Estimated prevalence of childhood end-stage renal disease in the state of São Paulo

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Summary

Objective: To estimate the prevalence of pediatric end-stage renal disease and evaluate demographics and renal disease characteristics in state of São Paulo over the year 2008. **Methods:** Observational, descriptive, and cross-sectional study based on a population sample with subjects < 18 years. The data collecting assumed three forms: 1. A questionnaire for dialysis units; 2. Search in the Transplant Center to determine the number and characteristics of patients who had been in a transplant waiting list over the study period; 3. Search in the database of patients registered at the Latin American Collaborative Registry of Pediatric Kidney Transplantation. **Results:** Data from 301 patients aged 9.0 ± 5.8, including 140 girls (46.5%), resulting in an estimate prevalence of 23.4 cases per million age-related population (pmarp). The age group most frequently found was 10 to 15 years (32.2%), and urinary tract malformation was the most usual known etiology (24.9%). Most children underwent kidney transplantation (62.1%) and among subjects on dialysis, hemodialysis was predominant (71.2%). The Sistema Único de Saúde – Unified National Health System – (SUS) provided the financial support for treatments. **Conclusion:** The prevalence of 23.4 cases pmarp found by the authors is lower than that reported in Western world. We believe data were underestimated in the present study, as few dialysis units returned the completed questionnaire. This potential bias does not invalidate the exploratory character of results. Further mechanisms for retrospective and earlier data collecting on pediatric chronic renal disease (CRD) are needed so that the burden of this serious health condition can be appropriately sized up.

Keywords: Kidney failure; prevalence; pediatrics; epidemiology.

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Introduction

End-stage renal disease (ESRD) is a greatly relevant public health issue and evidence shows incidence and prevalence of this condition keep growing. However, there are major differences in the estimate prevalence of ESRD in adults across the world, with estimates ranging from 2.5 cases per million age-related population (pmarp) in Nigeria to 1,403 cases pmarp in the United States of America[1].

Chronic renal disease, as considered in any of its severity stages, leads to a significant increase in morbidity and mortality for affected individuals, notably from cardiovascular events. In addition, caring for patients with this condition implies elevated cost for the health system due to the complex therapeutic resources required. In children and adolescents, these difficulties are even more important, given the unique characteristics of each age group, making these patients' treatment almost personalized and consequently more complex and more costly[2].

Most available epidemiological data focuses on adult studies, thus reducing the advantage that could come from recognizing the chronic renal disease in its earliest stages while occurring in children and adolescents. Within this age group, studies are particularly rare and when chronic renal disease is assessed in children, the cases are almost always studied in an advanced stage of renal impairing, especially when they are on dialysis or in transplanted patients.

The feasibility of epidemiological studies on chronic renal disease has been recently increased through the development of classification criteria in cases with clear-cut stages, ranging from 1 to 5 in a progressive severity scale, with stage-5 CRD corresponding to end-stage kidney failure with a glomerular filtration rate lower than 15 mL/min/1.73 m^2 or those on renal replacement therapy[2].

ESRD frequency in children is far lower than in adults, with a total of 7,209 pediatric patients in the USA being estimated to have received treatment for ESRD in 2007, resulting in a prevalence of 84.6 cases pmarp[3]. However, even concerning studies involving only children in stage-5 CRD, huge incidence and prevalence variations are reported in different countries. In Japan, the incidence estimate was 4 new cases pmarp in 1998, whereas in a survey involving 12 countries in Europe between 1985 and 1990, the incidence was 10 new cases pmarp[2].

Therefore, etiological and course profile differences seem to be present in this condition across different geographical regions, which suggests local studies are required. Several factors can contribute to the frequency variability of chronic renal disease in children, such as racial and ethnic distribution, types of prevalent renal diseases in the region and the quality of medical care for patients with early chronic renal disease. Generally, chronic renal disease frequency is lower in developing countries, likely from inefficient organization in the health system providing care to these patients, with a consequent rise in mortality associated with the disease in its earliest stages[4].

Unfortunately, epidemiological surveys involving CRD in children are virtually nonexistent in Brazil whatever the stage of the disease and this lack of studies drove the current study, aiming to estimate ESRD prevalence in children and adolescents in the state of São Paulo over the year of 2008. In addition, we also know the demographics (age and sex) and nephrological characteristics (underlying disease, disease duration, treatment type and patient's condition in the realization of renal transplantation) in children with chronic renal disease in the state of São Paulo over the year of 2008.

