLUSION

The Italkid Project data provide detailed information concerning the incidence, causes, and overall outcomes of mild to severe renal functional impairment acquired during developmental age, and, in the future, we expect to be able to clarify further the natural history of the disease and the factors that influence its course.

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