

Table 6 Patient and episode characteristics of effective and non-effective episodes

Patient and episode characteristics	Effective	<i>n</i>	Non-effective	<i>n</i>	<i>p</i> -value
Age (years)	55.57 ± 19.09	23	55.20 ± 15.36	20	n.s. ^a
BMI	24.01 ± 5.55	24	22.76 ± 4.15	16	n.s. ^a
Average number of LDL-A sessions	9.52 ± 2.55	25	9.77 ± 12.72	22	n.s. ^a
Average frequency of LDL-A sessions (per week)	1.92 ± 0.49	25	1.83 ± 0.47	20	n.s. ^a
Average amount of plasma per session (L)	3.37 ± 0.57	23	3.67 ± 0.98	20	n.s. ^a
Duration of NS before the treatment <8 weeks	11 (48.8 %)	24	2 (5.3 %)	19	<0.05 ^b
Male	14 (56.0 %)	25	14 (63.6 %)	22	n.s. ^b
Fatigue	17 (73.9 %)	23	13 (72.2 %)	18	n.s. ^c
Edema	23 (92.0 %)	25	16 (76.2 %)	21	n.s. ^c
First time	14 (56.0 %)	25	13 (61.9 %)	21	n.s. ^b
Renal biopsy	21 (84.0 %)	25	19 (86.4 %)	22	n.s. ^c
Cyclosporine A administration	12 (50.0 %)	24	12 (54.5 %)	22	n.s. ^b
Steroid pulse therapy	1 (4.2 %)	24	3 (13.6 %)	22	n.s. ^c

^a Student's *t* test^b Chi-square test^c Fisher's exact test

respectively), and also UP at pre-treatment also showed lower trend in effective episodes ($p = 0.075$) (Tables 5, 6). Not to be argued, UP and SP are distinctive indicators for severity of NS. It is suggested that patient's clinical condition has an influence on efficacy of LDL-A treatment. Hattori et al. reported that a higher selectivity index and lower degree of tubular damage were observed in pediatric patients with steroid-resistant NS who responded to LDL-A treatment compared to those who did not respond. We evaluated the duration after onset of NS dichotomized by within or more than 8 weeks. As shown in Table 7, of 13 episodes in which LDL-A was applied within 8 weeks after the onset, 11 (84.6 %) were effectively treated and recovered from nephrotic condition, whereas efficacy of the other episodes was poor (13/30, 43.3 %). Taken together, it could be considered that the less serious glomerular dysfunction and/or renal tissue damage of patients, the more likely for them to achieve effective treatment. Therefore, we suggest that LDL-A should be used immediately when a patient with NS appears not to respond to primary medication to prevent progression of renal injury.

The results of the study showed the short-term clinical efficacy of LDL-A for the treatment of drug-resistant NS in the population of patients in the POLARIS study. However, several limitations in this study need to be addressed. Most importantly, this study was conducted in an observational manner and did not intervene with concomitant therapies including medications. Therefore, the contribution of the concomitant therapies was not elucidated. In addition, the study was a single-arm study without a control group and accordingly it was difficult to directly demonstrate the efficacy of the treatment. Furthermore, the sample size was rather small to make a convincing evaluation. Although the above-mentioned limitations should be taken into consideration, this study was performed prospectively in a nationwide multicenter cohort with many more NS episodes

Table 7 Comparison of the therapeutic efficacy of LDL-A between patients who received treatment at less than ($n = 13$) and more than ($n = 30$) 8 weeks after onset of NS

Efficacy	Period before treatment	
	<8 weeks	≥8 weeks
Effective (<i>n</i>)	11	13
Non-effective (<i>n</i>)	2	17
Rate	84.6 %	43.3 %

The data for 4 episodes were not collected

than in previous studies and demonstrated comparable efficacy to that in the previous studies. It will be intriguing to see whether the improved clinical conditions produced by LDL-A will continue for a longer period. The final results of the POLARIS study may reveal the long-term clinical efficacy of LDL-A as an alternative therapy for drug-resistant NS.

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Conflict of interest None of the authors report a conflict of interest with this study.

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Prevalence and incidence of chronic kidney disease stage G5 in Japan

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Abstract The prevalence and incidence of end-stage kidney disease (ESKD) have continued to increase worldwide. Japan was known as having the highest prevalence of ESKD in the world; however, Taiwan took this place in 2001, with the USA still in third position. However, the prevalence data from Japan and Taiwan consisted of dialysis patients only. The prevalence and incidence of Kidney Transplantation (KT) in Japan were quite low, and the number of KT patients among those with ESKD was

regarded as negligibly small. However, the number of KT recipients has increased recently. Furthermore, there are no reports about nationwide surveys on the prevalence and incidence of predialysis chronic kidney failure patients in Japan. This review describes our recent study on the estimated number of chronic kidney disease (CKD) stage G5 patients and the number of ESKD patients living in Japan, obtained via the cooperation of five related medical societies. From the results, as of Dec 31, 2007, 275,242 patients had received dialysis therapy and 10,013 patients had a functional transplanted kidney, and as of Dec 31, 2008, 286,406 patients had received dialysis therapy and 11,157 patients had a functional transplanted kidney. Consequently, there were 285,255 patients with CKD who reached ESKD and were living in Japan in 2008 and 297,563 in 2009. We also estimated that there were 67,000 predialysis CKD stage G5 patients in 2009, 37,365 patients introduced to dialysis therapy, and 101 patients who received pre-emptive renal transplantation in this year. In total, there were 37,466 patients who newly required renal replacement therapy (RRT) in 2009. Not only the average ages, but also the primary renal diseases of the new ESKD patients in each RRT modality were different.

