20. Budde K, Becker T, Arns W et al. ZEUS Study Investigators. Everolimus-based, calcineurin-inhibitor-free regimen in recipients of de-novo kidney transplants: an open-label, randomised, controlled trial. Lancet 2011: 377: 837.
21. Rostaing L, Kamar N. mTOR inhibitor/proliferation signal inhibitors: entering or leaving the field? J Nephrol 2010: 23: 133.
22. Moorman NJ, Shenk T. Rapamycin-resistant mTORC1 kinase activity is required for herpesvirus replication. J Virol 2010: 84: 5260.
23. Brennan DC, Legendre C, Patel D et al. Cytomegalovirus incidence between everolimus versus mycophenolate in de novo renal transplants: pooled analysis of three clinical trials. Am J Transplant 2011: 11: 2453.

Clin Exp Nephrol (2015) 19:54–64
DOI 10.1007/s10157-014-0978-x

REVIEW ARTICLE

Prevalence and incidence of chronic kidney disease stage G5 in Japan

Kunihiro Yamagata · Takashi Yagisawa · Shigeru Nakai · Masaaki Nakayama · Enyu Imai · Motoshi Hattori · Kunitoshi Iseki · Takashi Akiba

Received: 19 September 2013 / Accepted: 23 April 2014 / Published online: 13 May 2014

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.

Keywords Chronic kidney disease · End-stage kidney disease · Renal replacement therapy

K. Yamagata (✉)
Department of Nephrology, Faculty of Medicine, University of Tsukuba, 1-1-1, Ten-oudai, Tsukuba, Ibaraki 305-8575, Japan
e-mail: k-yamaga@md.tsukuba.ac.jp

T. Yagisawa
Department of Renal Surgery, Jichi Medical University, Shimotsuke, Japan

S. Nakai
Fujita Health Medical University, Toyoake, Japan

M. Nakayama
Department of Nephrology and Hypertension, Fukushima Medical University School of Medicine, Fukushima, Japan

E. Imai
Imai Nakayama Temple Clinic, Takarazuka, Japan

M. Hattori
Department of Pediatric Nephrology, School of Medicine, Tokyo Women's Medical University, Tokyo, Japan

K. Iseki
Dialysis Unit, University Hospital of the Ryukyus, Okinawa, Japan

T. Akiba
Department of Blood Purification, Kidney Center, Tokyo Women's Medical University, Tokyo, Japan

Introduction

Chronic kidney disease (CKD) is known as not only a worldwide public health problem, but also a global socioeconomic 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 forth 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

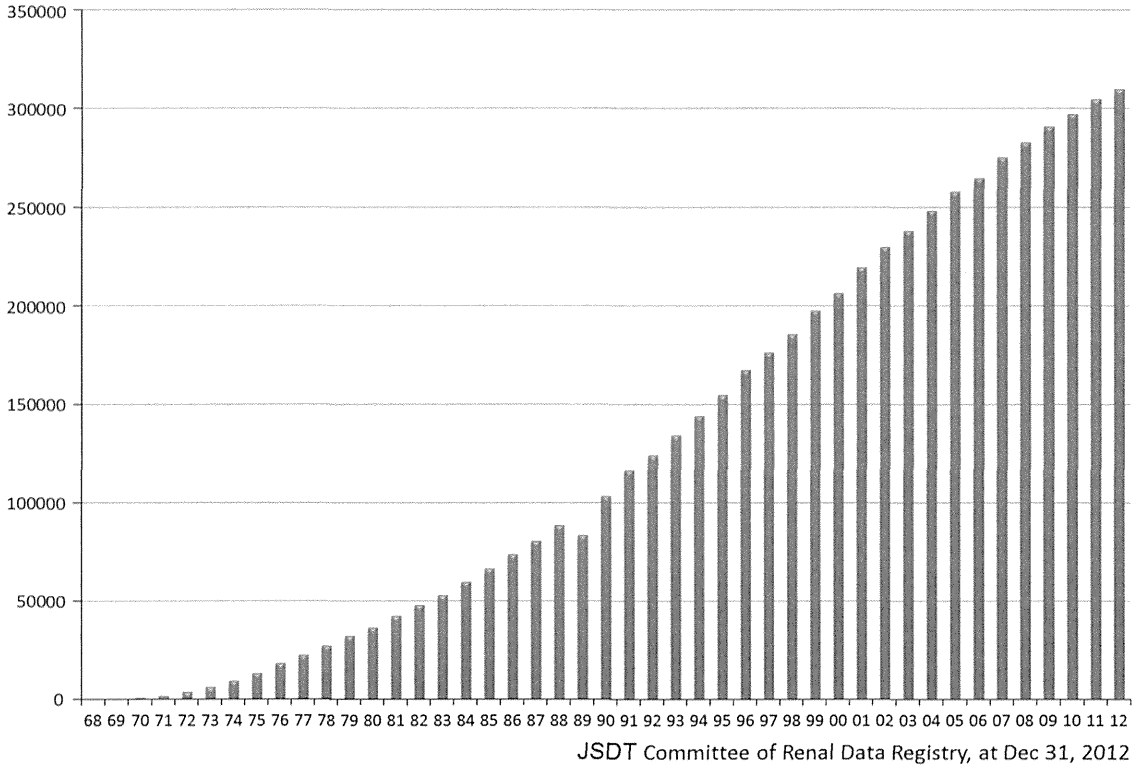

Fig. 1 Annual changes of prevalence of dialysis patients in Japan. In 1968, 215 dialysis patients were registered by JSDT committee of renal data registry, and a linear increment trend was seen until now. At Dec. 31, 2012, 309,946 subjects received dialysis treatment in Japan

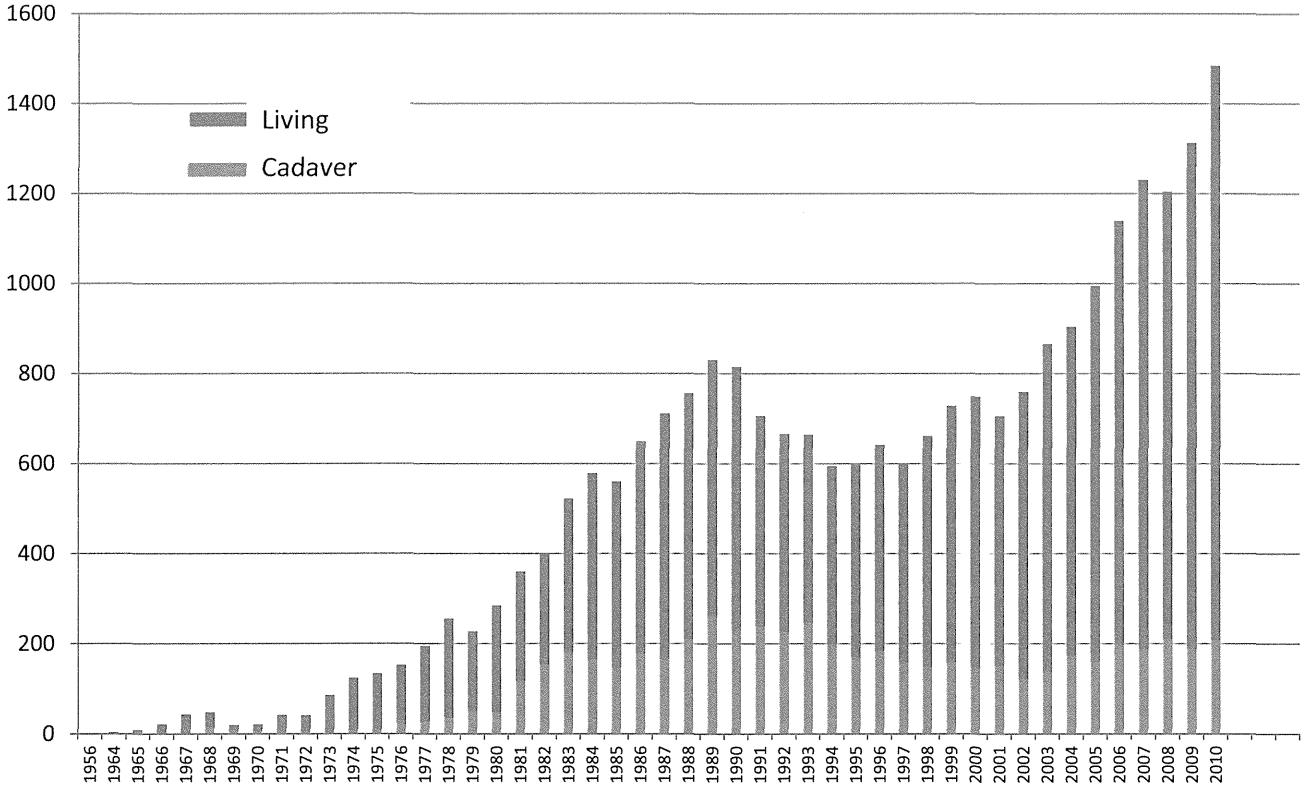

Fig. 2 Number of Renal Transplantations in Japan. The first cadaver renal transplantation was performed in 1956, and the first living-related renal transplantation was performed in 1964 in Japan. Although, numbers of renal transplantation were decreased since 1990, it was increased again after 1996, because organ transplantation law had passed