Methods

An observational, descriptive, and cross-sectional study was conducted in a population sample within the pediatric age group in the state of São Paulo over the year of 2008, with pediatric age group being defined as the individuals aged < 18 years.

By considering renal replacement therapy can be performed only by either dialysis centers or hospitals accredited for dialysis or pediatric renal transplantation, our study sought to encompass all units providing such a care in the state. Thus, the authors initially identified the facilities offering dialysis by using the available addresses from the following sources: a) Brazilian Society of Nephrology; b) Brazilian Association of Dialysis and Transplant Centers; c) Union of Kidney Failure Patients in São Paulo; d) centers registered at the State Secretary of Health of São Paulo. From this search, we established a database containing 225 addresses of clinics and dialysis facilities that were the source from which we formulated an invitation for a voluntary participation in the study.

Under the current legislation, patients in preparation for a deceased donor kidney transplant with, even in a procedure funded by the private health insurance system, must be registered in the National System of Transplants, managed by the State Secretary of Health in São Paulo. Only in rare cases of families choosing not to enroll their children in the deceased donor waiting list, exclusively aiming at living donor kidney transplant, the procedure can be performed without enrolling the patients in State Secretary of Health. For these reasons, data collection from ESRD patients was not restricted only to databases in dialysis clinics, but it was performed in three consecutive and redundant stages:

1. Telephone contact with renal replacement therapy units to identify and characterize pediatric patients on therapy at that unity and sending a specific questionnaire by electronic mail. Such questionnaire was designed to identify and characterize pediatric patients on renal replacement therapy at the unit.

2. Refer to the Transplant Center, as a part of the State Secretary of Health of São Paulo, which coordinates the State Transplant System, to determine the number, demographics, and most relevant clinical features of patients aged less than 18 years who had been for some time in the kidney transplant waiting list all over the year of 2008. Notably, the patients should already have been on dialysis or have a documented glomerular filtration rate lower than 20 mL/min/1.73 m^2 to be enrolled in the state of São Paulo transplant waiting list, which assured the authors' strategy of data collecting involving only individuals with ESRD in the study. This data source is important, as the absolute majority of children with end-stage renal disease are referred to be enrolled in the transplant waiting list.

3. Once the reporting of living donor kidney transplants to the Transplant Center is not mandatory in the state of São Paulo (Transplant Center receives compulsorily the enrollment entries into the deceased donor transplant waiting list) and in order to enhance the possibility of including pediatric patients receiving a kidney transplantation over the year of 2008, we added patients registered into the Latin American Collaborative Registry of Pediatric Kidney Transplantation[5], selecting from this database only data of patients transplanted over the year of 2008 in the state of São Paulo centers. This data source is important because children receiving living donor kidney transplants listed were not necessarily enrolled in the Secretary of Health waiting list.

As our database was constructed from three different and redundant sources, there was the risk for the same patient to be represented in two or three data sources used. In order to avoid repeating the subjects, we checked the cases individually by birth date, gender and diagnosis, then excluded individuals with a repeated registration into the database when we compiled data from different sources.

In the statistical analysis, we considered the population basis for the pediatric age group in the state of São Paulo according to Instituto Brasileiro de Geografia e Estatística (IBGE) data for the year of 2008. Point prevalence was estimated as the number of cases (on dialysis and transplanted over the year of 2008) per million age related population. In order to estimate the population basis in the state of São Paulo, data from the State Plan of Health 2008-2011[6] was used. This publication estimated São Paulo's population in 2008 was 41,055,761, with 12,869,544 individuals aged less than 18 years in that year[6].

Frequency tables were used to describe the results in case of continuous discrete qualitative and quantitative variables and, for continuous quantitative variables, calculation of mean, standard deviation, maximum, and minimum values was performed. Student's *t* test was used in independent samples to compare groups (transplanted versus non-transplanted patients); in this test, the rejection limit of the null hypothesis was established as 5% ($a < 0.05$).

This project was submitted to and approved by the Ethics in Research Committee of Hospital Samaritano, the coordinator center of the study, in 12.06.2007 under the protocol # SHS 19/07.