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Introduction

Chronic kidney disease (CKD) is known as not only a worldwide public health problem, but also a global socio-economic concern, with adverse outcomes including kidney failure, cardiovascular disease (CVD), and premature death [1]. In Japan as well as other developed countries, the

number of end-stage kidney disease (ESKD) patients has continued to increase [2, 3]. There are three types of treatment modality for ESKD: hemodialysis, peritoneal dialysis, and kidney transplantation (KT). The ESKD treatment modality is selected by several factors, including socio-economic status, educational status, and the patient's or their family's wishes. Therefore, the selection of ESKD treatment modality has varied markedly from country to country [4]. A nationwide survey of the incidence and prevalence of dialysis patients has been conducted since 1978 in Japan by the Japanese Society for Dialysis Treatment (JSDT). In addition, there have been annual reports of the incidence of kidney transplant (KT) recipients in Japan conducted by cooperation of both the Japanese Society for Transplantation (JST) and the Japanese Society for Clinical Renal Transplantation (JSCRT) [5]. In Japan, the prevalence and incidence of KT were quite low, and the number of KT patients among ESKD patients had been regarded as negligibly small. However, the number of KT recipients has been increasing recently. Furthermore, two Japanese nationwide surveys of renal replacement therapy (RRT) modality were performed separately, but there was no information transfer between the two surveys. In addition, there have been no reports about nationwide surveys on the prevalence and incidence of predialysis chronic kidney failure patients in Japan.

Annual reports of the United States Renal Data System (USRDS) provided international comparisons of the annual incidence and prevalence of ESKD patients among several countries [6]. In these reports, the incidence of new ESKD patients was shown per million population, with Taiwan in the first position, USA second, and Japan third. Japan was previously known to have the highest prevalence of ESKD in the world; however, Taiwan took this place in 2001, at which time Japan was second, and the USA was third. The order of these positions has been constant in recent years. Most countries have an ESKD registry, which includes the sums of the dialysis and KT populations, while in both Japan and Taiwan, the number of ESKD cases in such reports has referred to the dialysis population only. Furthermore, there has been a recent increase in patients receiving pre-emptive KT or KT after short-perioperative dialysis, especially in younger ESKD patients in Japan, resulting in an increased number of ESKD patients who were not registered in JSDT.

For not only international comparisons, but also for planning an effective treatment strategy for CKD, it is important to identify the total ESKD population. For this reason, we here attempt to estimate the sum of ESKD patients and CKD stage 5 patients in Japan, via the cooperation of the JSDT, JST, JSCRT, Japanese Society for Pediatric Nephrology (JSPN), and Japanese Society of Nephrology (JSN).

ESKD registry system in Japan

The JSDT registry

The JSDT has been conducting an annual questionnaire survey of dialysis facilities throughout Japan since 1968, and several papers based on these surveys have been published [7–9]. Since 1983, the JSDT has been compiling a computer-based registry. Details on the inception, limitations, validity, variables, and questionnaires used in the study are available online at the JSDT homepage (www.jsdt.or.jp). In brief, year-end survey questionnaires are sent to all dialysis facilities (4,255 facilities in 2011) in Japan each year. The questionnaire comprises four pages, the first page consists of facility data and second to fourth pages consist of detailed patient data of each facility, and the response rate in 2011 for the first page was 98.8 % and that for all the pages was 96.2 %. Questionnaires were administered by volunteers from among the staff of the facilities, the principal investigators in each prefecture, and the JSDT committee members. The JSDT funds a standing committee responsible for statistics and investigation [10]. This registry consisted of the patients who required maintenance dialysis only. Figure 1 shows the annual change of the prevalence of dialysis patients in Japan. When a dialysis patient received KT, the patient record was removed from the registry. If the same subject required dialysis again due to transplanted kidney failure, the subject registered as a new dialysis patient whose primary kidney disease was transplanted kidney failure.

JST and JSCRT registry

JST and JSCRT conducted an annual registry for new KT cases (Fig. 2), and they conducted follow-up surveys every 3 years. The follow-up surveys were subsequently conducted annually from 2009. The response rate (200 facilities) was 83.0 % in 2009 [5]. The patients who registered in this survey were restricted to those who had received their renal transplantation in Japan. Transplant tourism patients were excluded from the registry.

JSPN registry

A pediatric ESKD survey was conducted from 1999. The incidence of ESKD patients aged <20 years old was investigated in 1999–2000. Between 2001 and 2006, the survey was conducted on new ESKD patients aged <15 years old. The Committee of the Renal Data Registry of JSPN was established in 2007. In 2008, this committee investigated follow-up studies of new ESKD patients who started RRT in 1998–2005 in those aged <15 years old. After 2012, they conducted a national survey of pediatric