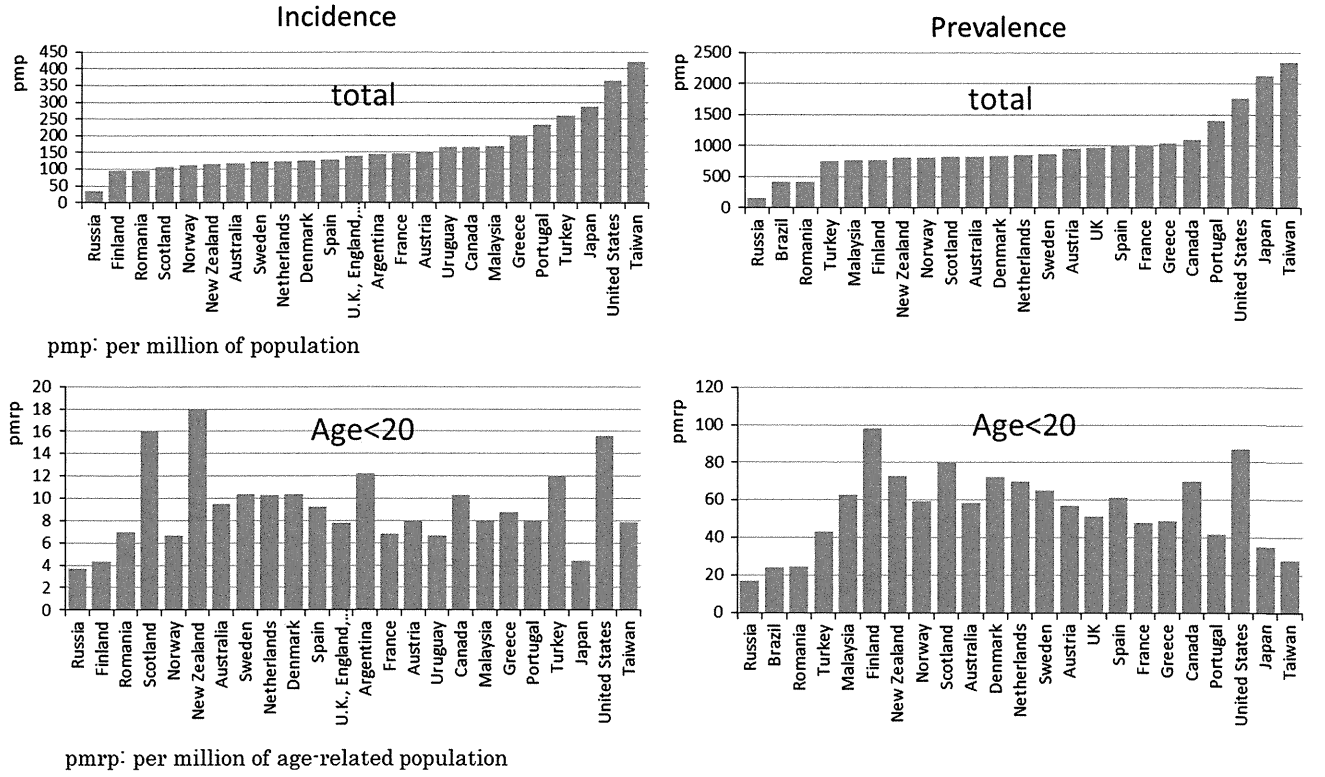

Fig. 3 International comparisons for incidence and prevalence of ESKD. Compared with adults, both the incidence and the prevalence of ESKD of both Japanese and Taiwanese pediatric ESKD were quite low. The reason for these differences in both incidence and prevalence between adult and pediatric cases 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 prevalence 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.

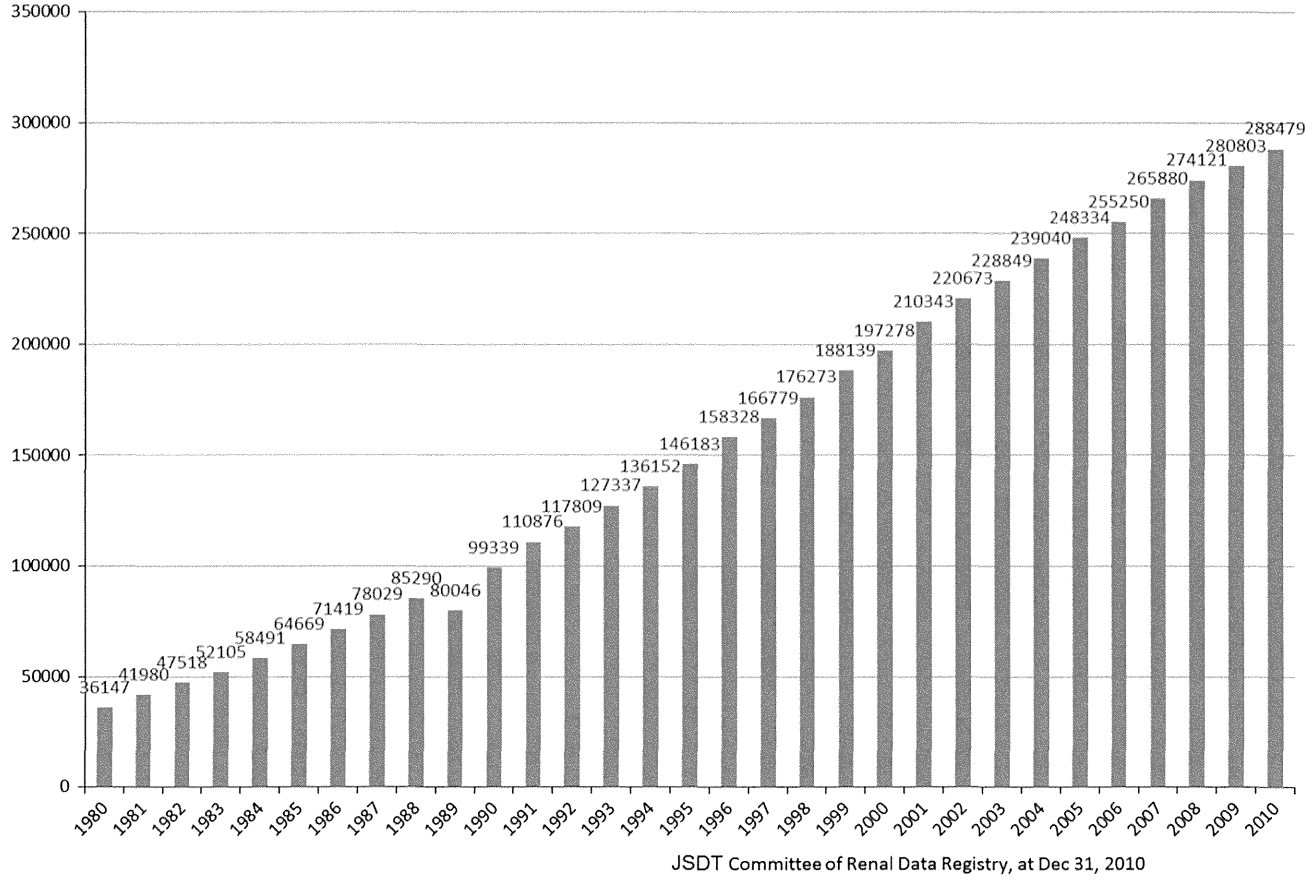

Fig. 4 Number of hemodialysis patients at the end of each year. Prevalence of hemodialysis patients was linearly increased

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.

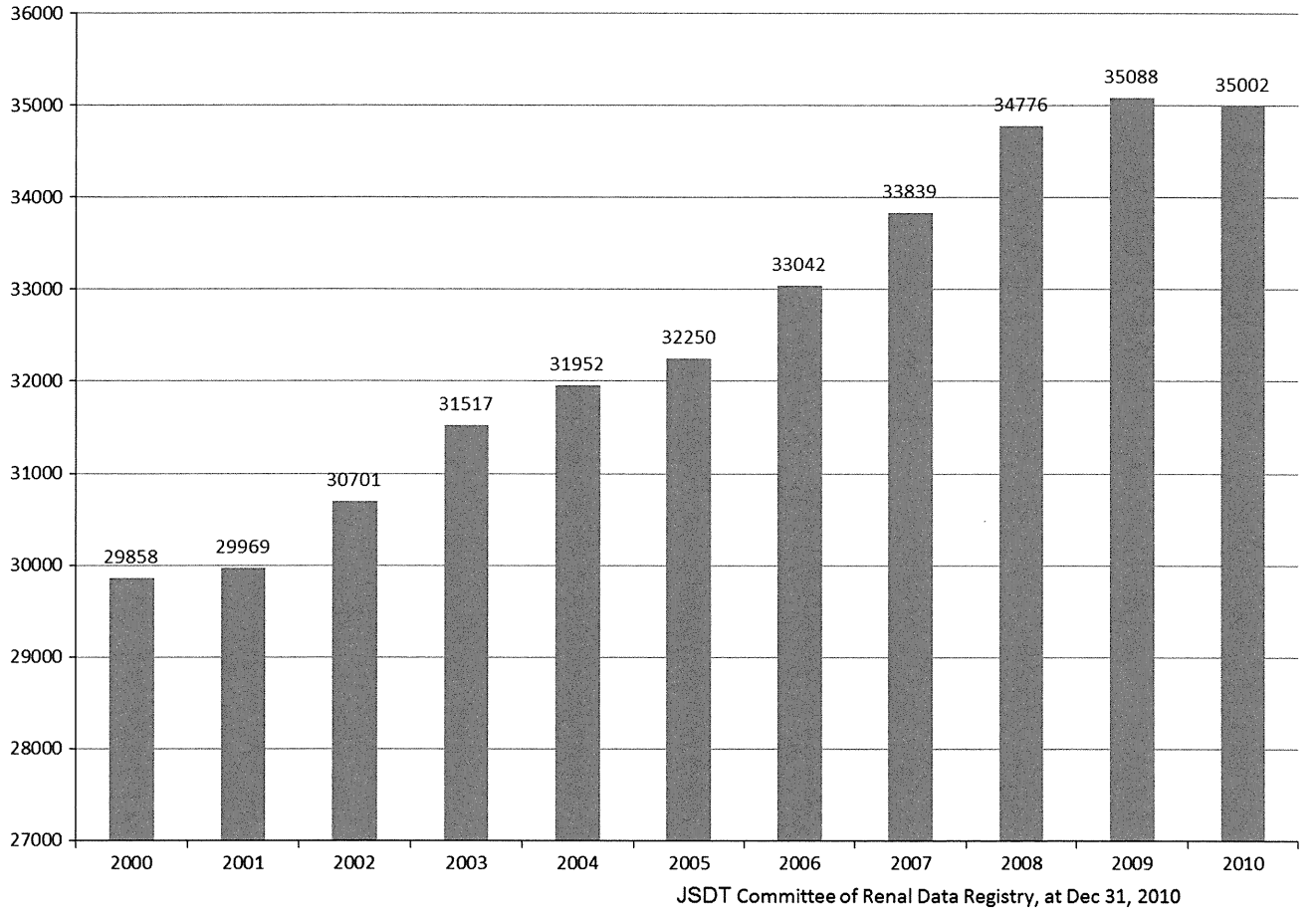

Fig. 5 Number of newly started hemodialysis patients. Number of newly started hemodialysis patients was increasing linearly, however, slight decrease of newly started hemodialysis patients was observed in 2010

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 faculty analysis ($= 200 \times (37{,}566/37{,}287) \fallingdotseq 201$) 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 (CAKUT) [5].

