의학석사 학위논문

# Outcomes of chronic dialysis in Korean children with respect to survival rates and causes of death

# 투석중인 한국 만성 신질환 소아의 생존률 및 사망원인 고찰

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# Abstract

## Outcomes of chronic dialysis in Korean children with respect to survival rates and causes of death

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*Purpose*: Adult Korean patients on chronic dialysis have a 10-year survival rate of 50%, with cardiovascular problems being the most significant cause of death. The 2011 annual report of the North American Pediatric Renal Trials and Collaborative Studies group reported 3-year survival rates of 93.4% and relatively poorer survival in younger patients. In this study, we have reviewed data from Korean Pediatric Chronic Kidney Disease Registry to assess survival rates and causes of death in Korean children on chronic dialysis.

*Methods*: We have analyzed the data from Korean Pediatric Chronic Kidney Disease Registry from 2002 to 2015. The study population was divided by age, sex and modality of dialysis. Survival rates were estimated at 1, 3, and 5 years from the initiation of dialysis. The most significant causative factor was designated as the cause of death.

*Results*: The overall estimated patient survival rates were 98%, 94%, and 90% at 1, 3, and 5 years, respectively. There was no significant difference in survival rates

between males and females. Patients for whom dialysis was initiated before 2 years of age (n=51) had significantly lower survival rates than those for whom dialysis was initiated at and over 6 years of age (n=327). No significant difference was observed in survival rates between all the patients on peritoneal dialysis (PD) and those on hemodialysis (HD). However, the 5-year survival of children less than 2 years of age on PD was significantly lower than that of children at and over 6 years of age and that on HD was significantly lower than that of children at and over 12 years of age. In all, 36 patients had died; the mortality rate was 23.7 per 1,000 patient years. The most common causes of death were infections and cardiopulmonary diseases.

*Conclusion*: The outcomes observed in this study were better than those observed in adults and comparable to those observed in pediatric studies in other countries. To improve the outcomes of children on chronic dialysis, it is necessary to prevent dialysis-related complications such as infection, congestive heart failure, or CNS hemorrhage and best control treatable comorbidities.

Keyword: Survival, Outcomes, End-stage renal disease, Dialysis, Child

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# Introduction

End-stage renal disease (ESRD), the terminal stage of chronic kidney disease (CKD), is a growing health problem worldwide. According to the United States Renal Data System (USRDS), the annual incidence of ESRD increased from 13 per million of the age-related population (MARP) in the 1988 to 15 per MARP in the 2003[1)]. European Dialysis and Transplant Association (EDTA) registry showed that the incidence of RRT in pediatric patients in Europe from 2009 to 2011 was 5.5 cases per million age-related population (pmarp) in patients aged 0–14 years and the prevalence of RRT was 27.9 pmarp and increased with age[2)]. In Korean children, according to the data from the Korean Health Insurance Review & Assessment Service in 2009, 435 children under the age of 20 were on RRT, and the incidence and the prevalence of ESRD were 10.5 and 38.5 per MARP , respectively (unpublished data).

Although the expected outcome of ESRD has improved substantially over the past 40 years, the overall 10-year survival remains approximately 80%, and the mortality rate (MR) is still 30–150 times higher than that of children without ESRD[3)]. The 2011 annual report of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) group reported 3-year survival rates while on dialysis of 93.4% and relatively poorer survival in younger patients[4)]. Cardiopulmonary problems and infection were the major causes of death.

In Korea, data on the outcomes of children on chronic dialysis was not reported yet. Adult Korean patients on chronic dialysis were reported by the Committee of the Korean Society of Nephrology in 2014 to have a 5-year survival rate of

approximately 70% and a 10-year survival rate of 50%. The most common cause of death was cardiovascular problems[5].

In this study, we analyzed the KPCKD registry data to assess the outcomes of chronic dialysis in Korean children.