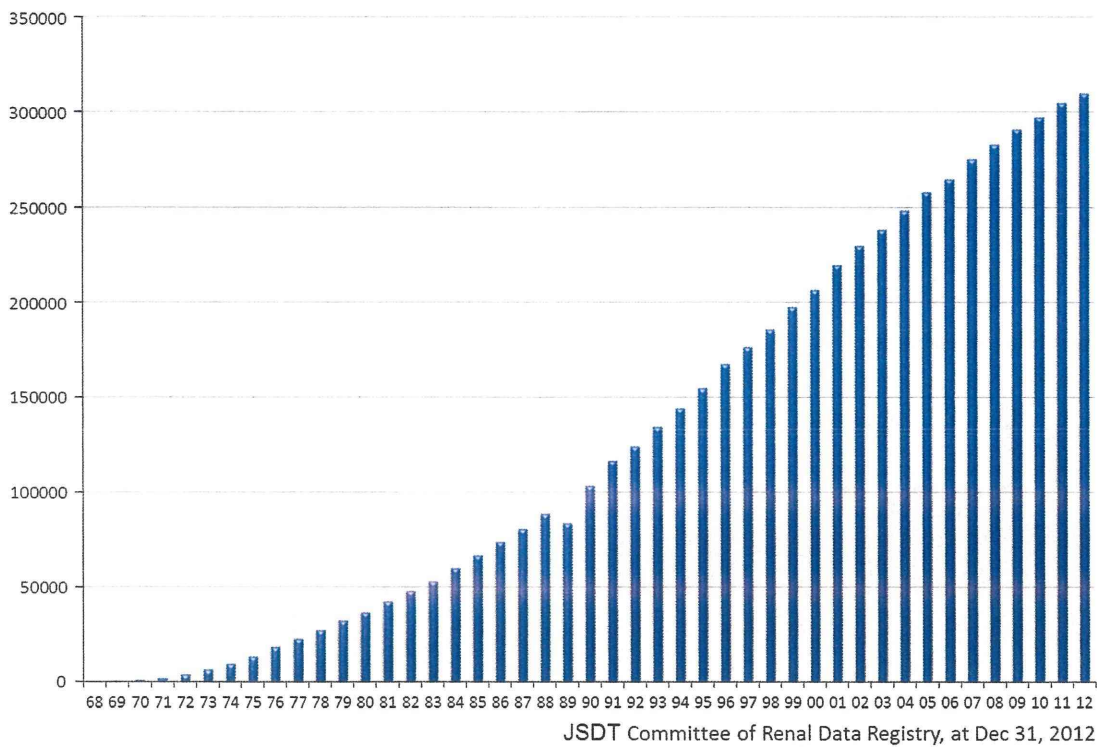


Fig. 1 Annual changes of prevalence of dialysis patients in Japan. In 1968, 215 dialysis patients were registered by JSDT committee of renal data registry, and a linear increment trend was seen until now. At Dec. 31, 2012, 309,946 subjects received dialysis treatment in Japan

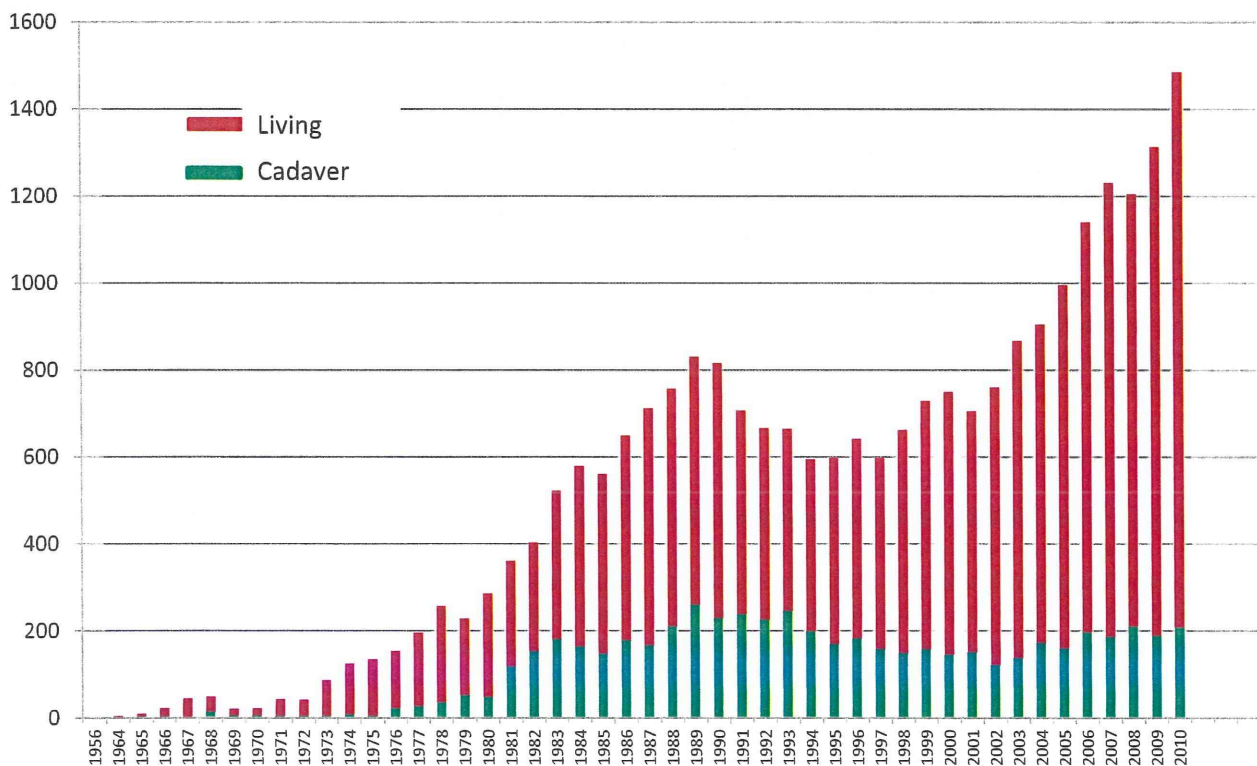


Fig. 2 Number of Renal Transplantations in Japan. The first cadaver renal transplantation was performed in 1956, and the first living-related renal transplantation was performed in 1964 in Japan.