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

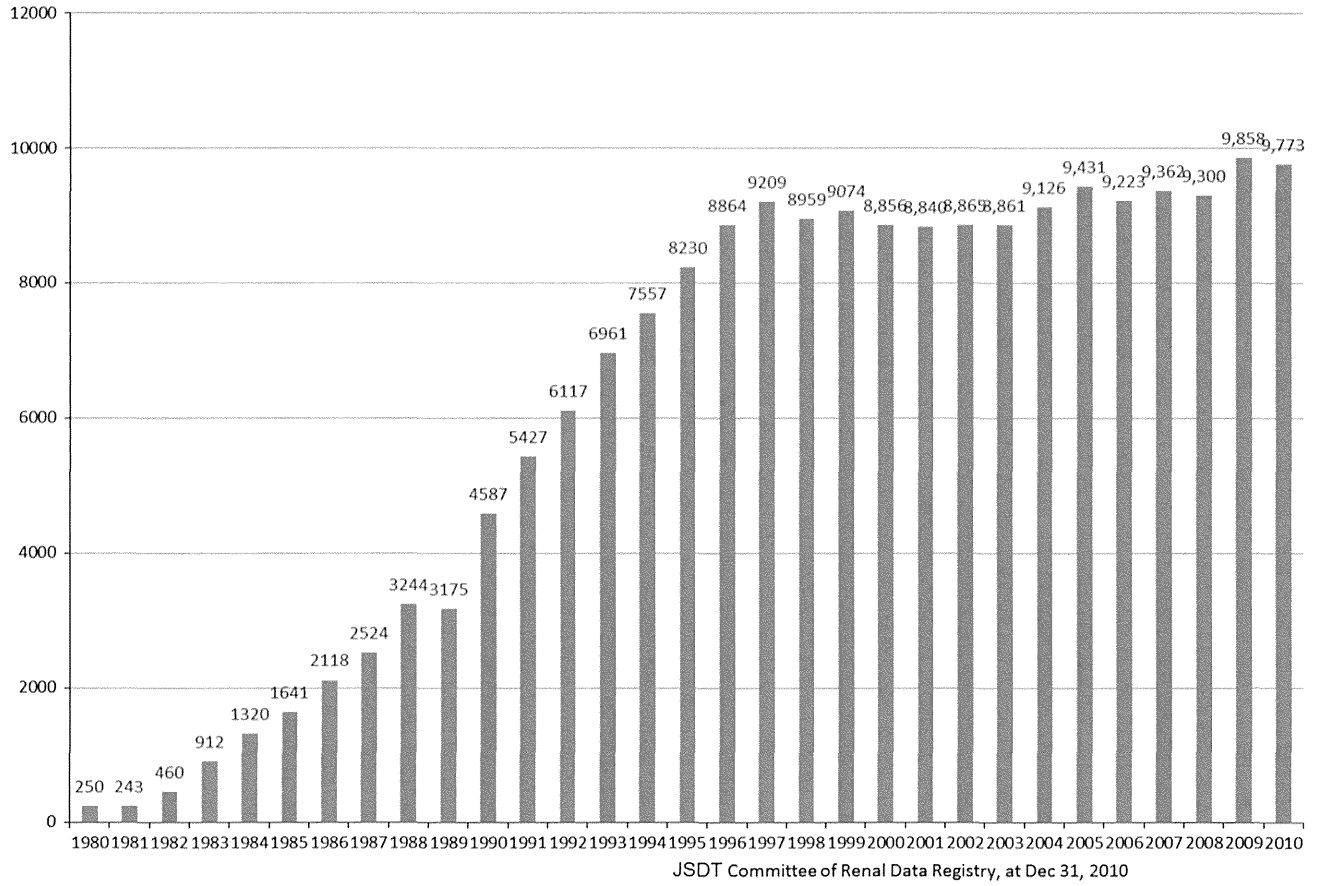

Fig. 6 Number of peritoneal dialysis patients at the end of each year. Number of peritoneal dialysis patients was increasing linearly until 1997. Nomoto et al. [21] reported that long-term peritoneal dialysis was regarded as an important risk factor for encapsulating peritoneal fibrosis. Avoidance of long-term continuation of PD was one of the main reasons for diminishing the increment trend after 1997

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, 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).

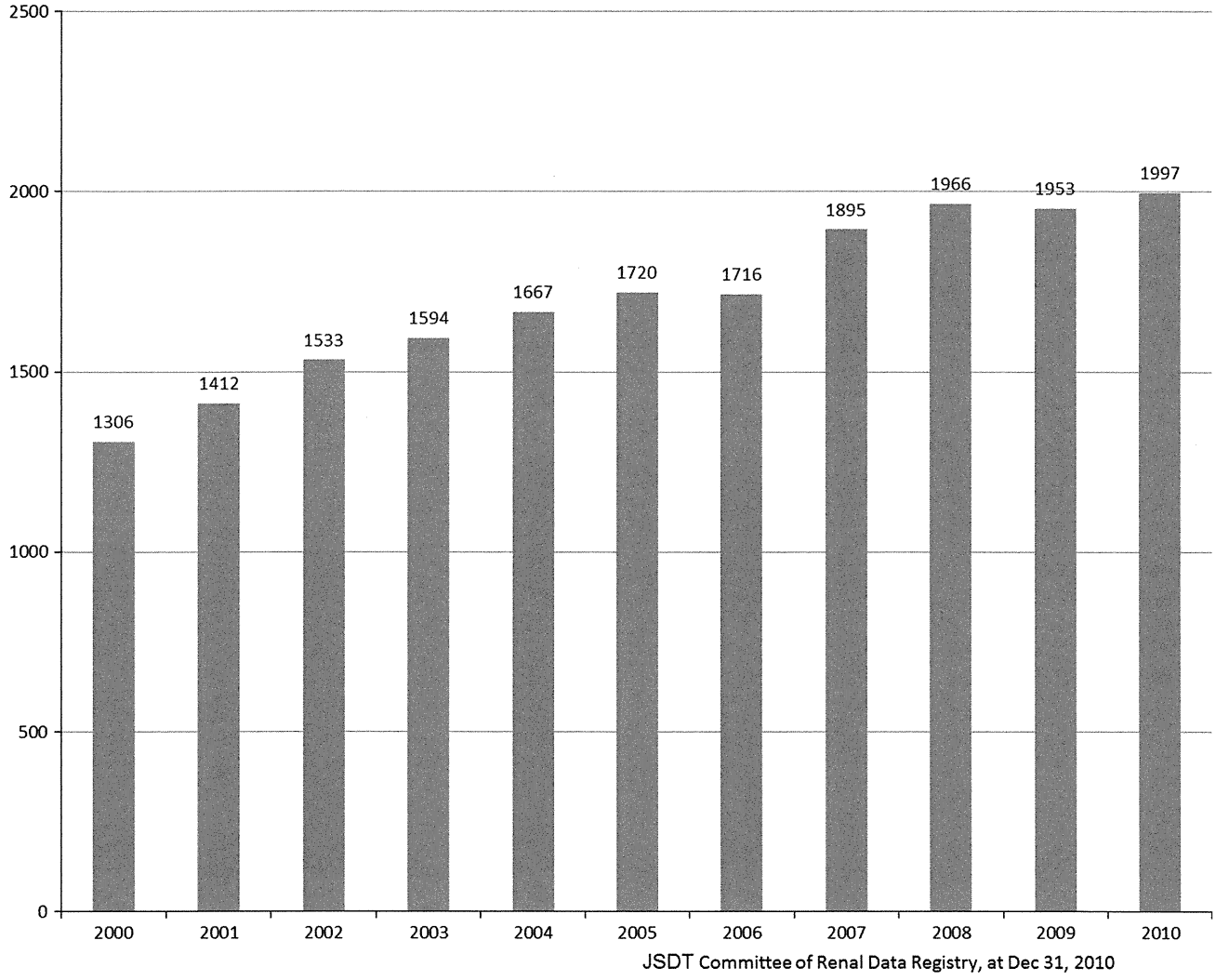

Fig. 7 Number of newly started peritoneal dialysis patients. Number of newly started peritoneal dialysis patients was slightly increasing year-by-year even after prevalence of peritoneal dialysis was almost constant

