



# Chronic kidney disease among children in Guatemala

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## ABSTRACT

**Objective.** To describe the distribution of pediatric chronic kidney disease (CKD) in Guatemala, estimate incidence and prevalence of pediatric end-stage renal disease (ESRD), and estimate time to progress to ESRD.

**Methods.** This study analyzed the registry of the only pediatric nephrology center in Guatemala, from 2004–2013. Incidence and prevalence were calculated for annual periods. Moran's index for spatial autocorrelation was used to determine significance of geographic distribution of incidence. Time to progress to ESRD and associated risk factors were calculated with multivariate Cox regression.

**Results.** Of 1 545 patients from birth to less than 20 years of age, 432 had chronic renal failure (CRF). Prevalence and incidence of ESRD were 4.9 and 4.6 per million age-related population, respectively. Incidence was higher for the Pacific coast and Guatemala City. The cause of CRF was undetermined in 43% of patients. Average time to progress to ESRD was 21.9 months; factors associated with progression were: older age, diagnosis of glomerulopathies, and advanced-stage CKD at consultation.

**Conclusions.** Prevalence and incidence of ESRD in Guatemala are lower than in other countries. This may reflect poor access to diagnosis. Areas with higher incidence and large proportion of CKD of undetermined cause are compatible with other studies from the geographic subregion. Findings on progression to ESRD may reflect delayed referral.

## Key words

Kidney diseases; kidney failure, chronic; renal insufficiency, chronic; risk factors; child health; epidemiology; Guatemala.

The epidemiology of chronic kidney disease (CKD) in children outside developed countries is not well-described. The Latin American Registry of Pediatric Renal Transplantation is the main

source for data in Latin America (1). In Guatemala, as is the case for most countries with limited resources, this type of data has not been previously reported (2). CKD prevalence and incidence rates among individuals less than 20 years of age vary from 10 to > 100 per million age-related population (PMARP), and 2–6 PMARP, respectively (2–14). Previous studies have reported that the largest proportions of CKD cases in children are caused by: congenital anomalies of the kidney and urinary tract (CAKUT), 30%–60%; hereditary nephropathies,

10%–35%; and glomerulopathies, 3%–25% (2, 10, 14–18). In studies that have analyzed progression to end-stage renal disease (ESRD), factors associated with progression to stage 5 were advanced-stage CKD at diagnosis and having glomerular disease (10, 19).

Natural and social environmental exposures have been reported to be associated with CKD in adults (20). In the Mesoamerican area—extending approximately from central Mexico to Belize, Guatemala, El Salvador, Honduras, Nicaragua, and northern Costa

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Rica—a number of studies have reported that such environmental exposures may be associated with geographic location (21–26). A large proportion of cases are of undetermined cause and the term “Mesoamerican Nephropathy” has been coined (27–30).

Guatemala has only recently had the capacity to comprehensively treat children with CKD through its public health care system. In 2003, the Fundación para el Niño Enfermo Renal (Foundation for Children with Kidney Disease; Guatemala City, Guatemala; FUNDANIER) was founded by parents of children with CKD. The creation of FUNDANIER is described in detail elsewhere (31, 32). FUNDANIER supported the development and maintenance of a Pediatric Nephrology Unit at the Roosevelt Hospital, one of the country’s tertiary-level referral hospitals in Guatemala City. The foundation established the country’s only exclusively pediatric renal replacement therapy (RRT) program in 2007 and created a database to track all of its patients. FUNDANIER’s Pediatric Nephrology Unit sees inpatients and outpatients from all of Guatemala, and also runs a general renal clinic. Patients do not pay any fees or donations in order to be admitted and can be referred by any health care provider or walk in on their own initiative. The main barriers to access are geographic (with associated costs) and linguistic, since there are no indigenous language interpretation services offered. FUNDANIER sometimes covers lodging costs for families in need. It can be assumed that many common renal problems are seen by general practitioners and pediatricians throughout the country, but that almost all complicated cases are eventually seen in FUNDANIER’s Pediatric Nephrology Unit.