Although, numbers of renal transplantation were decreased since 1990, it was increased again after 1996, because organ transplantation law had passed

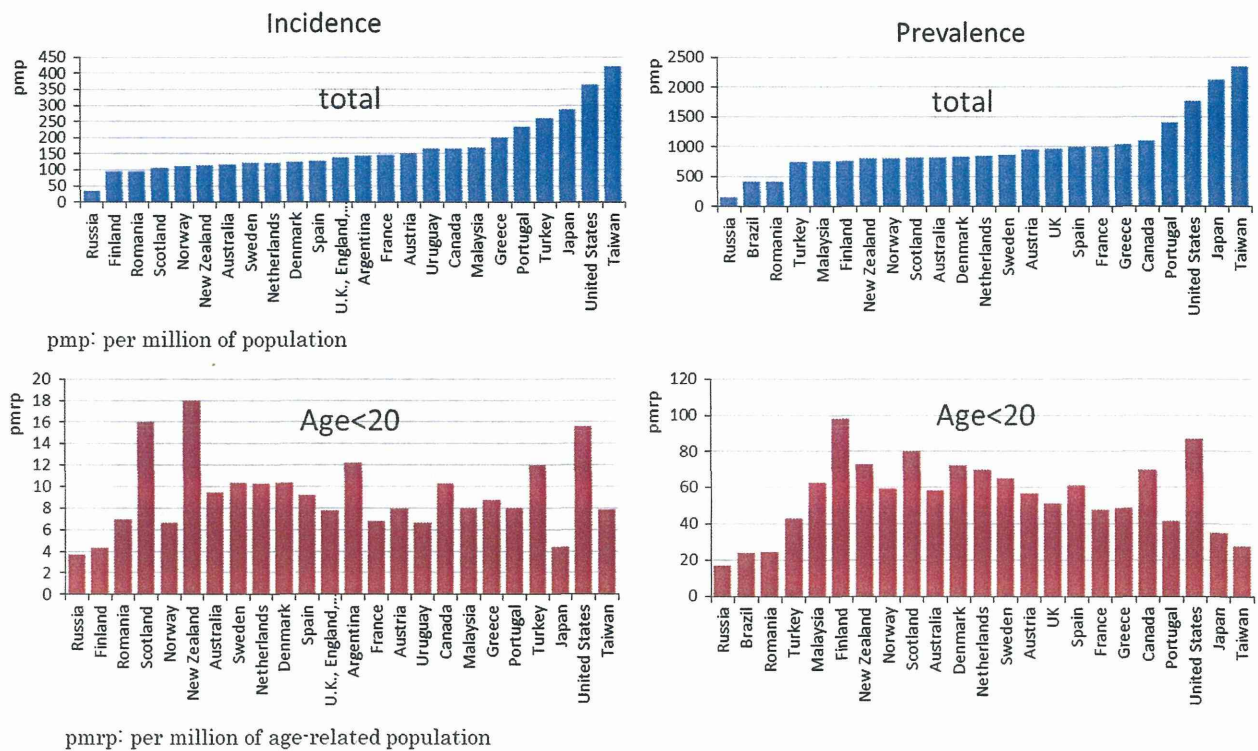


Fig. 3 International comparisons for incidence and prevalence of ESKD. Compared with adults, both the incidence and the prevalence of ESKD of both Japanese and Taiwanese pediatric ESKD were quite

low. The reason for these differences in both incidence and prevalence between adult and pediatric cases was unclear

dialysis and KT patients via the cooperation of both JSDT and JSCRT. Figure 3 shows an international comparison of total and pediatric (aged <20 years old) ESKD incidence and prevalence [4, 11]. Compared with adult cases, both the incidence and the prevalence of ESKD were quite different. In particular, the incidences of both Japanese and Taiwanese pediatric ESKD were quite low. The reason for these differences in both incidence and prevalence between adult and pediatric cases was unclear.

Registry for predialysis ESKD

Imai et al. [12, 13] reported the estimated number of CKD patients in Japan. This estimation was based on mass screening data of the general population [13]. However, most patients with CKD stage 5 were consulted and treated by nephrologists or general physicians; these patients may not have undergone the annual mass screening held by local governments. There were also no reports about the prevalence and incidence of CKD based on a national registry in Japan. Therefore, there were no detailed data of the preva-

lence of CKD stage 5 in Japan. However, Nakayama et al. [14, 15] reported the prevalence and follow-up results of CKD patients who consulted at nephrology clinics. From their 2,962 CKD cohort analysis, 96 patients of CKD stage G5 and 7 patients of CKD stage G4 received RRT at Dec. 31st 2009. Totally, 51.3 % of Gonryo CKD subjects were received maintenance dialysis at the end of 2009. In a dialysis registry held by JSDT, there were 37,555 subjects who started RRT in 2009, excluding subjects whose underlying renal disease was rapidly progressive glomerulonephritis ($n = 446$) and due to functional graft loss ($n = 202$), 36,907 subjects progressed to ESKD from CKD stage 5 during 2009 [16]. Consequently, there were ~67,000 subjects who were at predialysis CKD stage 5 in 2009. Furthermore, we hope that detailed estimation can be made using the CKD-JAC study, a prospective cohort study of 3,000 CKD patients at several Japanese nephrology departments [17], or using the FROM-J study, a randomized clinical trial of 2,500 CKD patients treated by general physicians [18]. These two studies were conducted mainly by JSN, and their final report will be published in the near future.