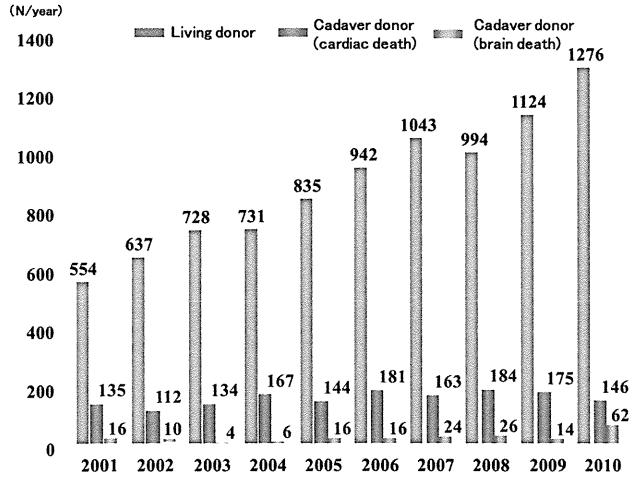

Fig. 8 Recent trend of number of kidney transplantations in Japan. The number of cadaver KT was almost constant, and the recent increase of KT was mainly due to an increase of living-related KT

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

Table 1 Annual incidence and primary renal disease of ESKD in Japan in 2009

Primary kidney diseases	Dialysis patients		Pre-emptive transplantation		Total	
	Number	%	Number	%	Number	%
Chronic glomerulonephritis	8,228	22.0	41	40.6	8,269	22.1
Diabetes	16,827	45.0	11	10.9	16,838	44.9
Nephrosclerosis	4,055	10.9	1	1.0	4,056	10.8
Polycystic kidney	873	2.3	7	6.9	880	2.3
Rapidly progressive glomerulonephritis	466	1.2	0	0.0	466	1.2
Others	6,917	18.5	41	40.6	6,958	18.6
Total	37,365	100.0	101	100.0	37,466	100.0

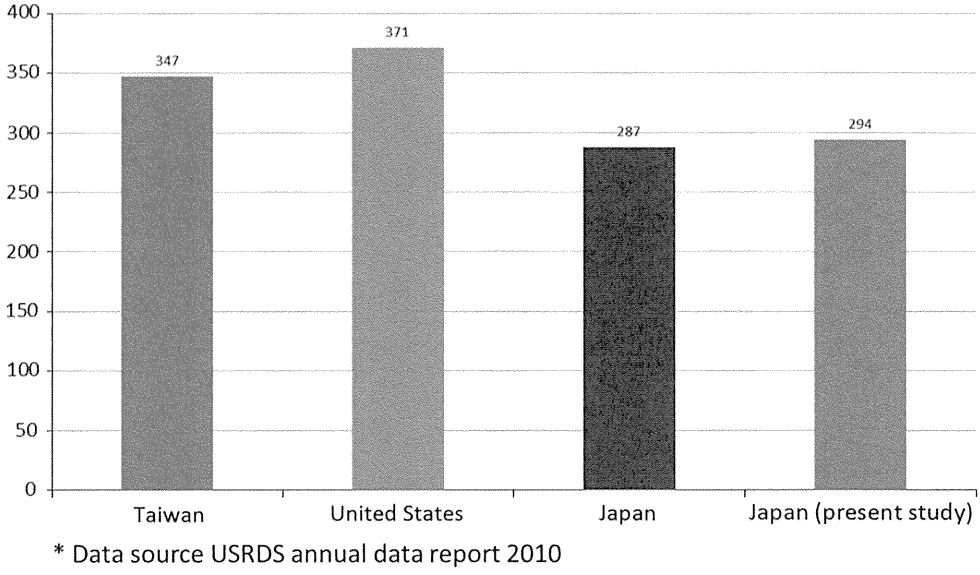

Fig. 9 Comparison of annual incidence of ESKD in 2009 among USA, Taiwan, and Japan. From the USRDS international comparison data, annual incidence of ESKD in Japan was 287 per million population, after our estimation, it was 294 per million population. The order of these countries was the same

Table 2 Prevalence and primary kidney disease of ESKD in Japan at Dec 31, 2007

Primary kidney diseases	Dialysis patients		Transplanted patients		Total ESKD	
	Estimated number	%	Number	%	Estimated number	%
Chronic glomerulonephritis	111,098	40.40	5,879	58.71	116,977	41.01
Diabetes	91,892	33.40	505	5.04	92,397	32.39
Nephrosclerosis	17,850	6.50	105	1.05	17,955	6.29
Polycystic kidney	9,287	3.40	252	2.52	9,539	3.34
Rapidly progressive glomerulonephritis	1,814	0.70	0	0.00	1,814	0.64
Others	43,301	15.70	3,272	32.68	46,573	16.33
Total	275,242		10,013	100.00	285,255	100.00

kidney transplantation in this year. In total, there were 37,466 patients who newly required RRT in 2009. Not only the average ages, but also the primary kidney diseases of the new ESRD patients in each RRT modality were quite different.

It is important to show the incidence and prevalence of the total ESKD population, including dialysis, KT, and predialysis ESKD patients, to determine an effective treatment and care strategy.

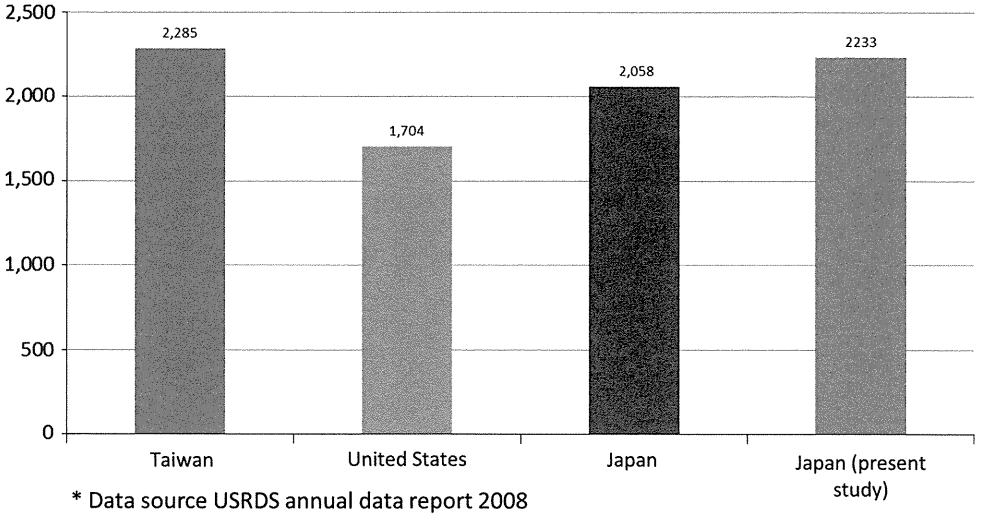

Fig. 10 Comparison of prevalence of ESKD at Dec 31, 2007, among USA, Taiwan, and Japan. Prevalence of ESKD at Dec 31, 2007 in Japan was 2,058 per million population. However, adding KT subjects, our final estimated total ESKD population in Japan as of Dec 31, 2007 was 2,233 per million population

Acknowledgments We thank, for all their efforts, the members in 2011–2012 of the committee for kidney failure general measures, subcommittee for CKD measures, and Ms. Chiho Iseki for data management. This study was supported by a Grant-in-Aid for Research on the Establishment of a Consulting System to Avoid Progression of CKD, Research on Renal Diseases, from the Ministry of Health, Labor and Welfare of Japan (H24-intractable-kidney-007).

Conflict of interest The authors have declared that no Conflict of interest exists.

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References

1. Levey AS, Atkins R, Coresh J, Cohen EP, Collins AJ, Eckardt KU, et al. Chronic kidney disease as a global public health problem: approaches and initiatives—a position statement from Kidney Disease Improving Global Outcomes. Kidney Int. 2007;72:247–59.
2. Nakai S, Iseki K, Itami N, Ogata S, Kazama JJ, Kimata N, et al. An overview of regular dialysis treatment in Japan (as of 31 December 2010). Ther Apher Dial. 2012;16:483–521.
3. Lysaght MJ. Maintenance dialysis population dynamics: current trends and long-term implications. J Am Soc Nephrol. 2002;13(Suppl 1):S37–40.
4. System, USRD: USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. 2009 USRDS Annual data report. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2009.
5. JSCRT, JST: Annual Progress report from the Japanese Renal Transplant Registry, 2010. Part III: results from 2009 Recipient Follow-up Survey. Transplantation 2010;45:608–630 (in Japanese).
6. Foley RN, Collins AJ. The USRDS: what you need to know about what it can and can't tell us about ESRD. Clin J Am Soc Nephrol. 2013;8:845–51.
7. Nakai S, Suzuki K, Masakane I, Wada A, Itami N, Ogata S, et al. Overview of regular dialysis treatment in Japan (as of 31 December 2008). Ther Apher Dial. 2010;14:505–40.
8. Iseki K, Nakai S, Yamagata K, Tsubakihara Y. Tachycardia as a predictor of poor survival in chronic haemodialysis patients. Nephrol Dial Transplant. 2011;26:963–9.
9. Yamagata K, Nakai S, Masakane I, Hanafusa N, Iseki K, Tsubakihara Y. Ideal timing and predialysis nephrology care duration for dialysis initiation: from analysis of Japanese dialysis initiation survey. Ther Apher Dial. 2012;16:54–62.
10. Nakai S. History of JSDT renal data registry (in Japanese). J Jpn Soc Dial Ther. 2010;43:119–52.
11. Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. Pediatr Nephrol. 2012;27:363–73.
12. Imai E, Horio M, Iseki K, Yamagata K, Watanabe T, Hara S, et al. Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. Clin Exp Nephrol. 2007;11:156–63.
13. Imai E, Horio M, Watanabe T, Iseki K, Yamagata K, Hara S, et al. Prevalence of chronic kidney disease in the Japanese general population. Clin Exp Nephrol. 2009;13:621–30.
14. Nakayama M, Sato T, Miyazaki M, Matsushima M, Sato H, Taguma Y, et al. Increased risk of cardiovascular events and mortality among non-diabetic chronic kidney disease patients with hypertensive nephropathy: the Gonryo study. Hypertens Res. 2011;34:1106–10.
15. Nakayama M, Sato T, Sato H, Yamaguchi Y, Obara K, Kurihara I, et al. Different clinical outcomes for cardiovascular events and mortality in chronic kidney disease according to underlying renal disease: the Gonryo study. Clin Exp Nephrol. 2010;14:333–9.
16. Nakai S, Iseki K, Itami N, Ogata S, Kazama JJ, Kimata N, et al. Overview of regular dialysis treatment in Japan (as of 31 December 2009). Ther Apher Dial. 2012;16:11–53.