The following is an analysis of the data available from the FUNDANIER clinical database. The study objectives were to describe the distribution of CKD in Guatemala, its causes and age distribution, provide estimates of incidence and prevalence rates of pediatric ESRD, the distribution of therapeutic modalities, and provide estimates of the time to progression to ESRD and its associated factors. This analysis represents the first effort to characterize pediatric CKD in Guatemala. The data may provide an insight into the causes of CKD in Central America.

## MATERIALS AND METHODS

### Data

Data were collected from the all patient records of the FUNDANIER database from May 2004–April 2013, and exported to Stata®/MP12.1 (StataCorp LP, College Station, Texas, United States) for statistical analysis. A total of 1 545 pediatric patients had been seen by the Pediatric Nephrology Clinic at least once during the study period, including inpatients and outpatients. Of these, 432 patients were classified as having chronic renal failure (CRF) or CKD stage 2 or more severe, indicated by an estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73m<sup>2</sup> recorded in the patient record.

### Population

The study population included individuals who were < 1 year to 20 years of age when presenting for care at FUNDANIER. All were residents of Guatemala and had been referred to FUNDANIER, either by the pediatric ward of Roosevelt Hospital in Guatemala City or from another clinic or hospital within the country. The study was approved by ethical reviewers at FUNDANIER. The compiled data made individual identities indistinguishable, thus protecting their privacy.

### Variables

Variables captured in the database were: name, birthdate, child place of residence, weight, height, blood pressure, serum creatinine, hematocrit, eGFR through Schwartz formula, syndrome at presentation/referral, definitive diagnosis, and type of therapy received.

Place of residence was documented at the department level. Guatemala is officially organized in 22 departments (counties), which are grouped into eight administrative regions: Metropolitan, Central, Northwest, Northeast, Southwest, Southeast, North, and Petén.

The eGFR was used to classify patients as having CKD and its severity (stage 2–5). The CKD categories were classified using the Guidelines of the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (33), classified by eGFR in mL/min/1.73m<sup>2</sup>. Stage 2 is a eGFR of 60–< 90; stage 3:

30–< 60; stage 4: 15–< 30; stage 5: < 15 or renal replacement therapy. All patients with eGFR < 90mL/min/1.73m<sup>2</sup> were classified as having CRF and all patients with a eGFR of <15 mL/min/1.73m<sup>2</sup> or on RRT were classified as having ESRD.

### Analysis

The patient population characteristics are described with frequencies and percentages for all the variables. Incidence was calculated as new cases per year, and the annual period prevalence included all patients that had at least one consultation in a given year. Both incidence and prevalence were estimated in the corresponding age group as PMARP. The study population under 20 years of age (used as the denominator) was the average from 2008–2012, as projected by the Guatemalan National Statistics Institute (34), using the following 5-year age groups: 0–4 years, 5–9 years, 10–14 years, and 15–19 years). The syndrome at presentation/referral and definitive diagnosis or cause of CKD were summarized for all patients and presented as a percentage.

Incidence rates were imported into ArcMap 10.2 (Environmental Systems Research Institute, Redlands, California, United States), and were then merged with a shape-file of Guatemala. Each department was given a different hue, reflecting the incidence rate’s standard deviation. In order to determine if the spatial pattern was statistically significant, a test of spatial autocorrelation was used. Spatial autocorrelation was used to determine if incidence rates for each department were relative to their proximity to one another (35). Moran’s Index (34), an index of spatial autocorrelation, was used with both Rook’s and Queen’s contiguity spatial weights for the 22 Guatemalan departments.

The time of progression from diagnosis of CKD to ESRD, and the significance of risk factors for progression, were calculated using a multivariate Cox regression, using the  $P < 0.05$  significance level. All patients in the FUNDANIER dataset with at least one clinic visit while in stages 2, 3, or 4, and a subsequent follow-up eGFR reading, were included in the survival analysis.

The co-variables used in the analysis were age category, sex, residence, CKD stage at diagnosis/referral, definitive diagnosis (undetermined cause, CAKUT,

glomerulopathies, or other diagnoses), and date of capture (before/after 2008, based on the start of the exclusively pediatric RRT program). Stata®/MP12.1 (StataCorp LP, College Station, Texas, United States) was used to conduct descriptive statistical analysis and a multivariate Cox regression.