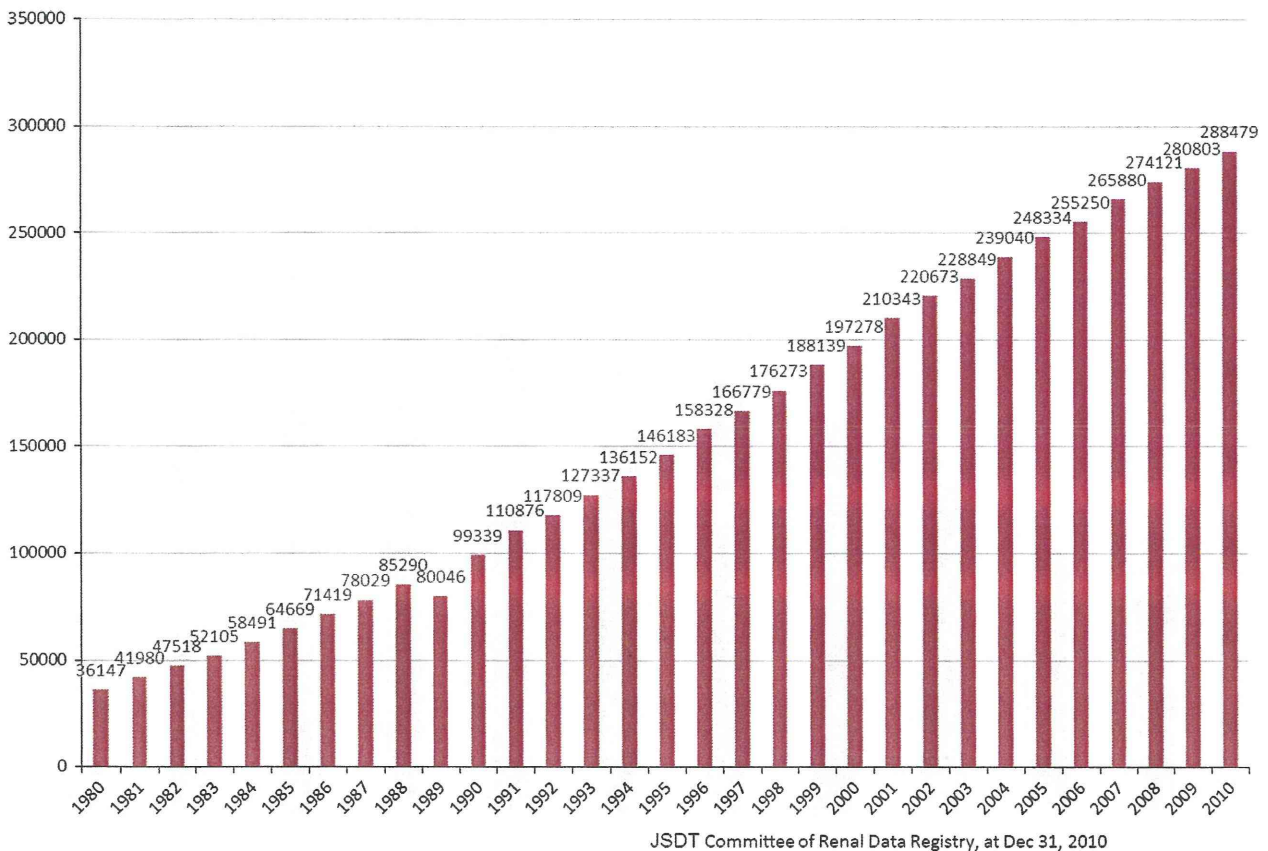


Fig. 4 Number of hemodialysis patients at the end of each year. Prevalence of hemodialysis patients was linearly increased

Incidence and prevalence by mode of RRT

Annual changes of the incidence and prevalence of patients receiving hemodialysis (HD) [2]

Figure 4 shows the annual changes of the prevalence of patients receiving HD. The number of patients with HD consisted of the sum of cases undergoing hemodialysis, hemodiafiltration, hemofiltration, acetate-free biofiltration, and hemoadsorption. The prevalence of HD patients increased linearly since we started the JSDT registry. Figure 5 shows the changes of the annual incidence of HD patients. The number of new HD patients also increased year-by-year, except in 2009 and 2010.

Annual changes of the incidence and prevalence of patients receiving peritoneal dialysis (PD) [2]

Figure 6 shows the annual changes of the prevalence of patients receiving PD. The number of PD patients was increasing, but this trend disappeared after 1997. Figure 7 shows the changes of the annual incidence of PD. The annual incidence of new PD patients increased over the last

10 years, while the prevalence of PD patients was constant owing to the increasing number of patients transferred from PD to HD.

Annual changes of incidence and prevalence of patients receiving kidney transplantation (KT)

There was no information about the annual changes of the prevalence of functional transplanted kidneys. Figure 2 shows the annual incidence of recipients of KT in Japan. In 2010, 1,484 patients received KT, among which 1,276 patients received living-related KT, while 208 patients received cadaver KT. Although the number of brain-death donors increased recently, the number of cardiac-death donors decreased. Consequently, the number of cadaver KT was almost constant, and the recent increase of KT was mainly due to an increase of living-related KT (Fig. 8). Furthermore, the number of pre-emptive renal transplantations increased recently. With the increase of pre-emptive renal transplantation, namely, cases in which dialysis was not received during the preoperative period, the difference in the count between the number of dialysis patients and the number of ESKD patients widened.

