Article

Incidence and Renal Survival of ESRD in the Young Taiwanese Population

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Summary

Background and objectives ESRD in the young represents a heavy burden to patients, families, and health care systems. This nationwide retrospective study characterized the incidence of ESRD and analyzed diagnoses associated with renal survival in the young population in Taiwan.

Design, setting, participants, & measurements Through use of Taiwan's National Health Insurance Research Database, the population of young patients (age<30 years, including children and young adults) with ESRD between January 1998 and December 2009 were enrolled. The medical claims were used to derive the date when the cause of ESRD was first determined. The medical data were reviewed and the renal survival time (time from first diagnosis of the cause to the start of ESRD) was calculated by experts, including clinical physicians and a large-database specialist.

Results The incidence rate of ESRD in the young population was high compared with the worldwide rate at 21.1 per million person-years, whereas the incidence in the pediatric group was still similar to that in other countries at 10.3 per million person-years. A total of 2304 patients with new-onset ESRD and identified renal diseases during the study period were enrolled. All preschool-age patients (100%) began receiving peritoneal dialysis as their initial treatment for ESRD. The leading causes, which varied by sex and onset age, were glomerulonephropathy followed by hypertension for the young adult group and glomerulonephropathy followed by congenital anomalies of the kidney and urinary tract (CAKUT) for the pediatric group. Renal survival was cause-dependent. The median overall renal survival duration was 0.8 year (interquartile range [IQR], 0.7–3.5 years). CAKUT-related ESRD had the longest progression time (median renal survival, 16.0 years; IQR, 10.7–23.5 years); glomerulonephropathy progressed more rapidly into ESRD and had the shortest median renal survival of 0.5 year (IQR, 0.1–2.7 years).

Conclusions The incidence and causes of ESRD greatly differ between pediatric patients and young adults. Moreover, renal survival in the young population markedly varies depending on the cause of renal disease.

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Introduction

ESRD refers to severe kidney failure requiring dialysis or kidney transplantation to maintain life. The incidence and etiology are well-studied in adults, but studies on ESRD in younger populations are limited. For instance, diabetes mellitus (DM) and hypertension are the leading causes of adult ESRD, with well-known natural history and incidence (1). Epidemiologic information on chronic renal failure in children and adolescents is scant and varies among different countries with diverse health care systems and research methods. Current studies on young patients with CKD, severe renal insufficiency, and chronic renal failure depend on multicenter investigations or renal replacement therapy registries (2–7). Some population-based studies are restricted to small reference populations, while nationwide studies are cross-sectional (8,9) or have assessed registry statistics (2,4) of patients who are undergoing dialysis or

have had transplantation (3,6). Differences in methods, such as case definitions and disease classifications, make it difficult to compare studies for the epidemiology of chronic renal failure in young populations in different geographic areas.

The National Health Insurance (NHI) program was implemented in Taiwan in March 1995 under the Bureau of NHI of the Department of Health. The Taiwan NHI Research Database (NHIRD) contains all medical behaviors and services recorded by codes for the International Classification of Diseases, Ninth Revision (ICD-9). Because ESRD is a catastrophic illness, all patients are registered for advanced management and payment waiver (10).

Through use of the NHIRD, this study evaluated the incidence density and causes of ESRD among the young Taiwanese population and analyzed the renal survival of patients with major renal diseases from diagnosis to end stage.

Materials and Methods

Data Source

Taiwan's NHI program covers most of the healthcare costs of more than 99% of the 23 million population under a single-payer system that finances health care for all citizens and offers unrestricted access to any health care provider of the patient's choice. The NHIRD includes almost all claims of medical services in Taiwan. Data released to the public for research purposes are de-identified and encrypted, so this study was exempted from full review by the Institutional Review Board of National Yang-Ming University Hospital.