## RESULTS

Table 1 presents sociodemographic variables, syndrome at presentation/referral, and stage of CKD at presentation/referral. The dataset captured 1 545 patients from May 2004–April 2013. The mean age was 6.19 years, with a standard deviation (SD) of 4.66 years; 49.5 % were male; and 58% came from the Metropolitan area (Guatemala

City); 13% from the Southwest; 10% from the Central; 8% from the Southeast; and the remaining 11%, from the Northwest, Northeast, North, and the Petén.

Of the 1 545 patients, 432 were classified as having CKD stage 2 or greater (CRF) based on the most recent available eGFR. Of these, 52% were male, 35% were 10–14 years of age, and 29% were 5–9 years of age. Fifty percent of the patients were from the Metropolitan area and 35% came from the Central, Southeast and Southwest regions of the country. Table 2 shows the total patients seen at FUNDANIER, by age and CKD stage at their most recent visit. Although percentages of patients with CKD stages 2–4 are similar for all age groups, the number of patients with ESRD is noticeably higher in the group above 10 years of age.

Table 3 presents the definitive diagnoses of patients with CKD stage 2 or greater. Of the final diagnoses, 43% correspond to an undetermined cause of CKD, followed by 28% due to CAKUT, and 12% due to glomerulopathies. Kidney disease of undetermined cause was higher among female patients. Four of the country's regions have proportions of patients with diagnoses of undetermined causes that are higher than the national average: Southwest, 49.2%; Metropolitan, 46.8%; Northwest, 46.4%; and Central, 43.9%; while the rest have the following: Petén, 37.5%; Southeast, 34.9%; Northeast, 25%; and North, 0.0%.

Of the 432 patients with CRF, 193 patients had CKD stage 5 (ESRD). The majority received peritoneal dialysis (40.4%), followed by hemodialysis (26.4%), transplant, (12.4%), and no renal replacement therapy (conservative management; 17.6%).

Average prevalence of ESRD was estimated to be 4.9 per million people less than 20 years of age. The prevalence is notably higher among those 10–14 year of age, with 23.4 per million people under the age of 20 during the same period. The average incidence rate of ESRD was calculated to be 4.6 per million inhabitants less than 20 years of age (4.7 for girls and 4.5 for boys). The incidence rate is notably higher in the population 10–14 years of age: 10.1 per million for the study period.

Figure 1 shows incidence rates of ESRD by department. These data were classified into four discreet classes: SD < -0.5; SD -0.5–0.5; SD 0.5–1.5; and SD 1.5–2.4, with 2.4 being the largest SD from the mean within the 22 departments of Guatemala. Varying shades were used to illustrate the different classes of standard deviation, varying from light gray (for SD < -0.5) to black (for SD 1.5–2.4). The incidence rate PMARP was higher than the national average in the departments of Sacatepéquez, 14.5; Guatemala, 12.4; Retalhuleu, 11.6; Escuintla, 7.9; Jalapa, 7.8; Jutiapa, 7.6; and Zacapa, 5.4. Using Rook's spatial weights, Moran's Index was 0.24 with a Z-score of 2.31. Queen's spatial weights also gave similar results with a Moran's Index of 0.20 and a Z-score of 2.07.

Descriptive statistics show that progression to ESRD was related to CKD stage at diagnosis/referral. Of the 87 patients captured with Stage 2 CKD, none

**TABLE 1. Sociodemographic and clinical characteristics of pediatric patients with chronic kidney disease (CKD) seen at the Foundation for Children with Kidney Disease (FUNDANIER) in Guatemala, May 2004–April 2013**