Results

Out of the universe of 225 dialysis facilities in the previously elaborated list, a telephone contact was established with 210 centers (15 attempts were unsuccessful because either no corresponding telephone number was in the referred sources or the telephone numbers were wrong, nonexistent or they belonged to physicians who were no longer in charge of the dialysis service and they could not inform the updated telephone number). However, adhesion of centers to the survey was effectively very low, with only eight of them returning completed questionnaires, despite the several and repeated contacts with every center for not returning the questionnaire. By this process, we obtained information about 111 patients who had been on dialysis in any time over the year of 2008, with 53 girls (47.7%) and 58 boys (52.3%). Out of this group of children who had been on dialysis, 15 (13.5%) underwent a kidney transplantation in 2008.

By looking up data from patients in the kidney transplant waiting list of the Transplant Center in any moment over the year of 2008, we obtained data from 158 children, with 70 girls (44.3%) and 88 boys (55.7%). From this database, 67 children (42.4%) were transplanted in 2008, whereas other 91 patients (57.6%) remained in the waiting list, and detailed information about dialysis in these individuals could not be found in the Transplant Center.

Finally, by searching the Latin American Transplant Registry, we retrieved data from other 32 patients transplanted in 2008 in the state of São Paulo, with 17 girls (53.1%) and 15 boys (46.9%). Accurate information about dialysis treatment employed in these patients was not either found.

By combining the three data sources used, we retrieved information from 301 patients aged 9.0 ± 5.8 years (minimum = 0; maximum = 18.4 years), with 140 girls (46.5%) and 161 boys (53.5%). This count makes up a prevalence estimate of 23.4 cases pmarp in the year of 2008. The main demographics in the study sample are shown in Table 1.

In the sample fraction where we have detailed data about the dialysis treatment (111 patients), in 95 cases (85.6%) the replacement renal therapy funding was observed to be provided by the Sistema Nacional de Saúde – Unified National Health System (SUS), whereas in 16 cases (14.4%) the therapy funding was provided by a private health insurance system.

By comparing the group of patients receiving a kidney transplantation versus a non-transplanted group, a statistically significant difference was observed in the mean age between the groups (11.3 ± 4.8 vs. 7.5 ± 5.8 years, respectively; $p < 0.001$).

Table 1 – Demographics and clinical characteristics of end-stage renal disease patients – São Paulo, 2008

Variable	n (%)
Gender	
Male	161 (53.5)
Female	140 (46.5)
Age group (years)	
0 to 5	84 (27.9)
5 to 10	68 (22.6)
10 to 15	97 (32.2)
> 15 and < 18	52 (17.3)
Diagnosis	
Urinary tract malformations	75 (24.9)
Glomerulonephritides (FSGS excepted)	57 (18.9)
Focal segmental glomerulosclerosis	30 (10.0)
Others (including systemic and congenital/inherited diseases, tumors, and unknown cause)	139 (46.2)
Dialysis mode (regarding 111 patients with available data)	
Hemodialysis	79 (71.2)
Peritoneal dialysis	32 (28.8)
Kidney transplantation performed over the year of 2008	
Yes	187 (62.1)
No	114 (37.9)

Discussion

ESRD prevalence of 23.4 cases pmarp found in the current study is lower than that reported in industrialized Western countries; on the other hand, our findings are consistent with scarce available data from Latin America. In the United States, this prevalence has been recently estimated as around 85 cases pmarp[3]; in Europe, a study including data from 12 countries reported a prevalence estimate of 62 cases pmarp in the year 2007[7]. More recently, an European meta-registry was set, compiling data regarding the year 2007 in 28 countries in that continent, with a prevalence estimate of 33.6 cases pmarp, but only cases up to 14 years of age were considered in this meta-registry[8]. However, in Australia and New Zealand, data from dialysis and transplant registry ANZDATA point to a current prevalence of 50 cases pmarp[9].

In Latin America, there is not much available data; in a relatively early survey in Chile, prevalence of chronic renal disease was estimated as 43 pmarp[10], but the data survey was not limited to patients either on dialysis or transplanted in this study, and the expected prevalence was higher, since the Chilean study encompassed kidney disease in a wider functional involvement range, including those not reaching end-stage disease yet.