Identification of the ESRD Cohort and Initial Treatment Modalities

ESRD Patients aged younger than 30 years at the time of disease onset during the study period (January 1, 1998–December 31, 2009) were identified from the NHIRD. Because fraudulent coding by hospitals or physicians was heavily penalized and the registry was under regular internal peer review, its accuracy was generally accepted. Each enrolled patient was followed-up until the first occurrence of ESRD, age older than 30 years, death, or end of the study. Before enrollment, each patient was observed for at least 1 year to determine the first occurrence of ESRD, which was then designated as the onset date. The incidence density method was used to estimate the age- and sex-specific incidences of ESRD.

Initial treatment was defined as the first treatment modality for ESRD after the onset date. Modalities such as peritoneal dialysis, hemodialysis, and renal transplantation were identified by hospitalization and outpatient databases within 6 months after the onset of ESRD. If multiple modalities were given, the initial treatment modality was considered in the order of transplantation, peritoneal dialysis, and hemodialysis. Patients without a complete record of treatment modalities were not included.

Determination of Causes and Index Dates of ESRD in the Young

The causes that preceded and were responsible for ESRD were determined by a differentiation algorithm and ascertained by expert review (Supplemental Appendix 1). Possible causes were identified by diagnosis codes from complete medical claims, outpatient visits, and hospitalization records linked and traced back to the date of birth or 1 year before the study period. The differentiation algorithm automatically sorted the possible causes of ESRD for each patient by date and importance. A pediatric nephrologist also reviewed the medical claims and determined only one valid contributory cause for ESRD per patient. The first occurrence date of the assigned cause was designated as the index date. Sensitivity analysis was performed to examine classification bias.

Classification of Causes of ESRD

The causes of ESRD were classified into five major categories according to ICD-9, Clinical Modification (Supplemental Table 1). Because the cause of many renal parenchymal diseases could not be determined if pathologic evidence or typical presentation was lacking, they were simply coded as "nonspecific glomerulonephritis" (ICD-9 codes 580–589). This study established an analytical priority ranking based on catastrophic registry, hospitalization, and outpatient records to establish tentative diagnoses other than "nonspecific glomerulonephritis" or "primary glomerulonephritis." Conditions such as systemic lupus erythematosus (SLE), Henoch-Schönlein purpura (HSP), and hemolytic-uremic syndrome were secondary glomerulonephrites defined as having significant unusual diagnoses. Other causes were classified as "unknown glomerulonephritis" because this category contained many uncertain renal diseases.

Renal Survival Analysis

Renal survival time, defined as the time to progression, from onset of the cause to confirmed ESRD, was calculated from the index date to the first date of confirmed ESRD diagnosis or use of hemodialysis (first registration date in the ESRD registry). As such, renal survival time actually indicated the duration of an enrolled patient with ESRD who had preserved renal function independent of renal replacement therapy, including dialysis or kidney transplantation, from the time of suspicion of an illness that can progress to ESRD. For congenital anomalies of the kidney and urinary tract (CAKUT) and some metabolic disorders that exist at birth (life-long disease in Supplemental Table 2), chronologic age (birthday) was used as the index date instead. The span of renal survival implied the length of time it took for an etiologic factor to affect the kidneys, from illness to exhaustion.

To ensure the validity of the index date, the patients were followed-up for at least 1 year; those with incomplete observation were not included in renal survival analysis. A comparison test showed no statistical difference between the patients in the renal survival analysis and those who were excluded (Supplemental Table 3).

Statistical Analyses

All of the data were linked using the SQL server 2008 (Microsoft, Redmond, WA) and analyzed using Stata software (Stata Corp., College Station, TX). The incidence density method was used to estimate the age- and sex-specific incidence rates as well as the overall incidence rate of ESRD. Chi-square and independent t tests were used to assess differences in age, sex, and comorbid conditions. Nonparametric methods, including the Kruskal-Wallis test and Wilcoxon rank-sum test, were used to compare the differences of median renal survival. Statistical significance was set at $P<0.05$.