Variable	All patients		Patients with CKD Stage 2–5 (last available eGFR) <sup>a</sup>	
	No.	%	No.	%
Total	1 545		432	
Sex				
Male	765	49.5	225	52.1
Female	780	50.5	207	47.9
Age (years)				
< 5	602	39.0	132	30.6
5 to < 10	493	31.8	126	29.2
10 to < 15	381	24.7	151	34.9
15 to < 20	46	3.0	22	5.1
Age not reported	23	1.5	1	0.2
Residence				
Metropolitan area	895	57.9	218	50.5
South	305	19.8	106	24.5
Other parts of the country	345	22.3	108	25.0
CKD Stage at presentation/referral				
1	—		33	7.6
2	—		87	20.1
3	—		99	22.9
4	—		57	13.3
5	—		156	36.1
Syndrome at presentation/referral				
Urinary tract infection	547	35.4	76	17.6
Chronic renal failure	294	19.0	237	54.9
Asymptomatic urinary tract anomalies	165	10.7	24	5.6
Nephrotic syndrome	155	10.0	23	5.3
Nephritic syndrome	91	6.0	18	4.2
Nephrolithiasis	93	6.0	8	1.8
Acute renal failure	61	3.9	20	4.6
Other syndrome at presentation/referral <sup>b</sup>	139	9.0	26	6.0
Date of presentation/referral				
2008–2013	1 366	88.4	360	83.3
2000–2007	179	11.6	72	16.7

<sup>a</sup> Estimated Glomerular Filtration Rate.

<sup>b</sup> Includes: obstructive uropathy, tubulopathy, and hypertension.

**TABLE 2. Number of pediatric patients seen at Foundation for Children with Kidney Disease (FUNDANIER), by age group and stage of chronic kidney disease (CKD) at last reported visit, Guatemala, May 2004–April 2013**

Age	No CKD or Stage 1		Stage 2 (eGFR <sup>a</sup> 60–89)		Stage 3 (eGFR 30–59)		Stage 4 (eGFR 15–29)		Stage 5 (eGFR <15)		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Not identified	22	95.7	0	0	0	0	0	0	1	4.3	23	100
< 1 year	187	76.6	28	11.5	19	7.8	6	2.5	4	1.6	244	100
1–4 years	283	79.0	38	10.6	21	5.9	5	1.4	11	3.1	358	100
5–9 years	367	74.4	34	6.9	21	4.3	13	2.6	58	11.8	493	100
10–14 years	230	60.4	16	4.2	22	5.8	10	2.6	103	27.0	381	100
> 14 years	24	52.2	1	2.2	3	6.5	2	4.3	16	34.8	46	100
Total	1 113	72.0	117	7.6	86	5.6	36	2.3	193	12.5	1 545	100

<sup>a</sup> Estimated Glomerular Filtration Rate.

**TABLE 3. Definitive diagnosis of patients with chronic renal failure/stages 2–5 of chronic kidney disease (CKD) at Foundation for Children with Kidney Disease (FUNDANIER), Guatemala, May 2004–April 2013**

Diagnosis	Female		Male		Total	
	No.	%	No.	%	No.	%
CKD—Undetermined cause	101	48.8	86	38.2	187	43.3
Congenital anomalies (CAKUT) <sup>a</sup>	49	23.7	66	29.3	115	27.7
Glomerulopathies	16	7.8	34	15.1	50	11.6
Miscellaneous causes	20	9.7	17	7.6	37	8.6
Dysfunctional voiding	8	3.8	10	4.4	18	3.6
Nephrolithiasis	5	2.4	7	3.1	12	2.8
Hereditary nephropathies	3	1.4	3	1.3	6	1.4
Tubulopathies	4	1.9	1	0.4	5	1.2
No diagnosis reported	1	0.5	1	0.4	2	0.0
Total	207	100	225	100	432	100

<sup>a</sup> Congenital anomalies of the kidney and urinary tract.

progressed to ESRD, while 15 of 99 (15%) captured at Stage 3 progressed to ESRD, and 22 of 57 (39%) captured at Stage 4 progressed to ESRD. Table 4 presents results of the analysis of progression to ESRD. The time of progressing from CKD stages 2, 3, and 4 to ESRD (CKD stage 5) was on average 21.9 months, with a SD of 18.7 months, and a range of 1–65.3 months.