# Materials and methods

*Study population*

Data from the KPCKD registry for the period from January 2002 to May 2015 were utilized. This web-based registry (http://pedckd.or.kr), launched in 2004 by the Korean Board of Collaboration for Pediatric CKD, has collected clinical data for patients with CKD. Patients who had initiated either peritoneal dialysis (PD) or hemodialysis (HD) before the age of 20 years were selected for this study. The follow-up duration was defined as the period from the initiation of dialysis to the date of renal transplantation, death, the date of transfer to internist or the last data entry. Patients with follow-up duration under 3 months were excluded in this study. To analyze the difference in outcome by the patient's age at the initiation of dialysis, the study population was divided into four subgroups: <2 years, 2–5 years, 6–11 years, and ≥12 years of age at the initiation of dialysis.

Patient survival data from the registry were obtained. In addition, recent information of patients whose data had not been updated or not sufficient was exploited by the physicians of each individual centers. For deceased patients, additional data were collected from the patient's medical records, including the age of death, the modality of RRT at the time of death, the total duration of RRT and the cause of death. When multiple causes of death were identified, the most direct or the most significant causative factor was designated as the cause of death.

*Statistics*

Patient survival rates were calculated by the Kaplan-Meier method using PASW

ver. 21.0 (SPSS Inc., Chicago, IL, USA) as the cumulative survival probability at the 1st, 3rd, 5th year of chronic dialysis and were described as 1-, 3- and 5-year survival. *P* values less than 0.05 were considered to be statistically significant.

The MR was calculated by dividing the number of deaths by the total patient follow-up time (i.e., the sum of the duration of chronic dialysis for all patients) in years and multiplying by 1,000, which shows the number of deaths per 1,000 patient years.

# Results

*Korean pediatric patients with ESRD*

Four hundred forty-four patients had initiated chronic dialysis before their age of 20 years at the time of data collection (Table 1). Their mean age at the initiation of chronic dialysis was 9.61±0.02 years (range, 0.00–19.85 years), and the mean duration of chronic dialysis was 103.9±0.3 months (range, 3.0–230.9 months). The number of patients treated with only PD was 297 and that of patients who did HD was 67. Eighty patients changed modality of dialysis at least once.

*Survival of ESRD patients*

The overall patient survival rate was 98% at 1 year, 94% at 3 years, and 90% at 5 years (Fig. 1). There was no significant difference in survival rates between males and females (*P=0.429*) (Fig. 2). The 5-year survival of patients who initiated dialysis at an age less than 2 years (n=51) was 61%, at 2 to 5 years (n=66) was 94%, at 6 to 11 years (n=157) was 91%, and at or over 12 years (n=170) was 96% (Fig. 3). The 5-year survival of children less than 2 years of age was significantly lower than that of children at and over 6 years of age (0–1 year vs. 2–5 years, *P*=0.118; 0–1 year vs. 6–11 years, *P*=0.004; 0–1 year vs. ≥12 years, *P*=0.001). The 1-, 3-, and 5-year survival rate for patients who started dialysis earlier than 2 years of age were 87%, 72%, and 61%, respectively. The overall 1-, 3-, and 5-year survival rate for PD patients were 95%, 92%, and 91%, and those for HD patients were 98%, 95%, and 89%, respectively (Fig. 4). There was no significant difference of survival between all the patients on PD and those on HD (*P*=0.621).

However, the survival rate by modality of dialysis was significantly different by age groups. The 5-year survival of children less than 2 years of age on PD was significantly lower than that of children at and over 6 years of age (0–1 year vs. 2–5 years, $P$=0.054; 0–1 year vs. 6–11 years, $P$=0.008; 0–1 year vs. ≥12 years, $P$=0.000). And the 5-year survival of children less than 2 years of age on HD was significantly lower than that of children at and over 12 years of age (0–1 year vs. 2–5 years, $P$=0.727; 0–1 year vs. 6–11 years, $P$=0.167; 0–1 year vs. ≥12 years, $P$=0.046).

*Mortality*

During the period from 2002 to 2015, a total of 36 patients (male:female, 18:18) died while on chronic dialysis (HD:PD, 10:26), at a mean age of 9.56±0.30 years (range, 0.32–22.61 years). Fourteen of 36 patients (38.9%) died at less than two years of age (male:female, 7:7). The MR of this study was 23.7 per 1,000 patient years. The mean age at the initiation of RRT was 6.12±0.27 years, and the mean duration from the initiation of dialysis to death was 104.7±5.3 months.