Results

Age- and Sex-Specific Incidence Rates of ESRD and Initial Treatments

At the beginning, a total of 2831 patients with ESRD younger than age 30 years were initially identified. The incidence rates of ESRD steadily increased with age, except for a small peak in infants (age 0–1 year). The overall incidence rate was 21.1 per million person-years, with 22.4 and 19.8 per million person-years in male and female patients, respectively. As in the pediatric group, the incidence rate in patients younger than age 15 years was 10.3 per million person-years. The 12-year cumulative prevalence was

83.1 per million population. The incidence rates in infants (age 0 years), toddlers (1–2 years), preschool age (3–4 years), school age (5–12 years), adolescents (13–17 years), and young adults (>18 years) showed that males had slightly greater rates than females after school age, but no significant difference was noted between sexes in populations younger than 12 years (Figure 1).

Initial treatment modalities for ESRD varied greatly by age of onset. Peritoneal dialysis was the choice in infants, toddlers, and preschool-age children. However, the proportion of patients undergoing hemodialysis increased rapidly in adolescents and young adults. The proportion of patients having renal transplantation peaked in the school-age population and declined with age (Figure 2).

Causes of ESRD in the Young Population

A total of 2304 patients with ESRD, excluding 527 patients with incomplete observation from the original 2831 patients, were included in the following analysis. The causes of ESRD varied with sex (Table 1). Glomerulonephropathy, followed by hypertension and genetic and metabolic diseases, was the most common cause of ESRD in the young population. Lupus nephritis and purpura nephritis accounted for 9.6% and 0.5% of cases, respectively, with female predominance (15.6% versus 4.5%; 0.9% versus 0.2% for females and males, respectively). Type 1 DM was the major metabolic cause of ESRD (8.9%).

The proportion of causes of ESRD was distributed differently depending on the onset age (Table 2). The proportion of glomerulonephropathy abruptly increased in school-age children and remained the major leading cause, while CAKUT-related ESRD occurred early but had a decreasing trend after school age. Genetic and metabolic causes of ESRD, mainly DM and hypertension, were always

discovered late and affected a higher proportion of adolescents and young adults.

Renal Survival Analysis of ESRD in the Young

Renal survival varied greatly by cause of ESRD (Supplemental Figure 1, Table 3). The overall renal survival was 0.8 year (interquartile range, 0.7–3.5 years). CAKUT had the longest progression time (median renal survival, 16.0 years) to ESRD, while glomerulonephropathy progressed more rapidly than in patients whose ESRD was due to diabetic nephropathy (median renal survival, 0.5 versus 3.2 years; $P<0.001$, Kruskal-Wallis test).

Among the glomerulonephropathy-related cases of ESRD, HSP and SLE had longer renal survival time compared with other glomerulonephropathies. The median renal survival time was much longer for HSP (3.1 years) than for SLE (2.7 years) and other glomerulonephropathies (0.3 year) (both $P<0.001$, Wilcoxon rank-sum test) (Supplemental Figure 2, Table 3).