The risk of progression to ESRD was greater in patients 20 years of age compared to the 0–5 year reference group (hazard ratio [HR]: 12.8, *P* = 0.02) and less in those not coming from the Metropolitan or southern coast regions (HR: 0.20, *P* = 0.04) as compared to the reference group (Metropolitan area). The variable that was associated most significantly with progression to ESRD was the CKD stage when first diagnosed. Patients beginning in stage 3 rather than stage 2 were significantly more likely to progress to stage 5 (HR: 20.5, *P* = 0.005). Patients beginning in stage 4 as compared to stage 2 were markedly more

likely to progress to stage 5 (HR: 138.92, *P* < 0.001). Patients with a diagnosis of glomerulopathies as compared to those with a diagnosis of CAKUT were significantly more likely to progress to stage 5 (HR: 4.84, *P* = 0.02).

**DISCUSSION**

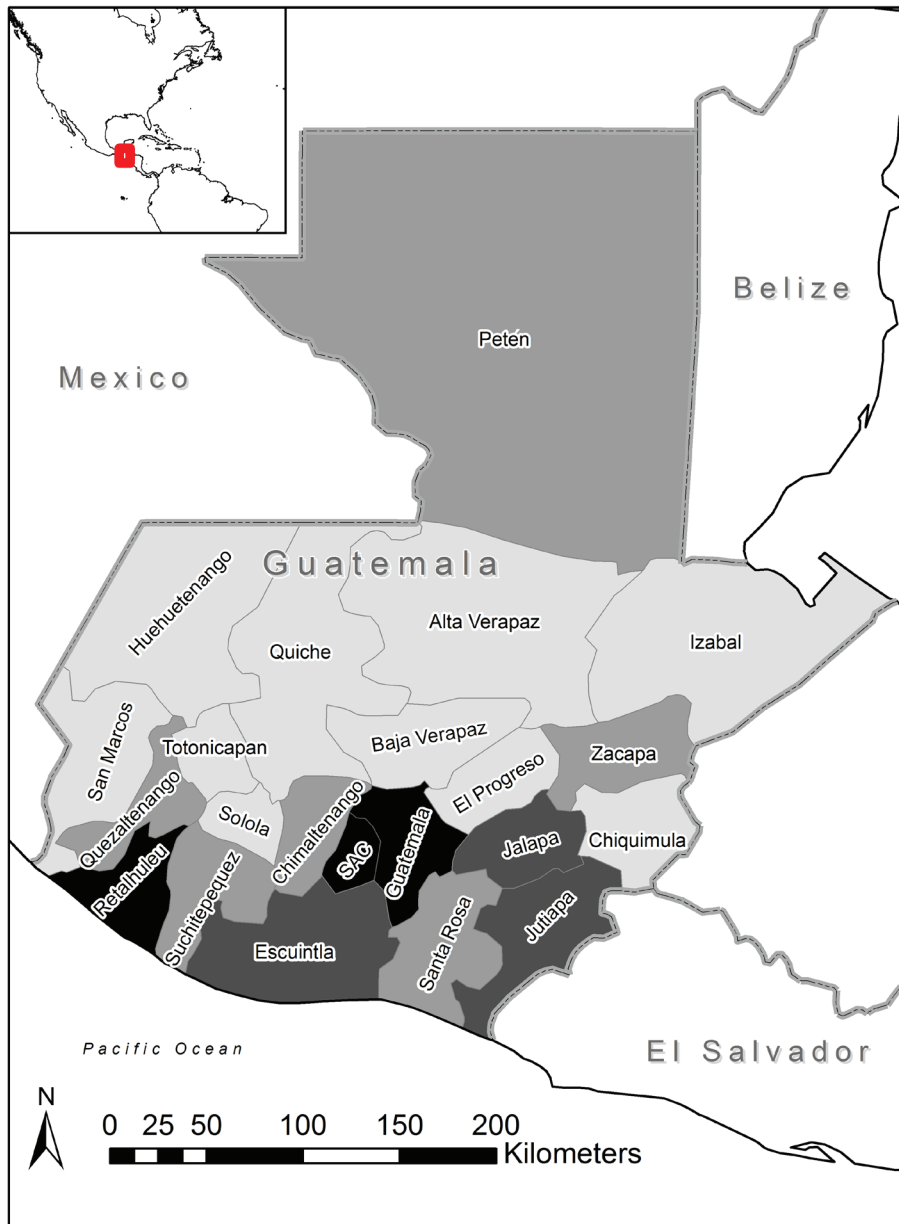
This study has characterized pediatric CKD in Guatemala from May 2004–April 2013. The prevalence and incidence rates reported for ESRD in Guatemalan children are notably lower than what has been reported in the literature in other countries with prevalence rates between 10 and > 100 PMARP and incidence rates for the same population ranging from 2–16 per million people (2–14). The prevalence and incidence rates reported here may indicate that the true prevalence and incidence rates in the country are lower than in other countries or, more likely, that a larger number of cases are not diagnosed and referred by the health system. The fact that the majority of the