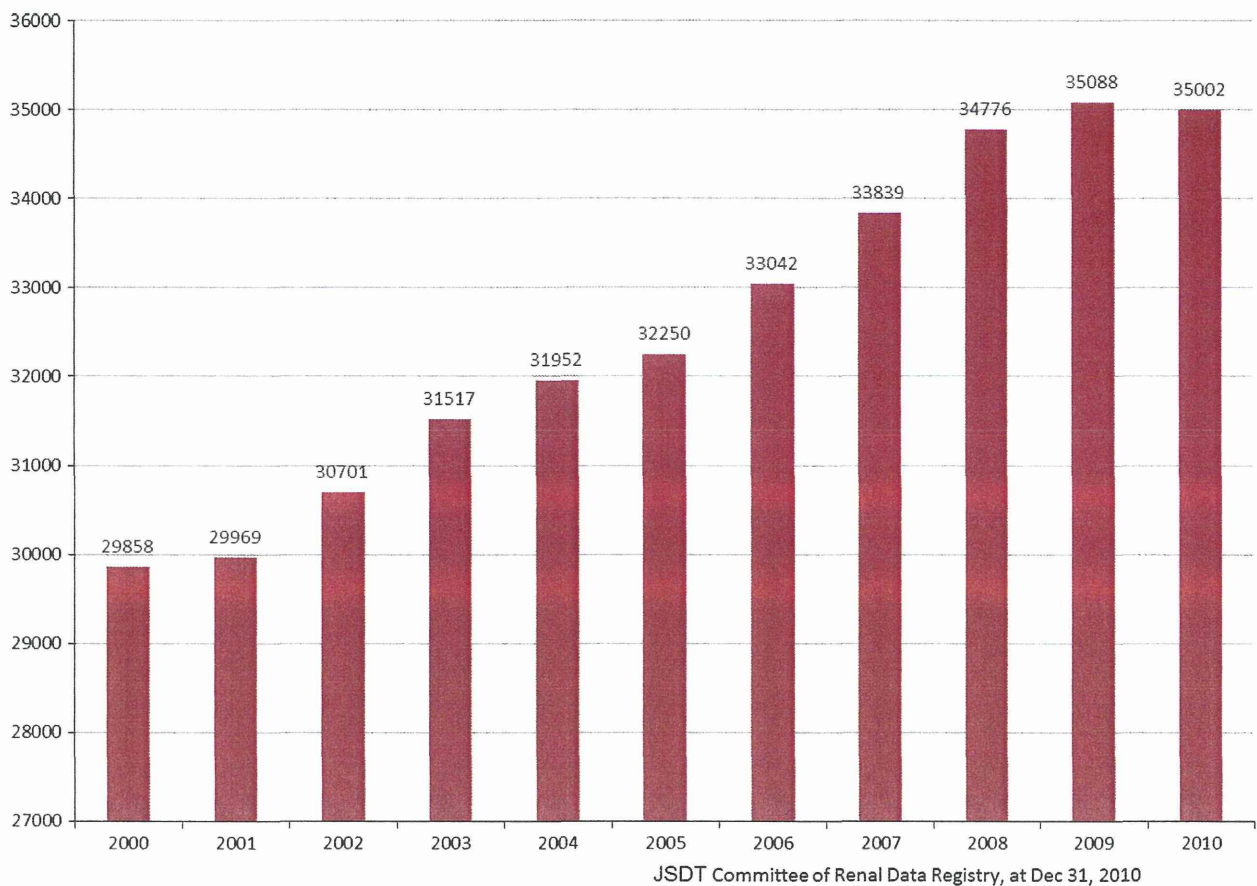


Fig. 5 Number of newly started hemodialysis patients. Number of newly started hemodialysis patients was increasing linearly, however, slight decrease of newly started hemodialysis patients was observed in 2010

Present status of ESKD in Japan

From each registry and the reported data, we attempted to estimate the number of ESKD patients in Japan. At this time, registry data on JST/JSRT were available up the end of 2007 and 2008, and to account for further editing of the JSDT registry data, we estimated the incidence of ESKD in 2009 and its prevalence in 2007 and 2008.

Estimated incidence of ESKD in 2009

We estimated who started RRT (sum of HD, PD, and KT cases) in 2009. In total, 37,566 patients started dialysis in 2009 from facility analysis in a dialysis facility report [16]. From detailed patient study, only 37,287 patients' records were obtained. Among the newly dialysis-initiated patients, 200 subjects underwent this due to graft dysfunction. We estimated the number of graft dysfunction cases from facility analysis ($= 200 \times (37,566/37,287) \cong 201$) and found that there were 201 estimated graft dysfunction

patients who started dialysis in 2009. From the JSR/JSRT registry, there were 101 pre-emptive KT recipients in 2009 [5]. Consequently, we estimated that the incidence of ESKD was $37,566 - 201 + 101 = 37,466$.

The average age of new dialysis patients in 2009 was 67.3 years old (males, 66.4 years old; females, 69.1 years old) [16]. The average age of patients who received pre-emptive KT was 34.9 years old (males, 35.5 years old; females, 33.8 years old) [5]; we estimated that the average age of new ESKD patients in 2009 was 67.2 years old.

The underlying kidney diseases in cases starting dialysis in 2009 were as follows: 22.0 % had chronic glomerulonephritis, 45.0 % diabetes, and 10.9 % nephrosclerosis [16]. In KT recipients, 40.6 % had chronic glomerulonephritis, 10.9 % diabetes, and 1.0 % nephrosclerosis. In transplanted patients, a certain number of patients had congenital abnormality of kidney and urinary tract (CAK-UT) [5].

In total, in terms of the underlying kidney disease in new ESKD patients in 2009 in Japan, 22.1 % had chronic