Discussion

This 12-year retrospective natural history case study used a comprehensive nationwide database to investigate the epidemiologic characteristics of ESRD incidence rate, initial treatment modality, and renal survival in the young population in Taiwan. Taiwan had a high incidence rate for ESRD in the young (<30 years old) compared with worldwide rates, whereas the incidence rate in the pediatric group (<15 years old) was still similar to that in other countries. The treatment modality of choice was peritoneal dialysis in the pediatric group and hemodialysis in young adults. Moreover, the causes and renal survival of ESRD greatly differ between pediatric patients and young adults. These results suggest that age- and cause-specific strategies be used to prevent ESRD.
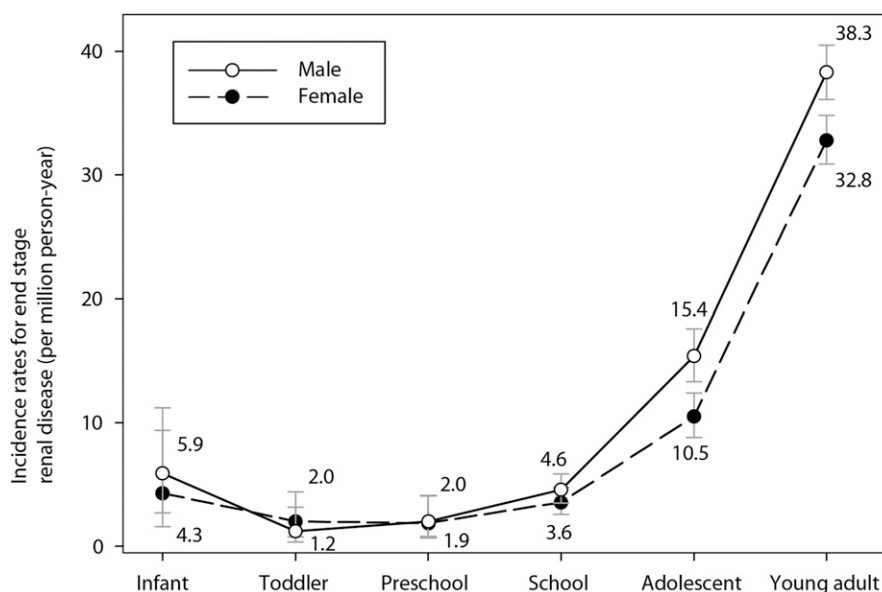
Figure 1. | **Age- and sex-specific incidence rates for ESRD in the young in Taiwan (n=8,104,970) from 1998 to 2009.** The error bars refer to 95% confidence intervals.
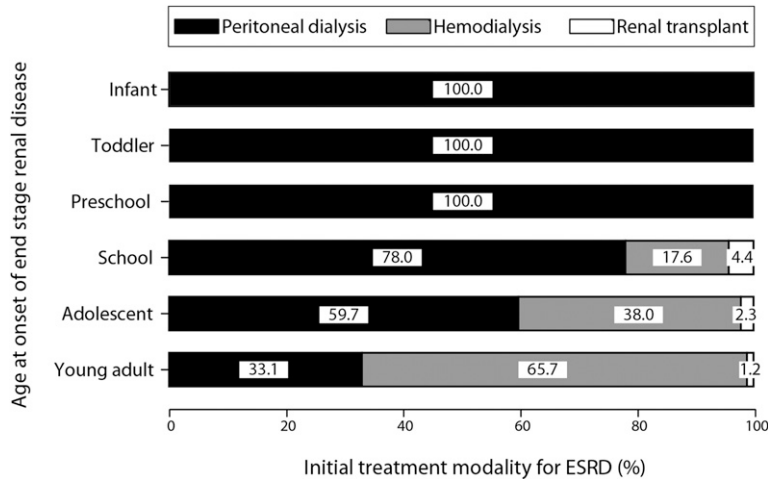
Figure 2. | **Initial treatment modality for ESRD in the young population, by age of onset.** Patients without complete record of treatment modalities were not included. Taiwan nationwide cohort, 1998–2009 (*n*=2471).

Table 1. Contributory causes of ESRD in young patients (*n*=2304, 1998–2009)