17. Imai E, Matsuo S, Makino H, Watanabe T, Akizawa T, Nitta K, et al. Chronic kidney disease Japan cohort (CKD-JAC) study: design and methods. Hypertens Res. 2008;31:1101–7.
18. Yamagata K, Makino H, Akizawa T, Iseki K, Itoh S, Kimura K, et al. Design and methods of a strategic outcome study for chronic kidney disease: frontier of renal outcome modifications in Japan. Clin Exp Nephrol. 2010;14:144–51.
19. Nakai S, Masakane I, Shigematsu T, Hamano T, Yamagata K, Watanabe Y, et al. An overview of regular dialysis treatment in Japan (as of 31 December 2007). Ther Apher Dial. 2009;13:457–504.
20. Nakai S, Suzuki K, Masakane I, Wada A, Itami N, Ogata S, et al. Overview of regular dialysis treatment in Japan (as of 31 December 2008). Ther Apher Dial Off Peer Rev J Int Soc Apher Jpn Soc Apher Jpn Soc Dial Ther. 2010;14:505–40.
21. Nomoto Y, Kawaguchi Y, Kubo H, Hirano H, Sakai S, Kurokawa K. Sclerosing encapsulating peritonitis in patients undergoing continuous ambulatory peritoneal dialysis: a report of the Japanese Sclerosing Encapsulating Peritonitis Study Group. Am J Kidney Dis. 1996;28:420–7.

20-Year Analysis of Kidney Transplantation: A Single Center in Japan

M. Tasaki, K. Saito, Y. Nakagawa, M. Ikeda, N. Imai, Y. Ito, I. Narita, and K. Takahashi

ABSTRACT

Background. Patient and graft survival after successful kidney transplantation (KT) have improved despite an increase in the number of challenging cases. Various factors have evolved during the long history of kidney transplantation.

Methods. Between 1988 and 2012, a total of 292 living donor and 56 deceased donor KTs were performed at Niigata University Hospital. Long-term patient and graft survival and changes in background during a 20-year period in a single center were retrospectively analyzed.

Results. Excellent patient survival rates of 95.1% at 20 years for living donor KT and 96.2% at 15 years for deceased donor KT were observed. Graft survival rates at 1, 5, 10, 15, and 20 years were 96.8%, 95.4%, 83.1%, 61.8%, and 56.2% in living donor KT, respectively. In contrast, graft survival rates at 1, 5, 10, and 15 years in deceased donor KT were 89.0%, 80.3%, 77.3%, and 33.8%, respectively. These survival rates have dramatically improved since 2002 (91.7% for living and 80.9% for deceased donor KT at 10 years post-transplantation). The number of elderly recipients (older than 60 years) and the percentage of grafts donated from spouses have increased. The rejection rate decreased and the cytomegalovirus antigenemia–positive rate increased during the 20-year period assessed. The percentage of pre-emptive KTs progressively increased, with graft survival in this group tending to be better than non-preemptive KTs. The causes of graft loss were chronic allograft dysfunction (54.7%), acute rejection (11.1%), and malignancies (9.4%). After living donor KT, the principal predictors of graft loss were if the recipient was younger than 30 years, if the donor was older than 50 years, and if the rejection episodes occurred after living donor KT. In contrast, the only risk factor in the case of deceased donor KT occurred after transplantation from donors who were older than 50 years.

Conclusions. A summary of the long-term outcome of KT over 20 years in a single center has been reported. Along with the changes in patient backgrounds, immunosuppressive drugs, and our knowledge of transplantation, patient and graft survival outcomes have also changed. Investigation into such outcomes during a different transplantation era is required to fully appreciate advances in KT.

FOR patients with end-stage renal disease (ESRD), successful kidney transplantation (KT) provides significantly improved patient survival rates and quality of life compared with dialysis treatment [1,2]. Various factors have changed during the long history of KT. Short- and long-term kidney graft survival rates have improved since immunosuppressive drugs such as calcineurin inhibitors and mycophenolate mofetil have been used in transplantation [3–5]. The population of patients who have ESRD is aging, and the number of patients requiring retransplantation is increasing. In addition to a severe organ shortage and the increasing number of older patients who have ESRD, the number of KTs being performed in challenging conditions,

From the Division of Urology, Department of Regenerative & Transplant Medicine (M.T., K.S., Y.N., M.I., K.T.), and the Division of Clinical Nephrology and Rheumatology (N.I., Y.I., I.N.), Niigata Graduate School of Medical and Dental Sciences, Niigata, Japan.

Address reprint requests to Masayuki Tasaki, MD, PhD, 1-757, Asahimachi-dori, Chuo-ku, Niigata, Japan. E-mail: masa1214@med.niigata-u.ac.jp

0041-1345/14/$-see front matter
http://dx.doi.org/10.1016/j.transproceed.2013.10.052

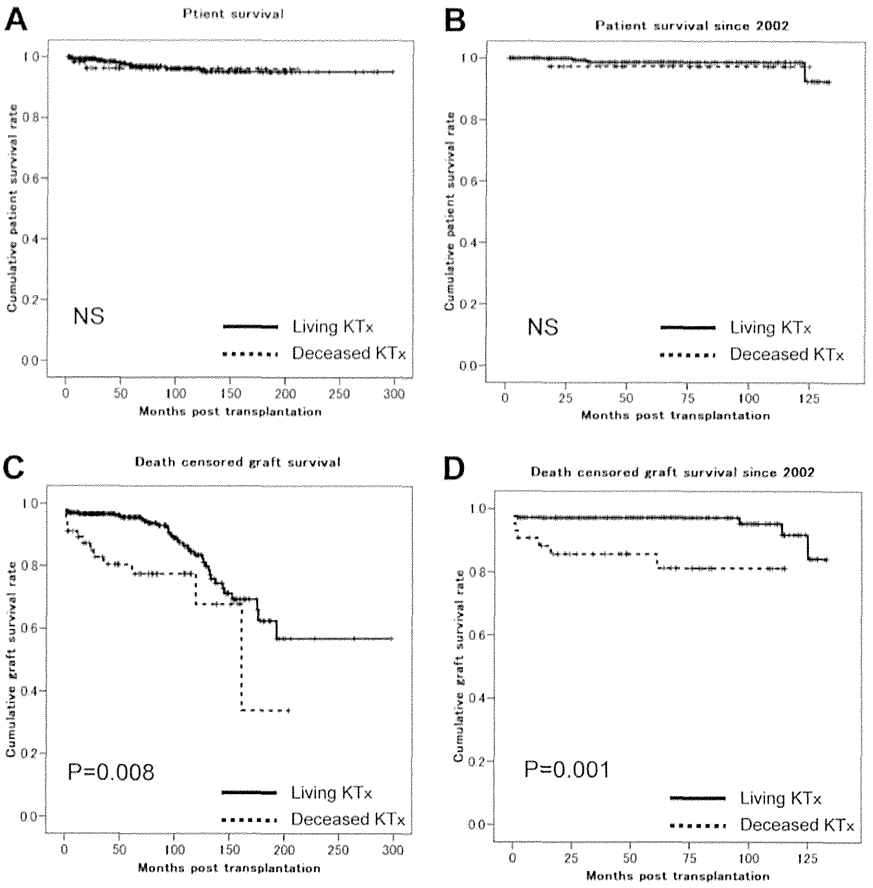

Fig 1. Patient survival during (**A**) 1988–2012 and (**B**) 2002–2012, and death censored graft survival during (**C**) 1988–2012 and (**D**) 2002–2012.

such as in cases of ABO incompatible KT, the presence of donor-specific antibody (DSA) or comorbidity are increasing.

In this study, a summary of the outcomes of living and deceased donor (cardiac death donor) KTs in our center for patients older than 20 years has been reported, including the changes of background.

PATIENTS AND METHODS

Between 1988 and 2012, a total of 292 living and 56 deceased donor KTs were performed at Niigata University Hospital. All kidney grafts were donated from cardiac death donors in deceased KTs, which have been performed in our center since 1995. Seventy-four ABO-incompatible (ABO-i) KTs, and 55 pre-emptive KTs (PKT) were only performed after living donor KT since 1994 and 1995, respectively. Medical records, including age, gender, human leukocyte antigen (HLA) mismatches, ABO-i, PKT, biopsy-proven rejection, duration of dialysis, and ischemic time were reviewed. Cytomegalovirus (CMV) infection was defined as the detection of CMV antigen (PP65) in peripheral blood leukocytes. Graft loss was defined as the return to chronic dialysis (death censored).

Results were expressed as frequency (percentage) or average (mean) for categorical data, and comparisons of baseline characteristics between non-graft loss and graft loss groups were made by chi-square analysis or two-sided *t* test. Patient and graft survival rate estimates were obtained by the Kaplan-Meier method. To determine independent predictive variables for graft loss, relevant factors in a univariate analysis were fitted into a multivariate-adjusted logistic regression analysis. All statistical analysis was performed using SPSS 15.0 (Chicago, Ill, United States) software for Windows.