*Causes of death*

The most common causes of death were infection and cardiopulmonary diseases. Six patients died from infection; 5 from sepsis, 1 from pneumonia. Five patients were on PD at the time of death (Table 2). Six patients died from cardiopulmonary diseases; 4 from congestive heart failure, 2 from pulmonary hypertension and pulmonary hemorrhage.

Five patients died due to the progression of an underlying malignancy (brain tumor, neuroblastoma, clear cell sarcoma and leukemia). Two patients died from gastrointestinal bleeding. A patient with acute tubular necrosis died because of increased bleeding tendency and the other patient with nephronophthisis died from uncontrolled varix bleeding. A patient with primary oxalosis died from hepatic fibrosis after hepatic transplantation. Two patients with Kearns-Sayre syndrome and nephronophthisis died from intractable seizure and a patient with hydrocephalus died from neurologic shock. Hemorrhage of the central nervous system (CNS) (n=3) was also significant cause of death. Two of 3 patients who died from CNS hemorrhages were on HD. Three patients died of hyperkalemia or acidosis. One of them could not keep any access for dialysis because of venous thrombosis and peritoneal problems. Another patient died from hyperkalemia due to inadequate dialysis. The other patient with Rabson-Mendenhall syndrome died due to intractable diabetic ketoacidosis.

Two patients died from choking and suicide. The causes of death of the other 5 patients were unknown.

The most common cause of death of patients with less than 2 years of age was infection (Table 3). Especially, 5 of 6 patients (83.3%) who died from infection had started dialysis at less than 2 years of age; 4 on PD, 1 on HD at the time of death. Two patients died due to GI bleeding and hepatic fibrosis, respectively. Two patients died from hyperkalemia due to inadequate dialysis. Only one patient died from congestive heart failure. Two patients died due to neurologic shock and CNS hemorrhage, respectively. There was not any patient who died from the progression of malignancy. The cause of death of 2 patients was unknown.

**Table 1.** Patient demographics and characteristics

| | Dialysis Modality | | | |
|---|---|---|---|---|
| | PD only | HD only | PD & HD | Total |
| N<br>(%) | 297<br>(66.9) | 67<br>(15.1) | 80<br>(18.0) | 444<br>(100.0) |
| M/F | 1.45/1 | 1.39/1 | 1.29/1 | 1.41/1 |
| Age | | | | |
| 0-1 year | 27 | 8 | 16 | 51 |
| 2-5 years | 45 | 9 | 12 | 66 |
| 6-11 years | 104 | 26 | 27 | 157 |
| ≥12 years | 121 | 25 | 24 | 170 |
| Age at initiation* | 9.87±0.04 | 9.68±0.12 | 8.21±0.12 | 9.61±0.02 |
| Duration of RRT† | 99.8±0.5 | 81.8±2.0 | 145.5±2.0 | 103.9±0.3 |

Values are presented as number (%).