Contributory Causes of ESRD	Female (*n*=1049)	Male (*n*=1255)	Total (*N*=2304)
Glomerulonephropathy			
Unknown GN	486 (46.3)	675 (53.8)	1161 (50.4)
Systemic lupus erythematous	164 (15.6)	57 (4.5)	221 (9.6)
Henoch-Schönlein purpura	9 (0.9)	3 (0.2)	12 (0.5)
Scleroderma	1 (0.1)	1 (0.1)	2 (0.1)
Hemolytic-uremic syndrome	2 (0.2)	3 (0.2)	5 (0.2)
Wegener granulomatosis		2 (0.2)	2 (0.1)
Goodpasture syndrome	7 (0.7)	2 (0.2)	9 (0.4)
Genetic and metabolic diseases			
Type 1 diabetes mellitus	100 (9.5)	106 (8.4)	206 (8.9)
Amino-acid transport disorders		1 (0.1)	1 (0.0)
Glycogen storage diseases	1 (0.1)		1 (0.0)
Mucopolysaccharidosis		1 (0.1)	1 (0.0)
Metabolic disorders	7 (0.7)	7 (0.6)	14 (0.6)
Lysosomal storage disorders	1 (0.1)	3 (0.2)	4 (0.2)
Tuberous sclerosis	3 (0.3)	1 (0.1)	4 (0.2)
Amyloidosis	1 (0.1)	1 (0.1)	2 (0.1)
Congenital anomalies (CAKUT)			
Renal hypoplasia, dysplasia, oligonephronia	18 (1.7)	26 (2.1)	44 (1.9)
Cystic kidney disease	9 (0.9)	27 (2.2)	36 (1.6)
Congenital anomalies of urinary system	2 (0.2)	2 (0.2)	4 (0.2)
Specified anomalies of kidney	8 (0.8)	13 (1.0)	21 (0.9)
Renal and urinary tract tumor	19 (1.8)	17 (1.4)	36 (1.6)
Nephrolithiasis	7 (0.7)	23 (1.8)	30 (1.3)
Renal trauma	1 (0.1)	4 (0.3)	5 (0.2)
ESRD with hypertension	203 (19.4)	280 (22.3)	483 (21.0)

Values are expressed as number (percentage) of patients. CAKUT, congenital anomalies of the kidney and urinary tract.

The incidence rate of ESRD in young populations markedly varies across countries, although the rates by age group appear to be consistent with those in the United States and Canada, according to a 2012 US Renal Data System report (11). In Taiwan, the incidence rate for ESRD in the young population was higher than the worldwide incidence (21.1 per million person-years) but the rate in the pediatric group was similar to the rate in other countries (10.3 per million person-years) (7,11). This finding is compatible with that of a previous registry study showing the successful implementation of two health policies: a nationwide urine screening program for school-age children and a routine abdominal ultrasound examination for pregnant women (12).

Table 2. Age at onset of ESRD in the young population in Taiwan, by sex and cause (n=2304, 1998–2009)

Variable	All (n=1049 [Female] and n=1255 [Male])	Infant (n=6 [Female] and n=9 [Male])	Toddler (n=6 [Female] and n=3 [Male])	Preschool (n=6 [Female] and n=6 [Male])	School Age (n=43 [Female] and n=51 [Male])	Adolescent (n=109 [Female] and n=166 [Male])	Young Adult (n=879 [Female] and n=1020 [Male])
Female							
Glomerulonephropathy	669 (63.8)	4 (66.7)	2 (33.3)	2 (33.3)	26 (60.5)	77 (70.6)	558 (63.5)
Genetic and metabolic diseases	113 (10.8)			1 (16.7)	4 (9.3)	7 (6.4)	101 (11.5)
Congenital anomalies (CAKUT)	37 (3.5)	2 (33.3)	2 (33.3)	3 (50.0)	9 (20.9)	8 (7.3)	13 (1.5)
Tumor	19 (1.8)				1 (2.3)		18 (2.0)
Nephrolithiasis	7 (0.7)						7 (0.8)
Trauma	1 (0.1)						1 (0.1)
ESRD with hypertension	203 (19.4)		2 (33.3)		3 (7.0)	17 (15.6)	181 (20.6)
Male							
Glomerulonephropathy	743 (59.2)	7 (77.8)	2 (66.7)	3 (50.0)	27 (52.9)	103 (62.0)	601 (58.9)
Genetic and metabolic diseases	120 (9.6)	1 (11.1)		1 (16.7)	4 (7.8)	8 (4.8)	106 (10.4)
Congenital anomalies (CAKUT)	68 (5.4)		1 (33.3)	2 (33.3)	13 (25.5)	25 (15.1)	27 (2.6)
Tumor	17 (1.4)	1 (11.1)				4 (2.4)	12 (1.2)
Nephrolithiasis	23 (1.8)				1 (2.0)		22 (2.2)
Trauma	4 (0.3)					1 (0.6)	3 (0.3)
ESRD with hypertension	280 (22.3)				6 (11.8)	25 (15.1)	249 (24.4)

Values are expressed as number (percentage) of patients.