reported cases come from the metropolitan (50% of CRF and 47% of ESRD) area suggests a bias due to disparity in access to health care, and may support the latter explanation. Given that ESRD prevalence and incidence rates were calculated over a period of 4 years (2008–2012), instead of point prevalence, both rates are very similar in magnitude (4.9 and 4.6), reflecting that the number of deaths and new cases were very similar in each of the 4 years included in the analysis.

In the geographic analysis, the map shows clustering in the southern part of the country, with higher incidence rates of pediatric ESRD especially in the districts of Escuintla, Guatemala, and Sacatepéquez. Lower incidences are observed in the departments at the center of the map, including Huehuetenango, Quiché, Baja Verapaz, Alta Verapaz, and Izabal. As shown by the Moran’s Index test, the clustering of CKD that is visible on the map is statistically significant and is due to something other than complete spatial randomness.

Other reports (27–30) have pointed to the Pacific Coast of Central America as an area endemic for CKD, characterizing Mesoamerican Nephropathy as occurring predominantly in men and presenting clinical manifestations in the third decade of life, with laboratory results showing low-grade proteinuria and tubular injury (27–29), and biopsy presenting extensive glomerulosclerosis, tubular atrophy, and interstitial fibrosis (30). Identified risk factors include higher environmental temperatures, dehydration, and exposure to contaminants (27–29). However, at this moment there is no evidence that the factors associated with Mesoamerican Nephropathy explain our findings; further research is needed.

**FIGURE 1. Map of pediatric end-stage renal disease incidence rates by department, Guatemala, 2008–2012**



Incidence rates per million-age-related population, by four classes of standard deviations



SAC = Sacatepéquez.

In addition, 43% percent of the CRF cases captured in the dataset were classified to be of undetermined cause. The percentage of unclassified diagnoses is higher than what has been documented in the literature. We consider that there are two possible explanations: first, there

may be limited diagnostic capacity at FUNDANIER for some entities, such as hereditary nephropathies; or the large number of cases in which the cause is undetermined may have origins similar to those documented in adults, i.e., Mesoamerican Nephropathy (27–30).

Upon referral to FUNDANIER, patients with CRF undergo renal and bladder ultrasound to identify possible urinary tract malformations. Those patients with ESRD are also routinely evaluated with voiding cystourethrogram. Kidney biopsy is performed in cases with Nephritic or Nephrotic syndrome, but not in all cases with CFR, due to limited access to the method. Given that the majority of patients with undetermined causes did not have clinical evidence of Nephritic/Nephrotic syndrome, biopsy was not performed.

Similar to previous studies in other settings, our study found that having advanced stage CKD and older age upon referral, were significantly associated with progression to ESRD. These findings may be explained by lack of access or delayed referral to specialized health care facilities. Patients with a definitive diagnosis of glomerulopathies were at higher risk of progression to ESRD.

**Study limitations**

The strength of this analysis is that it was conducted using the FUNDANIER dataset, which captures patients at the national referral hospital, and it is the first to describe CKD in children in Guatemala. However, there are a number of limitations. The results presented in this article are based on a data analysis of hospital prevalence and incidence, and are therefore sub-estimates of the true incidence and prevalence in the population. It should be noted that for the geographic analysis, only 22 departments were analyzed, whereas ideally, 30 or more units would be used; as Guatemala only has 22 departments, the data set was smaller than what is optimal.