In Brazil, a survey similar to ours has been performed in the state of Rio de Janeiro since 2005 and, in this study, the frequency of patients with ESRD in 2007 was 145 cases, making up an estimated prevalence of 24 cases pmarp in patients aged less than 24 years[11]. However, the survey in Rio de Janeiro concerns only cases on dialysis and thus patients receiving kidney transplantation without undergoing dialysis would not enter the registry, although the number of patients undergoing preemptive kidney transplantation is reduced in Brazil.

Possible explanations for the lower prevalence we found in our study, compared to other Western countries, should include the likely higher mortality in patients with ESRD in Brazil. Studies evaluating this issue and comparing data over time suggest that, in contrast with the data observed in adults, ESRD incidence in children and adolescents is not substantially growing. However, the prevalence is growing high, reaching values three times as high as those from the early 80's to today, suggesting reduced mortality in pediatric patients with ESRD[2,7,9]. From the data obtained, it is impossible to evaluate mortality linked to ESRD, but it is plausible to raise the hypothesis that mortality may be higher than that observed in industrialized countries. In the meta-registry from European countries, the prevalence difference observed according to the development degree of the countries is clear, with values in Eastern European countries being consistently lower than those observed in Western countries. The lowest value reported in this study was from Latvia, with 6.3 cases pmarp, and the highest was from Finland, with 92.4 cases pmarp[8].

On the other hand, it is also possible to credit our low prevalence to case underreporting. Our study is particularly susceptible to such a bias, since adhesion to dialysis was low and only 3.6% of units returned the questionnaire sent to them; this fact corroborates the well-known difficulty in conducting studies in which data is voluntarily provided in Brazil. However, our strategy of redundant data collecting must be born in mind, since patients on dialysis are those appearing in transplant statistics. Considering that, in addition to questionnaires sent to dialysis units, we also included patients enrolled in kidney transplant waiting list and living donor transplants from Latin American Transplant Registry, we believe this redundancy mitigates the gap left by the low adhesion in dialysis centers. In our sample, out of 111 cases from dialysis units, 89 also appeared in either one of the two other data sources (80% of redundancy) and, in

order to ensure that the same patient was not listed more than once in the present sample, data from dialysis units were the only data considered. This calculation allow us to raise the hypothesis around 20% of patients on dialysis are not listed in transplant statistics, but we deem it is impossible to accurately quantify such a bias from our data. From the severity of ESRD repercussion in the pediatric age range and from the great hope of improving life quality around kidney transplantation, a substantial number of patients is not likely kept on dialysis over one year with no referring to preparation for transplant. Yet we recognize there is a potential source for underreporting in our data reason why our prevalence can be underestimated and should be seen as a sample estimate of ESRD prevalence in pediatric group in the State of São Paulo, rather than a population determination.

Distribution of cases per age group in our sample also favors the underreporting possibility, since the age group > 15 years is the least frequent across our cases. Similar surveys from other countries and also from Brazil indicate this is the age group with the highest ESRD frequency[2,3,7,9,11], suggesting our data can involve underestimating of cases in this particular age group. On the other hand, dividing the study into age groups was particularly restrictive, since our upper limit of age was set at 18 years, whereas other studies consider 19 or 20 as a cutoff level.

However, the underreporting considered in our sample is not likely great, as the Dialysis Census of the Brazilian Nephrology Society (SBN) in 2008 detected 160 patients under the age of 20 on dialysis in the state of São Paulo (Sesso RC, personal communication, data not published). The percentage of dialysis units effectively returning the questionnaire was around 50% in the Southeastern region of Brazil as a whole in that census[12], plausibly acknowledging that if the Census had 100% of returning questionnaires, it could depict around 320 patients under the age of 20 years were on dialysis in our state. This figure is not substantially different from that we found in the current study, mainly if we consider the SBN Census age group involves individuals up to 20 years, whereas the current survey was limited to patients up to 18 years of age.

Finally, it is noteworthy the fact that, among the dialysis units which effectively returned the questionnaires, 4 of them are centers admittedly responsible for the treatment of a great number of adult patients and pediatric patients in particular (Hospital Samaritano, UNIFESP, UNICAMP, and USP Ribeirão Preto), making our sample representativeness stronger. Counterbalancing this underreporting trend we acknowledge in our data, there is a possibility of excess in the real prevalence estimate due to patients migrating from other states to get a chronic renal disease treatment in São Paulo. Several families are known to move out of their states when they are in the setting of seeking renal replacement therapy for one of their children, but precise figures are not known.