* Mean age at initiation of chronic dialysis (years); Mean±SD

† Mean duration of chronic dialysis (month); Mean±SD

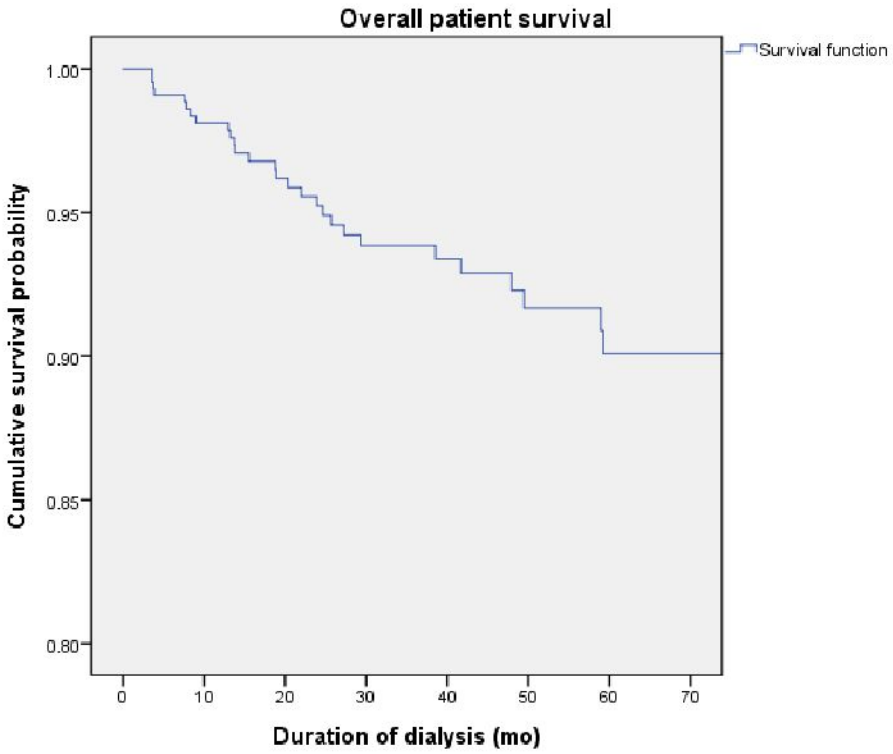


**Figure 1.** Cumulative survival rate of all the patients on chronic dialysis.

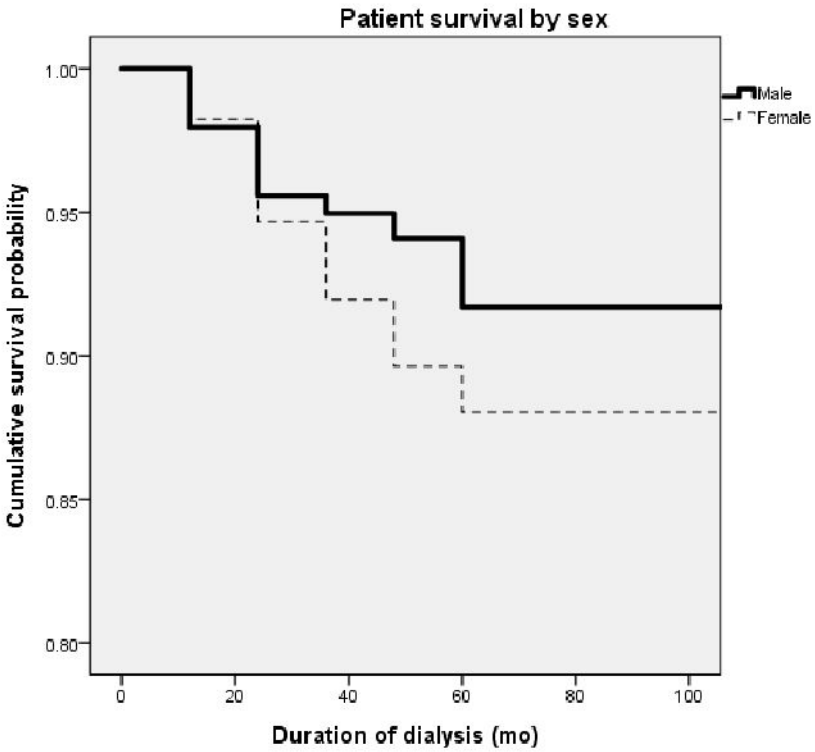


**Figure 2.** Cumulative survival rates of all the patients by sex.

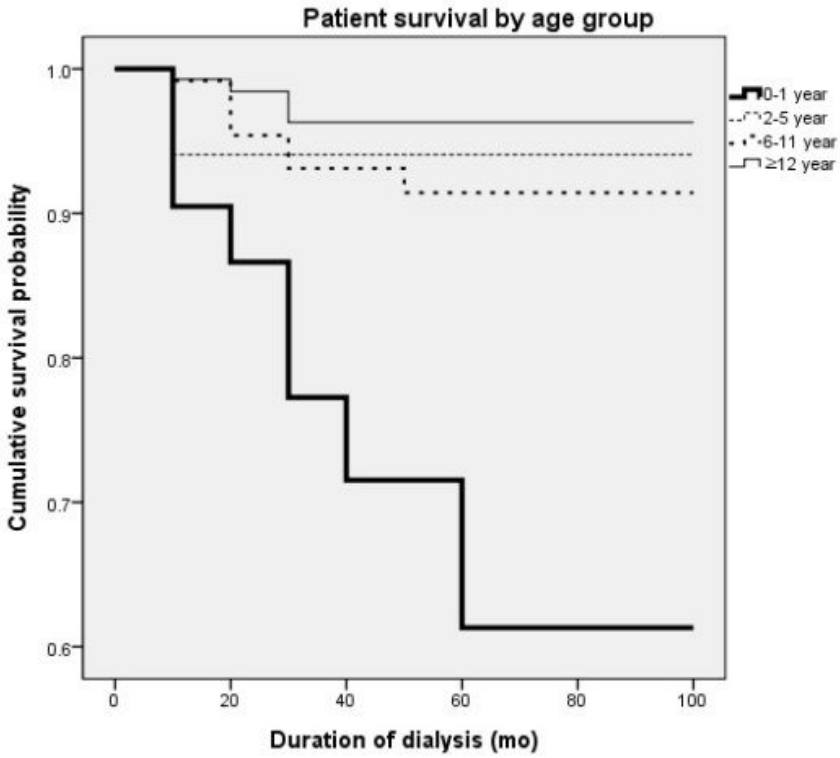


**Figure 3.** Cumulative survival rates of patients in whom dialysis was initiated at different age groups.

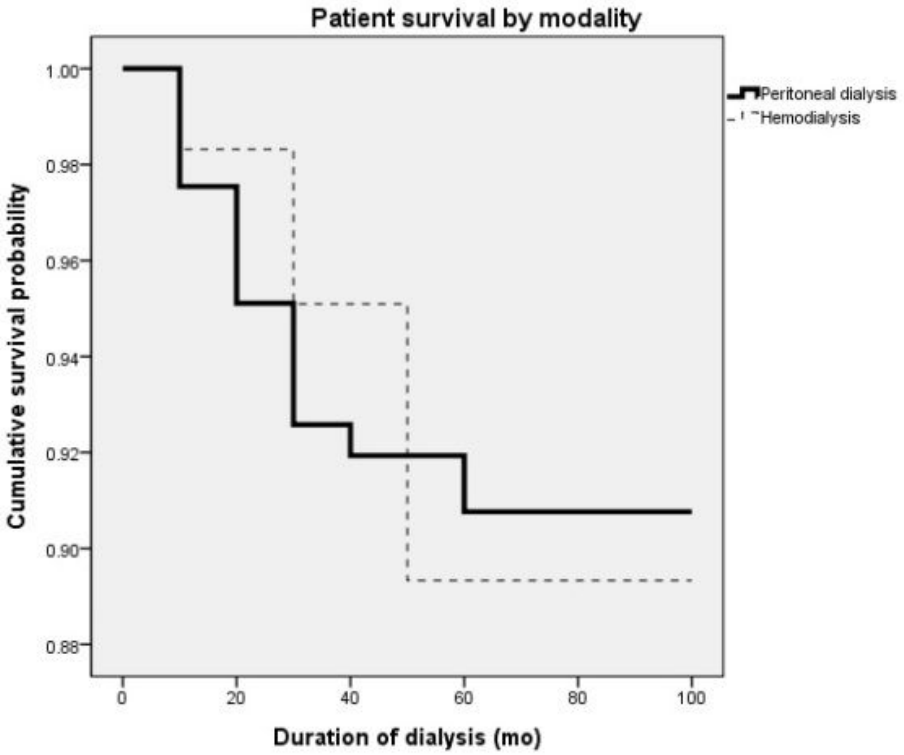


**Figure 4.** Cumulative survival rates of patients on different types of dialysis.

**Table 2.** Causes of death of Korean children on chronic dialysis

| | The Last Dialysis Modality | | |
|---|---|---|---|
| Causes of death | Total | PD | HD |
| Infection | 6 (16.7) | 5 (19.2) | 1 (10.0) |
| Cardiopulmonary | 6 (16.7) | 5 (19.2) | 1 (10.0) |
| Malignancy | 5 (13.9) | 4 (15.4) | 1 (10.0) |
| GI/Liver disease | 3 (8.3) | 1 (3.8) | 2 (20.0) |
| Neurologic disease | 3 (8.3) | 3 (11.5) | 0 (0.0) |
| CNS hemorrhage | 3 (8.3) | 1 (3.8) | 2 (20.0) |
| Hyperkalemia/ Acid-base imbalance | 3 (8.3) | 1 (3.8) | 2 (20.0) |
| Others* | 2 (5.6) | 2 (7.7) | 0 (0.0) |
| Unknown | 5 (13.9) | 4 (15.4) | 1 (10.0) |
| Total | 36 (100.0) | 26 (100.0) | 10 (100.0) |

Values are presented as number (%).