**Conclusions**

This study points to the importance of continued research and data collection on CKD in children in Guatemala and in other countries of Latin America (1, 36, 37). New research should analyze the differences in incidence rates by residence, for which disparities in access to and utilization of services and diagnostics are likely to be important variables. The high incidence of ESRD found along the southern coast is notable, therefore, a more focused study of possible explanations is recommended. We also would encourage greater atten-

**TABLE 4. Analysis of progression from chronic kidney disease (CKD) stages 2–4 to End-Stage Renal Disease, Guatemala, May 2004–April 2013**

Variable	No.	Hazard ratio	95% Confidence Interval	P value
	254			
Sex				
Male	152	1		
Female	102	1.30	(0.60, 2.84)	0.50
Age (years)				
< 5	68	1		
5 to < 10	74	2.81	(0.84, 23.00)	0.18
10 to < 15	70	1.50	(0.45, 5.04)	0.51
15 to < 20	37	1.40	(0.36, 5.46)	0.62
20 +	5	12.82	(1.45, 113.03)	0.02
Residence				
Metropolitan area	133	1		
South	59	1.04	(0.45, 2.37)	0.93
Other parts of the country	62	.20	(0.04, .90)	0.04
Stage at which presented				
2	125	1		
3	85	20.51	(2.54, 165.60)	0.005
4	44	138.92	(14.69, 1088.76)	<0.001
Diagnosis				
Congenital anomalies (CAKUT) <sup>a</sup>	96	1		
Chronic kidney failure of undetermined cause	45	2.24	(0.87, 5.79)	0.10
Glomerulopathies	45	4.84	(1.31, 17.91)	0.02
Other diagnosis	68	2.96	(0.85, 10.32)	0.09
Date of presentation				
2008–2012	195	1		
2004–2007	59	0.55	(0.23, 1.32)	0.18

<sup>a</sup> Congenital anomalies of the kidney and urinary tract.

tion on diagnosing CKD in children to establish whether there are, in fact, more cases that have non-traditional causes, or if diagnoses of undetermined cause are recorded because it has not been possible to dismiss other causes. Finally, we recommend continued efforts to maintain the FUNDANIER database with a specific emphasis on improved standardization of the data captured on each individual.

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**Conflicts of interest.** None.

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## RESUMEN

### Enfermedad renal crónica en niños de Guatemala

**Objetivo.** Describir la distribución de enfermedad renal crónica en niños en Guatemala, y calcular la incidencia y la prevalencia de nefropatía terminal en niños, así como el tiempo de progresión hasta la nefropatía terminal.

**Métodos.** Este estudio analizó el registro del único centro de nefrología pediátrica de Guatemala, del 2004 al 2013. La incidencia y la prevalencia se calcularon por períodos anuales. Se utilizó el índice de Moran como medida de la autocorrelación espacial con objeto de determinar la significación de la distribución geográfica de la incidencia. El tiempo de progresión a la nefropatía terminal, así como los factores de riesgo asociados, se calcularon mediante la regresión de Cox de variables múltiples.

**Resultados.** De 1 545 pacientes menores de 20 años, 432 padecían insuficiencia renal crónica. La prevalencia y la incidencia de nefropatía terminal fueron de 4,9 y 4,6 por millón de habitantes de esa misma edad, respectivamente. La incidencia fue mayor en la costa del Pacífico y en la Ciudad de Guatemala. En 43% de los pacientes la causa de la insuficiencia renal crónica era indeterminada. El tiempo promedio de progresión a una nefropatía terminal fue de 21,9 meses; los factores asociados con esa progresión fueron: la edad mayor, el diagnóstico de glomerulopatía y la enfermedad renal crónica en etapa avanzada en el momento de la consulta.

**Conclusiones.** La prevalencia y la incidencia de la nefropatía terminal en Guatemala son inferiores a las de otros países. Ello podría reflejar un acceso limitado al diagnóstico. La mayor incidencia y la amplia proporción de enfermedad renal crónica de causa indeterminada en algunas zonas son compatibles con las de otros estudios de la subregión geográfica. Los resultados en cuanto a progresión a una nefropatía terminal podrían ser el reflejo de la tardanza en la derivación.

### Palabras clave

Enfermedades renales; fallo renal crónico; insuficiencia renal crónica; factores de riesgo; salud del niño; epidemiología; Guatemala.