In the current study, we observed the already well-known characteristic of a slight preponderance of boys over girls[2], with a female-male ratio of 1:1.5. This observation is traditionally attributed to the higher frequency of urinary tract obstructive malformations in boys, and the current data is in line with the literature[2,13].

When we considered end-stage renal disease etiology in our data, the first information to draw attention is the elevated frequency of patients classified as "other" etiology. This category encompasses several settings, such as inherited diseases, systemic diseases, vascular diseases, and tumors. However, among our cases, this category means mainly ESRD cases with an unknown etiology, bearing out the frequency of cases receiving a late renal disease diagnosis, often upon starting the renal replacement therapy. Recent report about Brazilian population starting dialysis shows between 2000 and 2004, 90,356 patients started dialysis and an undetermined cause was the main ESRD etiologic factor, accounting for 44% of cases, which is consistent with the findings in this study[14]; this data suggests diagnosis of chronic renal disease in Brazil is late and should be improved.

Another point deserving some discussion in our study is the type of renal replacement therapy (RRT) employed, which was predominantly kidney transplantation. In Brazil, this data differs from that observed among adults, in whom dialysis[14,15] is the most often employed RRT. This can be partly due to the lack of accurate information from our data collect sources on dialysis, although it seems to us this observation should also match reality. We attribute this difference to a successful policy of prioritizing children for deceased donor kidney allocation, which has been employed in the state of São Paulo for more than ten years and has been recently extended to all national territory. This policy consists of allocating organs from donors under the age of 18 years to recipients in the same age group, which succeeded in significantly reducing the waiting time for children and adolescents to undergo kidney transplantation in the state of São Paulo[16]. Currently, the mean waiting time of a minor until he/she undergoes kidney transplantation is around 7 months in our state (Nogueira PCK, personal communication, data not published).

We found a significant difference upon comparing patients undergoing transplantation with those not undergoing transplantation, with transplanted children being older. The age difference could be suggested as resulting from a longer waiting time up to kidney transplantation in children reaching such an endpoint, but in our cases the time on dialysis for the group of transplanted patients was comparable with that observed among those not receiving transplantation (1.4 ± 1.1 vs. 1.6 ± 1.7 years, respectively; $p = 0.439$), suggesting age differences observed among the groups are not simply mirroring the transplanted patients had waited longer.

The age difference observed among our groups allows us to raise a hypothesis that access to transplantation is faster among older children and adolescents. In kidney transplantation clinical practice, a known fact is younger children have more often urinary tract malformations representing a complex challenge. Although there is no consensus on this respect, most evidence suggests urinary tract preparation is required prior to transplantation[17], and these patients' preparation is complex, frequently involving urinary bladder augmentation, which can cause these small patients to take longer to reach kidney transplantation. This hypothesis could not be put to test in this study, but, in our view, a study dedicated to this major issue is warranted.

Finally, the current data bears out a patent predominance of SUS as RRT provider in Brazil. Quite similar results were found in SBN Dialysis Census[12].

In conclusion, the current study provides data allowing us to devise some important characteristics in this severely ill group of individuals, despite the possibility of ESRD underreporting occurring in children. As positive points for the current study, we consider the prevalence estimate for ESRD in pediatric patients, which had not been studied in our state, can support new investigating questions concerning ESRD care in children. We further consider deepening ESRD epidemiological understanding in children and adolescents as a mandatory requirement, mainly when we take into account proved strategies to reduce the impact or delay the disease progression are available[18]. Inaccurate and mainly late diagnosis suggested by the present data leads to retarding the adoption of therapeutic measures which could have a potential impact on ESRD course. Given SUS has a leading funding role in renal replacement therapy in Brazil, it seems desirable the timely establishment of cooperation mechanisms of all sectors involved in these children's care with SUS in prospectively searching data capture and analysis mechanisms on chronic renal disease in the pediatric age group, not only in an end stage, but also in earlier disease stages, taking as data source the own SUS cost management data.

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