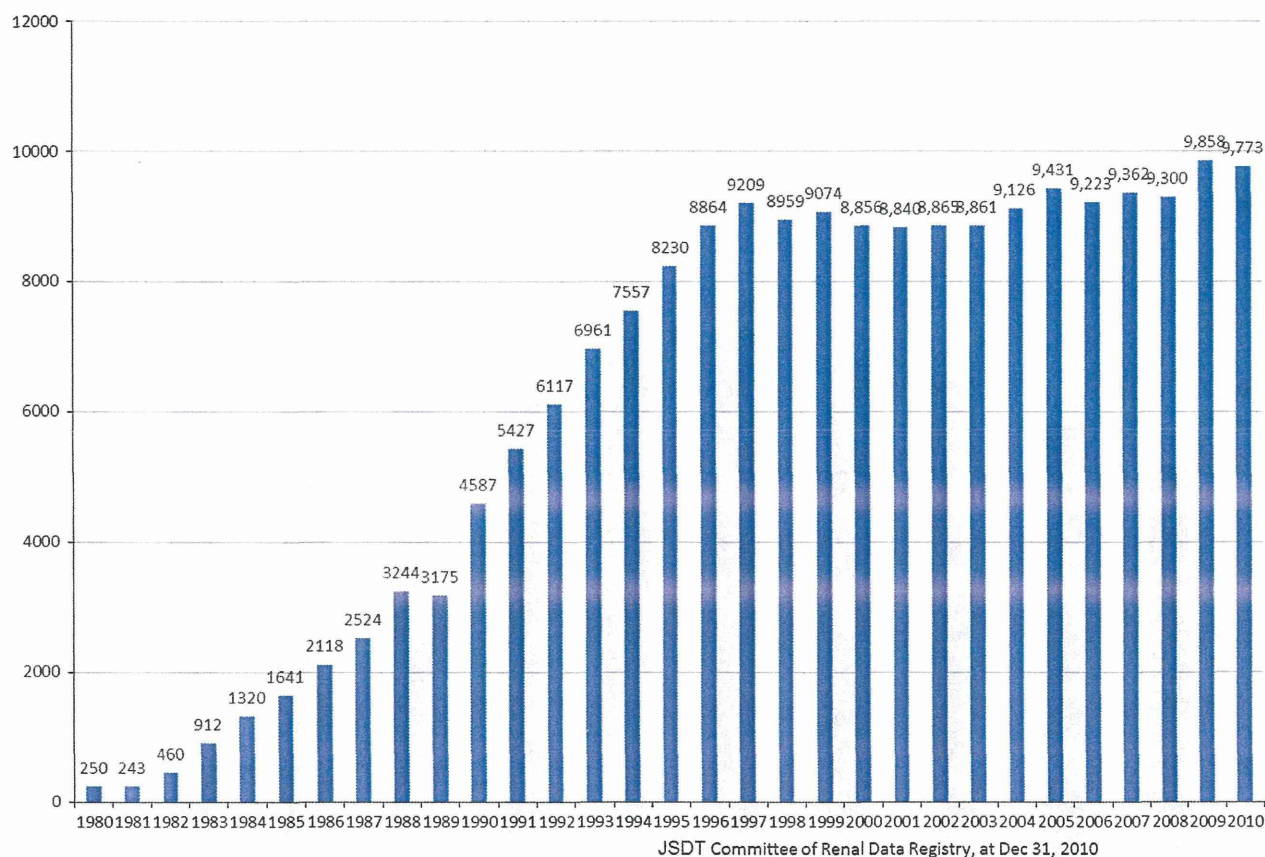


Fig. 6 Number of peritoneal dialysis patients at the end of each year. Number of peritoneal dialysis patients was increasing linearly until 1997. Nomoto et al. [21] reported that long-term peritoneal dialysis

glomerulonephritis, 44.9 % had diabetes, and 10.8 % had nephrosclerosis. The proportions of cases with polycystic kidney disease and rapidly progressive glomerulonephritis were unchanged (Table 1).

Figure 9 shows a comparison of the annual incidence of ESKD in 2009 among USA, Taiwan, and Japan. In 2009, 201 patients were re-introduced to dialysis treatment due to functional graft loss, and 101 patients received pre-emptive renal transplantation in Japan. We provided the detailed number of patients as study data to USRDS for international comparison, which was 287 per million population. After our estimation, it was 294 per million population. Finally, the order of these countries was the same (Fig. 9).

Estimated prevalence of ESKD patients as of Dec 31, 2007 and 2008, in Japan

From the JSDT registry, there were 275,242 subjects who received maintenance dialysis treatment in Japan in 2007 [19] and 286,406 in 2008 [20]. From the JST/JSRT registry, there were 10,013 subjects who had functional kidney graft in Japan in 2007 and 11,157 in 2008. Consequently,

was regarded as an important risk factor for encapsulating peritoneal fibrosis. Avoidance of long-term continuation of PD was one of the main reasons for diminishing the increment trend after 1997

there were 285,255 ESKD subjects who required RRT as of Dec 31, 2007, and 297,563 ESKD subjects who required RRT as of Dec 31, 2008 in Japan.

The mean age of dialysis patients on Dec 31, 2007 was 64.9 years old (males, 64.2 years old; females, 66.0 years old). The mean age of KT patients who had a functional renal graft on Dec 31, 2007 was 43.7 years old (males, 44.2 years old; females, 42.8 years old). As a result, the mean age of ESKD patients in Japan on Dec 31, 2007 was 64.2 years old (males, 63.4 years old; females, 65.1 years old).

The most common primary kidney disease of dialysis patients was chronic glomerulonephritis (40.4 %), while 33.4 % of the patients had diabetic nephropathy, 6.5 % nephrosclerosis, and 3.4 % polycystic kidney disease, as of Dec 31, 2007, in Japan. In KT patients who had a functional graft on Dec 31, 2007, in Japan, 58.7 % of cases had chronic glomerulonephritis, 5.0 % diabetic nephropathy, 1.1 % nephrosclerosis, and 2.5 % polycystic kidney disease. Consequently, in terms of the primary kidney disease of ESKD patients on Dec 31, 2007, in Japan, 41.0 % of cases were chronic glomerulonephritis, 32.4 % diabetic nephropathy, and 6.3 % nephrosclerosis (Table 2).