RESULTS

Patient Characteristics

The mean age of recipients and donors for living donor KT was 36.5 years (range, 3 to 65 years) and 54.6 years (range, 25 to 78 years) at the time of transplantation, respectively. The mean age of recipients and donors for deceased donor KT was 47.0 years (range, 6 to 72 years) and 45.7 years (range, 1 to 70 years) at the time of transplantation, respectively. Median duration of dialysis was 45.3 months (range, 0 to 333 months) and 209.8 months (range, 13 to 576 months) for living and deceased donor KT, respectively. The average total ischemic time and warm ischemic time was 90.6 and 5.3 minutes for living donor KT and 926.1 and 7.3 minutes for deceased donor KT, respectively. CMV antigenemia–positive rates were 55.1% and 42.6% for living and deceased donor KT, respectively. Biopsy-proven rejection rates were 40.0% and 30.4% in living and deceased donor KT, respectively. The primary causes of ESRD were immunoglobulin A nephritis (24.2%), chronic glomerulonephritis (12.3%), Alport syndrome (5.0%), diabetic

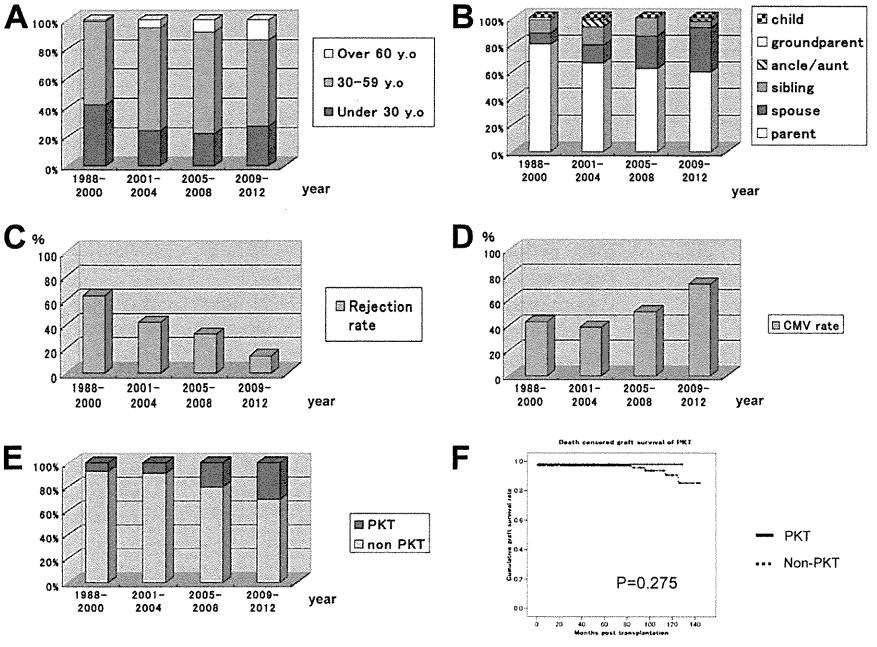

Fig 2. The changes of kidney transplantation in our center. (**A**) The recipient age. (**B**) The donor source. (**C**) Biopsy-proven rejection rate. (**D**) Cytomegalovirus antigenemia positive rate. (**E**) The percentage of pre-emptive kidney transplantation. (**F**) The graft survival of pre-emptive kidney transplantation.

nephritis (5.0%), focal segmental glomerulosclerosis (3.8%), membranoproliferative glomerulonephritis (3.8%), reflux nephropathy (3.8%), polycystic kidney disease (3.5%), renal hypoplasia (3.2%), pregnant nephropathy (1.8%), lupus nephritis (0.9%), obstructive nephropathy (0.9%), membranous nephropathy (0.6%), others (5.3%), and unknown (26.2%). The causes of graft loss were chronic graft dysfunction, including chronic rejection (54.7%), acute rejection (11.1%), recurrent nephritis (9.4%), renal graft thrombosis (5.7%), malignancy of the graft (3.8%), primary non-function (3.8%), drug non-adherence (1.9%), infection (1.9%), and others (7.6%).

Long-term Patient and Graft Survival Rates

The 1-, 5-, 10-, 15-, and 20-year patient survival rates were 99.3%, 97.5%, 96.2%, 95.1%, and 95.1% after living donor KT, respectively (Fig 1A), and the 1-, 5-, 10-, and 15-year patient survival rates were 98.2%, 96.2%, 96.2%, and 96.2% after deceased donor KT, respectively (Fig 1A). Survival rates for patients transplanted most recently were slightly higher, being 98.7% and 97.4% for living and deceased donor KT at 10 years after KT, respectively (Fig 1B). The 1-, 5-, 10-, 15-, and 20-year graft survival rates were 96.8%, 95.4%, 83.1%, 61.8%, and 56.2% after living donor KT, respectively (Fig 1C), and the 1-, 5-, 10-, and 15-year graft survival rates were 89.0%, 80.3%, 77.3%, and 33.8% after deceased donor KT, respectively (Fig 1C). These graft survival rates dramatically improved in both KT groups after the introduction of mycophenolate mofetil and basiliximab in addition to calcineurin inhibitors for immunosuppression at our center. The 10-year graft survival rates were 91.7% and 80.9% in living and deceased donor KT, respectively (Fig 1D). Although immunosuppressive therapy was improved, graft survival rate was significantly better in living KT than deceased donor KT. The 15-year graft survival rate was not significantly different between ABO-compatible and -incompatible KT (data not shown). The most recent graft survival rate for ABO-i KT was 96.2% at 7 years after KT.

The Evolution of Transplantation

The transplantation period was divided into four eras: 1988–2000, 2001–2004, 2005–2008, and 2009–2012. The number of elderly recipients increased as time progressed (Fig 2A). Parents were the principal donors in living donor KT; however, the percentage of donors who were spouses had continuously increased (Fig 2B). Rejection episodes decreased (Fig 2C), whereas the CMV antigenemia–positive rate increased (Fig 2D). The number of PKTs increased (Fig 2E), and the long-term graft survival rate tended to be higher in PKT, although it was not statistically significant ($P = .275$; Fig 2F). The primary disease characteristics of ESRD remained unchanged (data not shown).

Risk Factors of Graft Loss in Living and Deceased Donor KT

A univariate analysis was performed to investigate the risk factors of graft loss. In living donor KT, the percentage of younger recipients, older donors, and rejection episodes were significantly higher in the graft loss group (Table 1). In a multivariate logistic analysis, recipients who were younger than 30 years, donors who were older than 50 years, and rejection episodes were significant predictors for reduced long-term graft survival (Table 2).

Table 1. Risk Factors of Graft Loss in Living Kidney Transplantation: Comparison of Characteristics in Living KTx

Characteristics	Graft loss		*P* value
	−	+	
Recipient age			
<30, n (%)	75 (29.8)	19 (47.5)	
30–49, n (%)	115 (45.6)	14 (35.0)	.042
50≧, n (%)	62 (24.6)	7 (17.5)	
Male: Female, n	160:92	27:13	.624
ABO incompatible, n (%)	60 (23.8)	14 (35.8)	.131
Donor age			
Less than 50, n (%)	76 (30.2)	6 (15.0)	.047
More than 50, n (%)	176 (69.8)	34 (85.0)	
HLA mismatch, mean	2.78	2.46	.246
Preemptive KTx, n (%)	50 (19.9)	3 (7.7)	.066
Rejection, n (%)	81 (31.5)	28 (73.7)	.000
Time on dialysis, mean, (mo)	45.2	46.6	.580
Total ischemic time, mean, (min)	91.4	84.2	.290
Warm ischemic time, mean, (min)	5.22	6.15	.398
Graft weight, mean, (g)	179.4	154.4	.475

In deceased donor KT, both univariate and multivariate analyses showed that a donor older than 50 years was a significant risk factor for long-term graft loss (Tables 3 and 4).

DISCUSSION

The data from our center showed excellent patient and graft survival rates after both living and deceased donor KT, which was further improved by the use of calcineurin inhibitors, mycophenolate mofetil, and basiliximab in the immunosuppressive regimen. Administration of rituximab contributed greatly to graft survival rates in ABO-i KTs performed since 2004 at our center [6]. During 20 years of transplantation, a number of factors have changed. In 2012, the average of age of initiation of chronic hemodialysis in Japan was 68.9 years. Along with the aging of patients with ESRD, the percentage of older patients who received KT also increased. Living donor KT is more frequently performed in Japan than deceased donor KT, and inevitably, the donors for older recipients were their spouses, with 84.2% of the recipients being older than 60 years receiving kidney grafts from their spouses. Spousal transplantation with poor HLA matching and a history of pregnancy in husband-to-wife KT is considered a high risk factor for accelerated rejection [7,8]. In our study, rejection and long-term graft survival rates were not significantly different between spousal and non-spousal KTs because the numbers of HLA mismatches were similar in both groups and many spousal KTs were ABO-i, for which desensitization therapy was administered [6]. The reduction in rejection rates in this study may have been associated with improvements in the immunosuppressive therapy. In contrast, there were increases in the CMV antigenemia-positive rate. The increasing number of high risk cases with ABO-incompatibility and/or DSAs who were administered heavier immunosuppressive therapy may explain this observation. Prophylactic therapy for CMV infection was not conducted in these cases, except when KT was performed from seropositive donors to seronegative recipients. PKT has been reported to have superior outcomes for graft and patient survival rate compared with non-PKT [9]. In this study, PKT had a slightly better graft survival rate than the non-PKT group, although there was no significant difference. Many PKTs have only been performed recently and longer observation periods may be needed.