Table 3. Renal survival in ESRD of the young population in Taiwan, by cause (*n*=2304, 1998–2009)

Variable	Patients (*n*)	Observed Person-Years	Renal Survival (yr)		
			First Quartile	Median	Third Quartile
Glomerulonephropathy	1412	2433.6	0.1	0.5	2.7
Systemic lupus erythematosus	221	749.9	0.7	2.7	5.3
Henoch-Schönlein purpura	12	42.9	0.6	3.1	4.8
Other glomerulonephropathy	1179	1640.9	0.0	0.3	2.0
Genetic and metabolic diseases	233	1196.4	1.3	3.7	7.1
Diabetic nephropathy	206	782.6	1.1	3.2	6.2
Congenital anomalies (CAKUT)	105	1718.8	10.7	16.0	23.5
Tumor	36	71.1	0.2	1.3	2.7
Nephrolithiasis	30	76.9	0.7	1.1	3.1
Trauma	5	14.7	0.1	3.3	5.6
Hypertension	483	1014.6	0.1	0.7	3.5

In Taiwan, ESRD in the pediatric population may have different underlying causes than in other parts of the world. Compared with the US Renal Data System findings, for example, males are at no higher risk for ESRD than females in this population in Taiwan, whereas incidence was associated with a male predominance in Japan (13) and the United States (9); however, this trend varied with time in Canada (3). In Taiwan, patients with CAKUT, the well-known male-predominant renal diseases, had markedly longer renal survival time than patients with other renal disease; most of these patients did not start their renal replacement treatment until teenage or adulthood. Similar findings have been reported in the study of the European Renal Association-European Dialysis and Transplant Association Registry (14) and a longitudinal study in the United States (15). Moreover, Taiwan's nationwide urine screening program for school-age children may play a role in early detecting CAKUT or reversible cause of ESRD and may explain the difference between Taiwan and other countries (16,17).

The usefulness of preventive urine screening among asymptomatic school-age children for kidney disease is still debatable. This study reveals that the progression of renal disease (renal survival) in children not only substantially differs from that in adults but also heterogeneously varies by cause. Predominant causes of ESRD, such as glomerulonephropathy, progress very quickly and may thus require a screening program for the early detection of potential risk factors. Because the incidence of glomerulonephropathy-related ESRD markedly increases from school age, the findings here support a screening program that targets school-age children in glomerulonephropathy-dominant countries such as Japan (18), Korea (19), Lebanon (20), and Taiwan (21). However, a cost-effectiveness analysis is needed to justify a universal screening program for pediatric ESRD (22).

The modality for initial treatment of ESRD was an age-dependent choice of peritoneal dialysis in the pediatric group and hemodialysis in the young adults. The preemptive transplants were received only in school children, adolescents, and young adults. The choice of initial treatment modality is similar to that in other countries, such as Japan (4) and the United States (6,11). However, the proportion of pediatric renal transplantation was lower than

that in the aforementioned countries and suggests room for improvement in treatment of pediatric ESRD (4,11).

The causes of ESRD greatly differ between pediatric patients and young adults. This finding is consistent with studies that used biopsy-based registries in other countries (23). However, the nature of the NHIRD, which lacks chart-level data, such as biopsy and blood chemistry results, precludes a more detailed analysis of specific causes of ESRD in the young, such as IgA nephropathy (the major leading cause of pediatric ESRD in Asia) (18), minimal-change disease, or FSGS. Moreover, in Taiwan, hereditary nephropathy and congenital nephrotic syndrome are usually labeled as "nephritis and nephropathy" (ICD-9 code 583) and then categorized as "unknown glomerulonephritis." Hence, "unknown glomerulonephritis" accounts for a majority of cases in this study, as opposed to CAKUT in other studies (14). This part of the results should be interpreted cautiously, especially in comparing it with findings from other biopsy-based studies.