* Choking and suicide.

**Table 3**. Causes of death of patients with less than 2 years of age at initiation of dialysis

| | The Last Dialysis Modality | | |
|---|---|---|---|
| Causes of death | Total | PD | HD |
| Infection | 5 (35.7) | 4 (44.4) | 1 (20.0) |
| Cardiopulmonary | 1 (7.1) | 1 (11.1) | 0 (0.0) |
| GI/Liver disease | 2 (14.3) | 1 (11.1) | 1 (20.0) |
| Neurologic disease | 1 (7.1) | 1 (11.1) | 0 (0.0) |
| CNS hemorrhage | 1 (7.1) | 0 (0.0) | 1 (20.0) |
| Hyperkalemia | 2 (14.3) | 0 (0.0) | 2 (40.0) |
| Unknown | 2 (14.3) | 2 (22.2) | 0 (0.0) |
| Total | 14 (100.0) | 9 (100.0) | 5 (100.0) |

Values are presented as number (%).

# Discussion

To the best of our knowledge, this is the first report on the outcomes of chronic dialysis in Korean children. The MR of our study population was 23.7 per 1,000 dialysis patient years. This rate is comparable to USRDS data from 2014 reporting an adjusted MR of 35 per 1,000 patient years for pediatric dialysis patients (aged 0–19 years) in 2007-2011[6], Dutch data from 2002 reporting an MR of 15.7 per 1,000 patient years[7] and Japanese data from 2015 reporting an MR of 18.2 per 1,000 dialysis patient years (in patients aged 0–19 years)[8]. Longer-term patient survival data are available from the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry (n=1,634), which has the longest longitudinal follow-up period. The ANZDATA results show a 10-year survival of 79% and a 20-year survival of 66% for children less than 20 years of age who started RRT between 1963 and 2002[9]. Although the length of observation was relatively short in the present study, the 5-year overall patient survival (91%) was slightly better than that of ANZDATA (86%).

Our study found that there was no significant difference of survival between the patients on PD and those on HD ($P$=0.621). This result corresponds with a report from Taiwanese renal registry which showed no difference of survival between chronic HD and PD in patients less than 20 years of age ($P$=0.4878)[10].

Our study also found that younger patients, especially those patients who started dialysis at less than 2 years of age, had poorer survival. The 2011 annual report of NAPRTCS group also reported significantly lower survival rate in children younger than 2 years of age at the beginning of dialysis[4]. Additionally, the

ANZDATA registry identified a younger age at the initiation of dialysis as a risk factor for poor survival[9]. In this study, patients who started dialysis at less than 2 years of age died from sepsis exceptionally more than the patients of other age groups did. Sepsis can be regarded as a catheter-related complication of dialysis. So the poorer outcome in younger patients can be explained by the higher incidence of life threatening complications of chronic dialysis[11,12]. In addition, the shortage of medical equipment and experienced personnel necessary to care them can be another reason for high mortality of younger chidren.

The most common causes of death in this study were infection in which dialysis-related sepsis to be most frequent and cardiopulmonary diseases. Wood et al.[13] reported that infection was the most common primary cause of death, accounting for 15 of 51 deaths (29.4%). ESRD is an immunologically compromised condition[14], and the accesses for chronic HD or PD make the patients highly vulnerable to infectious complications. And just like in adults patients[6,15], cardiovascular disease is one of the most significant causes of death in children on chronic dialysis; cardiac arrest is the most commonly reported cause of death in children[16]. ANZDATA reported that the most common cause of death in children on dialysis was cardiovascular disease (45%), with the second most common being infection (21%)[9]. And the rate of cardiovascular death in pediatric patients with ESRD in USRDS was up to 37%[6]. Mortality by cardiovascular origin in this study (16.7%) was lower than that of adults or other pediatric studies. And pulmonary hemorrhage, a common manifestation of severe congestive heart failure, was the cause of death in only one patient.. The difference could be originated by the fact that pediatric ESRD patients undergo renal transplantation earlier than adults before severe uremic cardiomyopathy develops. In addition, relatively shorter