In this study, younger recipients, older donors, and rejection episodes correlated with reduced graft survival after living donor KT. High donor age and rejection episodes are well known to have an important influence on graft survival [10,11]; however, the role of younger recipient age on long-term graft survival remains controversial [11,12]. Younger recipients had a shorter period of dialysis and may be immunologically healthier, explaining stronger rejection responses. In addition, most of the donors for younger recipients in our study were their parents, who were relatively older and whose grafts likely had fewer nephrons. Older kidneys may have a limited capacity to respond

Table 2. Risk Factors of Graft loss in Living Kidney Transplantation: Multivariate-adjusted Logistic Regression in Living KTx

Characteristics	Odds ratio	95% CI	*P* value
Recipient age less than 30 years	3.249	1.484–7.111	.003
Donor age over 50 years	3.273	1.215–8.816	.019
Rejection episode	5.631	2.528–12.543	.000

Table 3. Risk Factors for Graft Loss in Deceased Kidney Transplantation: Comparison of Characteristics in Deceased KTx

Characteristics	Graft loss		*P* value
	−	+	
Recipient age			
<30, n (%)	5 (11.6)	1 (7.7)	
30–49, n (%)	18 (41.9)	6 (46.2)	.184
50≧, n (%)	20 (46.5)	6 (46.2)	
Male: Female, n	27:16	9:4	.671
Donor age			
Less than 50, n (%)	27 (62.8)	4 (30.8)	
More than 50, n (%)	16 (37.2)	9 (69.2)	.042
HLA mismatch, mean	2.74	2.12	.186
Rejection, n (%)	11 (25.6)	6 (46.2)	.101
Time on dialysis, mean, (mon)	204.5	227.2	.475
Total ischemic time, mean, (min)	909.1	996.0	.641
Warm ischemic time, mean, (min)	7.59	6.36	.644
Graft weight, mean, (g)	205.7	205.6	.989

Table 4. Risk Factors for Graft Loss in Deceased Kidney Transplantation: Multivariate-Adjusted Logistic Regression in Deceased KTx

Characteristics	Odds ratio	95% CI	*P* value
Donor age over 50 years	3.797	1.004–14.36	.049

appropriately to increases in physiological or metabolic demands in younger recipients leading to a greater reduction in renal function. In this study, recipients who were younger than 30 years who received kidney grafts from donors who were older than 50 years had significantly higher rates of rejection (Tasaki et al. in press). Therefore, younger recipients, older donors, and rejection episodes may be considered as closely related factors. Furthermore, younger recipients may show drug non-adherence [13,14]. In deceased donor KT, donor age was the principal risk factor for long-term graft loss as previously reported [15–17]. In Japan, cardiac death donors were the principal donor organ source until the transplantation law was revised in 2010. Longer ischemic time, which was on average 926 minutes in this study, may have severely damaged kidney grafts, particularly those donated from older donors.

This study presents the limitation of any retrospective study. Because this study was a complex cohort of patients incorporating different phases of immunosuppressive regimens, changes in patient background, evolution of immunosuppressive therapy, and data from each era should be investigated in isolation for a better understanding of changes in patient and graft survival. However, it is necessary to understand how the background and outcomes have been changed by what we have done.

In conclusion, long-term patient and graft survival rates improved and rejection rates decreased after recent improvements in immunosuppression therapy. In addition to increasing numbers of older recipients, the number of donor organs obtained from spouses has also increased. After living donor KT, younger recipients had inferior effects of graft function. Stronger immunosuppressive therapy may be required in these cases to prevent rejection after kidney grafts from older donors.

REFERENCES

[1] Evans RW, Manninen DL, Garrison LP Jr, et al. The quality of life of patients with end-stage renal disease. N Engl J Med 1985;312:553–9.

[2] Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med 1999;341:1725–30.

[3] Calne RY, White DJ, Thiru S, et al. Cyclosporin A in patients receiving renal allografts from cadaver donors. Lancet 1978;2: 1323–7.

[4] Jensik SC. Tacrolimus (FK 506) in kidney transplantation: three-year survival results of the US multicenter, randomized, comparative trial. FK 506 Kidney Transplant Study Group. Transplant Proc 1998 Jun;30(4):1216–8.

[5] Sollinger HW, Deierhoi MH, Belzer FO, et al. RS-61443 –a phase I clinical trial and pilot rescue study. Transplantation 1992;53:428–32.

[6] Saito K, Nakagawa Y, Suwa M, et al. Pinpoint targeted immunosuppression: anti-CD20/MMF desensitization with anti-CD25 in successful ABO-incompatible kidney transplantation without splenectomy. Xenotransplantation 2006;13:111–7.

[7] Long DG, Vernon WB, Yanover MJ. Increased acute rejection episodes among recipients of living unrelated donor compared with cadaver and living related donor renal transplants. Transplant Proc 2002;34:1673–4.

[8] Ghafari A. Offspring-to-mother and husband-to-wife renal transplantation: a single-center experience. Transplant Proc 2008;40: 140–2.

[9] Roake JA, Cahill AP, Gray CM, et al. Preemptive cadaveric renal transplantation–clinical outcome. Transplantation 1996;62: 1411–6.

[10] Lim WH, Clayton P, Wong G, et al. Outcomes of kidney transplantation from older living donors. Transplantation 2013;95: 106–13.

[11] Noppakun K, Cosio FG, Dean PG, et al. Living donor age and kidney transplant outcomes. Am J Transplant 2011;11:1279–86.

[12] Morales JM, Marcén R, del Castillo D, et al. Risk factors for graft loss and mortality after renal transplantation according to recipient age: a prospective multicentre study. Nephrol Dial Transplant 2012;27(suppl 4):iv39–46.

[13] Couzi L, Moulin B, Morin MP, et al. Factors predictive of medication nonadherence after renal transplantation: a French observational study. Transplantation 2013;95:326–32.

[14] Brahm MM, Manfro RC, Mello D, et al. Evaluation of adherence to immunosuppressive drugs in kidney transplantation by control of medication dispensing. Transplant Proc 2012;44: 2391–3.

[15] Rudich SM, Kaplan B, Magee JC, et al. Renal transplantations performed using non-heart-beating organ donors: going back to the future? Transplantation 2002;74:1715–20.

[16] Locke JE, Segev DL, Warren DS, et al. Outcomes of kidneys from donors after cardiac death: implications for allocation and preservation. Am J Transplant 2007;7:1797–807.

[17] Summers DM, Johnson RJ, Allen J, et al. Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: a cohort study. Lancet 2010;376:1303–11.

Int Urol Nephrol
DOI 10.1007/s11255-014-0655-8

NEPHROLOGY – ORIGINAL PAPER

Effect of donor–recipient age difference on long-term graft survival in living kidney transplantation

Masayuki Tasaki · Kazuhide Saito · Yuki Nakagawa · Masahiro Ikeda · Naofumi Imai · Ichiei Narita · Kota Takahashi

Received: 24 October 2013 / Accepted: 28 January 2014

Abstract
Purpose We aimed to examine the influence of donor age on living-donor kidney transplantation (KTx), particularly with regard to long-term graft survival in young recipients with aged kidney grafts.
Methods Between 1988 and 2012, 287 living-donor KTxs were performed in our center. The recipients were divided into 3 groups according to age in years: under 30 (young), 30–49 (middle-aged), and over 50 (old). The data regarding the influence of kidneys from donors aged over 50 years were retrospectively analyzed.
Results Graft survival at 1, 5, 10, and 15 years was 94.7, 94.7, 90.2, and 75.2 %, respectively, in young recipients who received grafts from donors aged under 50 years, and 96.4, 91.9, 65.4, and 41.4 %, respectively, in young recipients who received grafts from donors aged over 50 years ($P = 0.023$). In contrast, there were no significant differences regarding graft survival and donor age in the middle-aged and old recipient groups. Multivariate analysis revealed that young recipient and rejection episode were significant predictors of graft loss in transplantation from older donors. Histological examination revealed significant age-related changes in the grafts before transplant and a significant higher rate of glomerular hypertrophy at the 1-month protocol biopsy in young recipients with aged kidney grafts.
Conclusions Kidney grafts from older living donors affected long-term graft survival in young recipients. In addition to the damage from rejection, aged kidney grafts, which have less nephron mass, may have a limited capacity to appropriately respond to increases in physiological or metabolic demands of young recipients, leading to a greater reduction in renal function.

Keywords Living-donor kidney transplantation · Young recipient · Aged kidney graft · Rejection · Glomerular hypertrophy

M. Tasaki (✉) · K. Saito · Y. Nakagawa · M. Ikeda · K. Takahashi
Division of Urology, Department of Regenerative and Transplant Medicine, Niigata Graduate School of Medical and Dental Sciences, 1-757, Asahimachi-dori, Chuo-ku, Niigata, Japan
e-mail: masa1214@med.niigata-u.ac.jp; masa1214@med.niigata-u.ne.jp

N. Imai · I. Narita
Division of Clinical Nephrology and Rheumatology, Graduate School of Medical and Dental Sciences, Niigata University, Niigata, Japan

Introduction

In many countries, the lack of donor organs coupled with an increasing number of end-stage renal disease patients has placed greater emphasis on living kidney donation. Along with an improving in long-term graft survival, death with a functioning graft has been increasing, particularly in aged recipients [1–4]. However, patient survival is not the main limitation to long-term graft survival in young recipients, who have a low risk of death after kidney transplantation (KTx).

The adverse impact of increasing donor age on renal allograft survival is well established for deceased donor KTx [4–7]; however, this has not yet been evaluated for long-term graft survival over 10 years in living-donor KTx. Most donors for young recipients are their parents, who belong to the relatively aged donor population.

Thus, the present study aimed to assess graft survival over 20 years in living-donor KTx for young recipients with aged kidney grafts and determine the possible causes for graft loss.

Published online: 13 February 2014

Materials and methods

Patients

A total of 287 living-donor KTxs in Niigata University hospital from 1988 to 2012 were included in this study. The recipients were divided into 3 groups according to their age in years: under 30 (young), 30–49 (middle-aged), and over 50 (old). To investigate the effect of donor age, the donor groups were categorized into 2 groups according to their age in years: younger than 50 years (younger donors) and older than 50 years (older donors). Aged kidney grafts were defined as grafts donated by older donors.