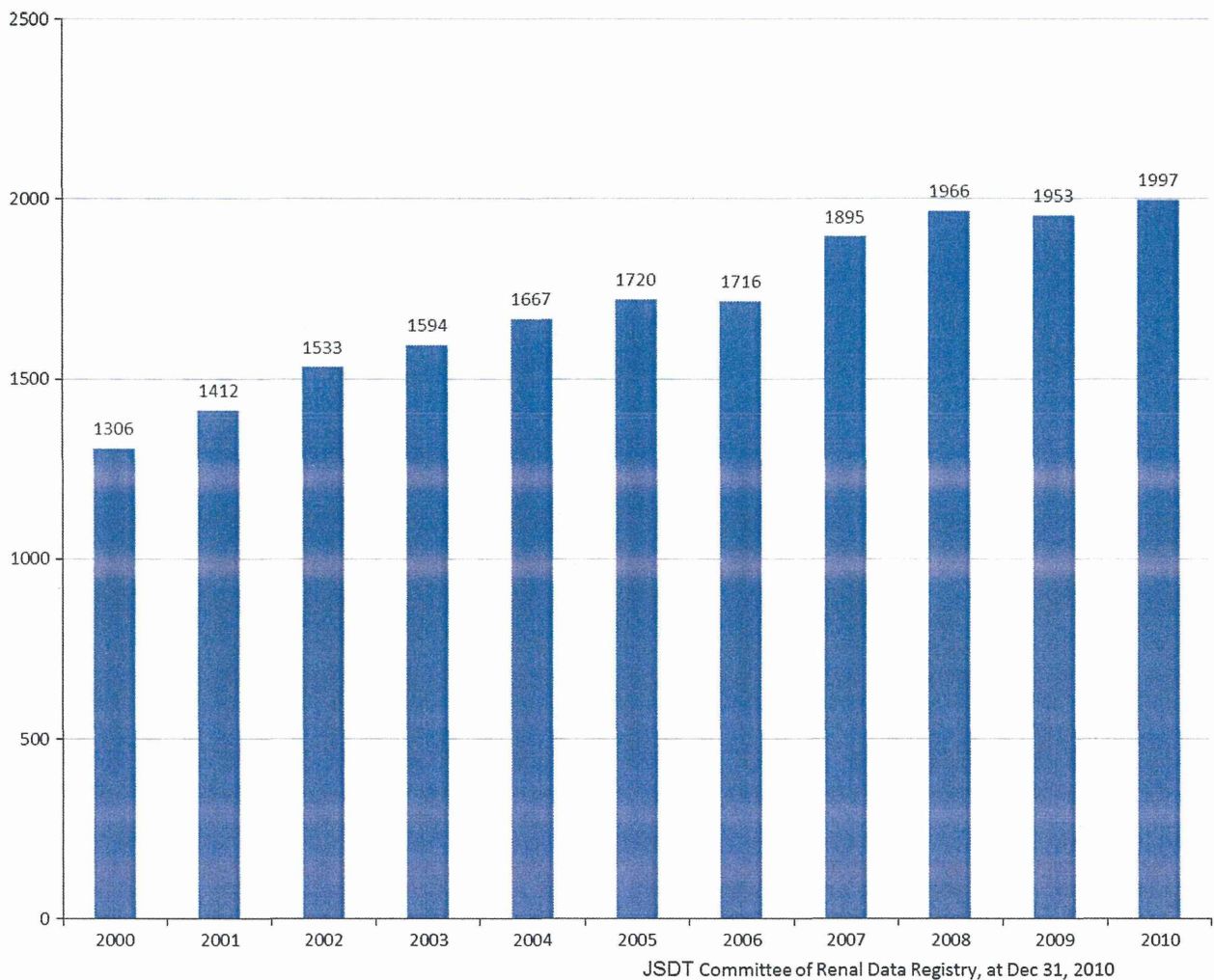


Fig. 7 Number of newly started peritoneal dialysis patients. Number of newly started peritoneal dialysis patients was slightly increasing year-by-year even after prevalence of peritoneal dialysis was almost constant

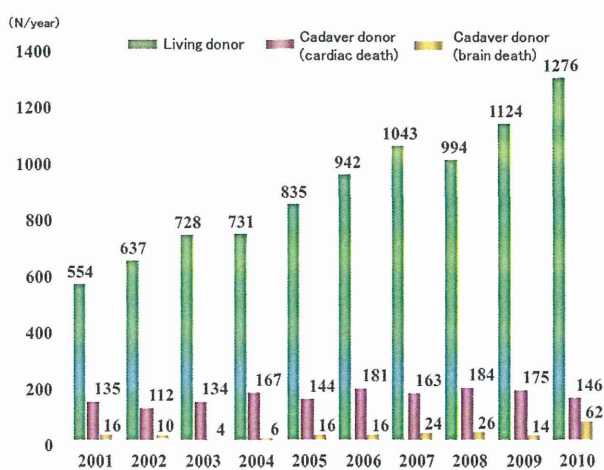


Fig. 8 Recent trend of number of kidney transplantations in Japan. The number of cadaver KT was almost constant, and the recent increase of KT was mainly due to an increase of living-related KT

Figure 10 shows an international comparison of the prevalence of ESKD among Taiwan, USA, and Japan on Dec 31, 2007. As mentioned above, we provided the detailed number of patients as study data to USRDS for international comparison. It was 2,058 per million population. However, our final estimated total ESKD population in Japan as of Dec 31, 2007 was 2,233 per million population.

Finally, we describe our recent study about the estimated number of CKD stage 5 patients and the number of ESKD patients living in Japan, via the cooperation of JSDT, JST, JSCRT, JSPN, and JSN. From the results, as of Dec 31, 2007, 275,242 patients received dialysis therapy and 10,013 patients had a functional transplanted kidney. Consequently, there were 285,255 patients with CKD who used RRT and were living in Japan in 2008. In addition, there were 67,000 predialysis CKD stage G5 patients in 2009, 37,365 patients introduced to dialysis therapy, and 101 patients who received pre-emptive