follow-up duration of this study could be another reason. Furthermore, the patients with unknown causes of death might have died from cardiovascular diseases. Current data on cardiovascular death in pediatric patients with ESRD suggest that endothelial dysfunction appears early in renal failure in children, and is followed by arterial medial calcification. This calcification causes arterial wall stiffening and subsequently left ventricular hypertrophy. And high systolic blood pressure and serum concentrations of intact parathyroid hormone, calcium and phosphate, as well as long-term dialysis, seem to be important risk factors for cardiovascular disease in pediatric patients with ESRD[17]. In this study, there was only one child who had died from cardiovascular disease in less than 2 years of age at initiation of dialysis. It seems that younger patients on chronic dialysis are more fragile to dialysis related infection than cardiovascular disease because death by cardiovascular diseases in pediatric patients on chronic dialysis increases over duration of dialysis.

Another common cause of death in our study was malignancy. Comorbidities including malignancies, hepatic fibrosis, diabetes and CNS diseases lead to death in 11 patients (30.6%). Shroff et al.[18] reported that in a cohort of 98 children chronic dialysis, 76% of the mortalities was associated with comorbidities. Additionally, NAPRTCS data have identified comorbidities such as pulmonary hypoplasia and severe developmental delay, oliguria/anuria, and a younger age at the initiation of dialysis as risk factors for increased mortality in infants and young children[13].

It is assumed that the CNS Hemorrhage, which was the cause of death in 3 children, is associated with uncontrolled hypertension or accompanying

cerebrovascular diseases.

A limitation of our study is that it is based on the data from the KPCKD registry, which were input by the participating centers, and the registration rate was only 52%. It is speculated that internists who do not participate in the KPCKD registry are treating many adolescent patients with ESRD. Because all patients are eventually transferred to the internist, we, the authors, cannot know the accurate number of the dead patients. Additionally, the follow-up durations were not long enough to provide data for a long-term survival. To obtain long-term survival data, cooperation with internists is indispensable.

In conclusion, the outcomes of chronic dialysis in Korean children were better than those of adults, and comparable to pediatric studies of other countries as well. To improve the outcomes of children on chronic dialysis, prevention of dialysis-related complications, such as infection or congestive heart failure or CNS hemorrhage due to uncontrolled hypertension, and more aggressive management of treatable comorbidities are necessary.

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# 국문 초록

**목표:** 만성 투석을 시행중인 우리나라 소아 환자의 생존률 및 사망의 원인을 분석하여, 성인 및 외국 소아 환자의 결과와 비교하고자 한다.

**방법:** 2002년부터 2015년까지 대한소아신장학회의 한국소아만성콩팥병등록에 등록된 만성 투석을 시행중인 소아 환자를 대상으로, 투석 시작으로부터 1, 3, 5년 뒤 전체 생존률 및 투석의 종류, 연령, 성별에 따른 생존률 차이를 조사하였다. 또한 사망한 환자를 대상으로 사망의 주요 원인을 확인하였다.

**결과:** 만성 투석중인 한국 소아 환자의 전체 생존률은 투석 시작으로부터 1, 3, 5년 뒤 각각 98%, 94%, 90%였으며, 복막투석 환자와 혈액투석 환자 사이에 유의미한 생존률의 차이는 없었다. 또한 2세 이전에 투석을 시행한 환자(51명)는 6세 이후 투석을 시행한 환자(327명)보다 낮은 생존률을 보였다. 전체 환자중 36명이 사망하였으며, 사망의 가장 흔한 원인은 감염과 심폐질환이었다.

**결론:** 이번 연구를 통해, 만성 투석중인 우리나라 소아가 성인에 비해 나은 생존률을 보이며, 외국의 소아와도 견줄만한 생존률을 보임을 확인할 수 있었다. 향후 감염, 울혈성 심부전 혹은 중추신

경계 출혈과 같은 투석과 관련된 합병증을 예방하고 동반 질환의 적극적 치료를 통하여 만성 투석 소아 환자의 생존률을 향상시킬 수 있을 것이다.

**주요어:** 생존, 결과, 말기 신장질환, 투석, 소아

**학번:** 2012-23645