Immunosuppresive therapy

The immunosuppressive therapy commonly used was the triple therapy consisting of a calcineurin inhibitor as the base, a steroid, and an antimetabolite [8]. Mycophenolate mofetil has been used instead of azathioprine and mizoribine since 2001. Basiliximab has been administered since 2002 for induction therapy. In ABO-incompatible KTx, the triple immunosuppresion was given prior to KTx as a desensitization therapy. Rituximab has been used before ABO-incompatible KTx instead of splenectomy since 2004 [8].

Data collection

Recorded baseline data included age, gender, ABO incompatibility, number of human leukocyte antigen (HLA) mismatches, preemptive KTx, biopsy-proven rejection, duration of dialysis, warm and total ischemic times, transplant era, and histological data. The primary clinical outcome of this study was graft survival (death-censored graft survival). Complement-dependent cytotoxicity (CDC) cross-match and flow cytometric cross-match (FCXM) tests were negative before transplantation in all cases of this study. However, panel-reactive antibody (PRA) test was not routinely examined in our hospital. The data were retrospectively analyzed. The present study was approved by the Ethics Committee of Niigata University Faculty of Medicine and conducted in accordance with its ethical principles.

Histological data

Biopsies were performed before transplantation and 1 month after transplantation to evaluate kidney grafts. Mayer's hematoxylin–eosin (HE), alcian blue-periodic acid-Schiff reaction (PAS), and elastic staining were used. In addition to Banff classification, a unique scoring system was used to evaluate kidney grafts in our center. Intimal thickness of the artery and glomerular global sclerosis have been reported to be indicative of age-related changes [9]. To examine the effects of aging in the kidney grafts, the following parameters were analyzed: intimal thickness of interlobular artery (0: no intimal thickness, 1: two layers of internal elastic lamina, 2: three layers, 3: four layers), glomerular global sclerosis (0: 0 %, 1: 0–24 %, 2: 25–49 %, 3: 50–74 %, 4: 75–100 %), and glomerular hypertrophy (0: no glomerular hypertrophy, 1: glomerular hypertrophy). All pathologic specimens were reviewed by one pathologist.

Statistics

Results were expressed as the frequency (percentage) or average (mean) for categorical data. Baseline characteristics between the non-graft loss and graft loss group were compared by Chi-squared analysis or two-sided *t* test. Graft survival estimates were obtained by using Kaplan–Meier methods. To determine the independent predictive variable for graft loss, relevant factors in univariate analysis were fitted into multivariate-adjusted logistic regression analysis. All statistical analyses were performed using SPSS software 15.0 for Windows.

Results

The effect of donor age on long-term death-censored graft survival

The graft survival at 1, 5, 10, 15, and 20 years in the group receiving kidney grafts from young donors aged <50 years

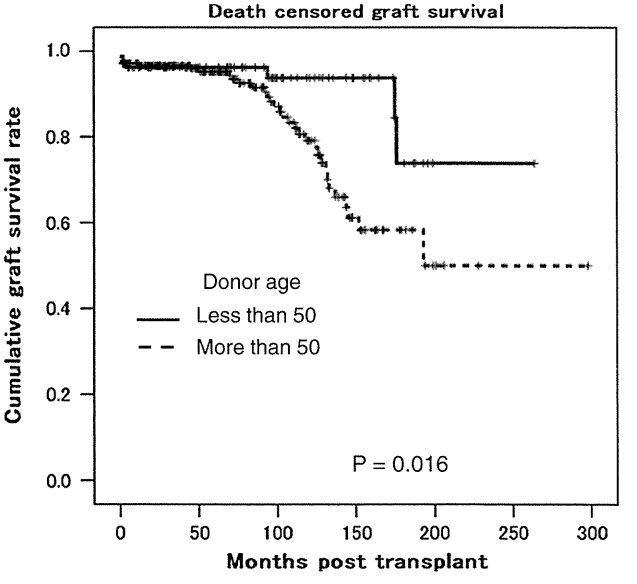

Fig. 1 Kaplan–Meier graft survival by donor age (*black line* donors <50, *dotted lines* donors over 50-year old)

was 96.2, 96.2, 93.8, 73.8, and 73.8 %, respectively (Fig. 1), which was significantly higher than the group receiving grafts from old donors aged over 50 years (97.3, 95.3, 79.1, 58.2, and 49.9 %, respectively; $P = 0.016$). When graft survival was examined for the recipients who received kidney grafts from old donors, no significant differences between the three groups were observed until 8 years after transplantation (84.8 % in young recipients, 91.5 % in middle-aged, and 81.9 % in old). However, the graft survival in young recipients was significantly decreased 9 years after transplantation compared with middle-aged recipients (Fig. 2). Figure 3 shows graft survival for each recipient group. Long-term graft survival with aged grafts was significantly worse only in young recipients ($P = 0.023$).

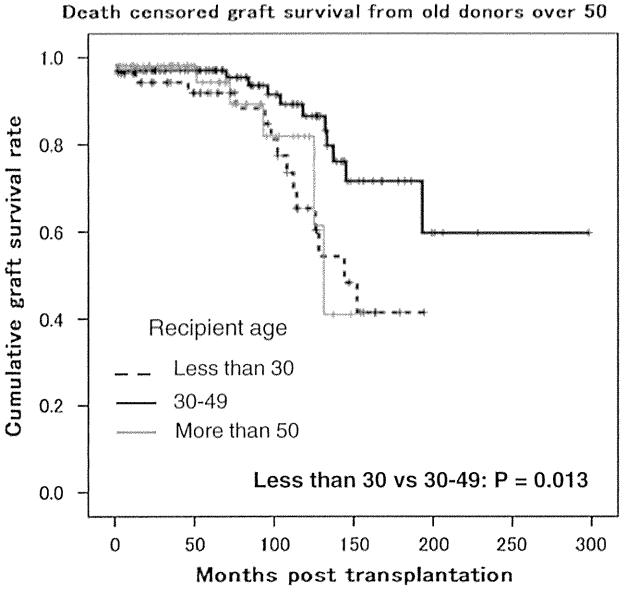

Fig. 2 Kaplan–Meier graft survival in the recipients who received aged kidney grafts over 50 years (*dotted lines* recipient <30, *black line* 30–49, *gray line* over 50-year old)

Risk factors for graft loss in kidney transplant from elderly donors

We first undertook univariate analyses to find out possible risk factors for graft loss in recipients receiving kidney grafts from older donors. Young recipient age, history of rejection, long warm ischemic time, and early transplant era were significantly associated with the higher incidence of graft loss (Table 1). Subsequently, multiple logistic regression analysis was employed to identify independent risk factors for graft loss among these variables. When all the variables were included, just transplant era, which is a persistent factor, was involved in graft loss; without transplant era, young recipient age and history of rejection were risk factors independently associated with graft loss (Table 2).

Age-related changes in kidney grafts

Biopsies before transplantation were performed to evaluate kidney grafts. When we compared the intimal thickness of the interlobular artery and glomerular global sclerosis between the two donor groups, we found histological changes in the aged kidney grafts (over 50 years) before transplantation (Fig. 4a). The average intimal thickness

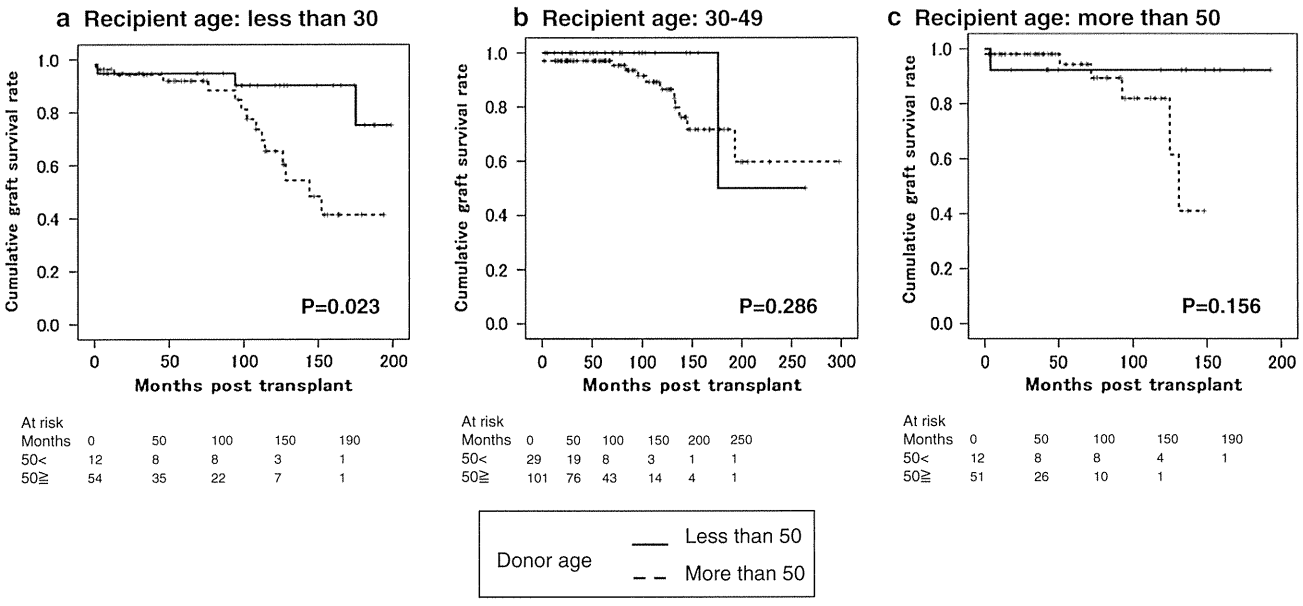

Fig. 3 Kaplan–Meier graft survival in each recipient group. Donor group was divided into two according to their age (*black line* donors <50, *dotted lines* donors over 50-year old)