Early detection, correct diagnosis, and close follow-up are crucial in the management of all patients with ESRD, not only in children and adolescents with CKD. This study provided cause-specific epidemiologic information for optimal ESRD prevention and treatment of CKD. For example, GN developed abruptly and variously depending on the diverse GN causes. Moreover, the reasonable follow-up period for SLE and HSP should be at least 3 years for renal function; CAKUT requires a long-term follow-up of up to 16 years. The incidence of ESRD in type 1 DM was nine times higher than that in the United States and warrants public attention on disease management (24). These findings are compatible with and also strengthened the current knowledge in pediatric ESRD (25,26).

This study has several limitations. Systematic bias may exist in renal survival analysis because of the exclusion of patients with incomplete observation (*i.e.*, left censoring). Truncating the left-censored patients may establish the validity of the cause of ESRD and its index date, but renal survival analysis may preferentially favor patients with a more rapid decline in kidney function. Although the sensitivity test shows no statistical difference between participants and excluded patients (Supplemental Table 1), the patient characteristics may

not be exactly representative of the general population. The patients were included in the incidence analysis to enable the estimation of incidence of ESRD and for comparison with other studies.

In addition, classification errors of the causes of ESRD may still exist despite the sophisticated design of the differentiating algorithm in this study. As mentioned above, half of the patients in this study had a diagnosis of "unknown glomerulonephritis," a miscellaneous item containing many glomerulonephritides that may be classified into other conditions by different methods. This is a limitation that should be interpreted with caution in comparison with other studies. Although the NHIRD provides de-identified data without links to imaging findings and biopsy results, the Bureau of National Health Insurance in Taiwan regularly cross-checks and validates medical charts to ensure the accuracy of the diagnosis coding. A recent validation study also suggests the reliability of diagnostic codes in the NHIRD (27). Furthermore, the disparity in health utilization is minimal under the scheme of Taiwan's national health insurance. Everyone can easily get medical assessments or consultations for their needs. This greatly reduces the recall bias of registry-based studies and minimizes the issue of classification error.

Identification of the cause of hypertension in these young patients with ESRD is limited by chart-level information. The most common cause of hypertension in young patients with CKD varies by age. For school-age children, CKD with hypertension is more commonly caused by scarring of the kidneys, dysplasia, GN, obstructive nephropathy, and polycystic kidney disease, whereas hypertension in the neonate may be due to renal artery thrombosis, coarctation of the aorta, obstructive nephropathy, or bronchopulmonary dysplasia (5,11,28). In general, the younger the child is, the more often hypertension is secondary. However, more detailed information is needed for clarification.

The length-time bias may also exist in estimating renal survival time. Such estimation can accurately calculate the actual time from diagnosis to end stage by the comprehensiveness of the NHIRD. However, if some patients with only mild symptoms do not visit the doctor until symptoms worsen, the time from diagnosis to renal failure is much shorter than the time from symptom onset to renal failure. Among all causes of ESRD, hypertension is the one most likely to have length-time bias. Because hypertension is often asymptomatic, it is not uncommon for children to have long-standing and uncontrolled hypertension when they first present to a physician (29). Although this study accurately calculates time from diagnosis to renal failure, there is always a time lag between onset and diagnosis of hypertension that may lead to an underestimation of renal survival time or an overestimation of progression toward ESRD.

In conclusion, the incidence and causes of ESRD in the pediatric group greatly differ from those in the young adult populations. Onset age and renal survival time markedly vary depending on the cause of ESRD. The reason that the underlying causes and natural disease course for Taiwan's ESRD pediatric population vary from those in other countries deserves further investigation. Age- and cause-specific strategies aimed at ESRD prevention for young population are warranted.

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