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Demographic trends in the Okinawa Dialysis Study (OKIDS) registry (1971–2000)

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Demographic trends in the Okinawa Dialysis Study (OKIDS) registry (1971–2000).

Background. The clinical demographics of chronic dialysis patients are changing worldwide. However, long-term data from regional dialysis registries have not yet been analyzed and reported.

Methods. The Okinawa Dialysis Study (OKIDS) registry included all chronic dialysis patients treated in Okinawa, Japan, since 1971. Data for the years 1971 to 1990 were analyzed to predict trends for 1991 to 2000. The predicted values were then compared to the actual values and analyzed statistically, with particular attention being paid to relative risk of death. Multivariate Cox proportional hazards analysis was done to analyze the time factors of relative risk of death.

Results. A total of 5246 patients (2981 men and 2265 women) were registered and the total duration of observation was 28,431 patient-years. The prevalence and incidence of dialysis patients expressed per million population were 2320 and 297, respectively, in 2000, values that were significantly higher ($P <$ 0.02 for both) than the predicted values. The gross mortality rate per 1000 patient-years was 118.4 for 1971 to 1980, 63.3 for 1981 to 1990, and 77.7 for 1991 to 2000. The adjusted hazards ratio (95% confidence interval) for mortality was 0.743 (0.650 to 0.862) for 1981–1990 and 0.721 (0.659 to 0.790) for 1991 to 2000 in comparison to the risk of mortality in 1971 to 1980. The decrease in mortality rate was largely due to the drop in cardiac deaths from 71.0 for 1971 to 1980 to 17.2 for 1991 to 2000.

Conclusions. The incidence and prevalence of chronic dialysis patients increased more than expected over the past decade in Okinawa, Japan. Despite the rapid change in patient demographics, the survival rate did not decrease significantly.

The number of patients with end-stage renal disease (ESRD) requiring chronic dialysis is increasing worldwide [1, 2]. Patients with predialysis comorbidities, patients with diabetes mellitus (DM), and the elderly are now accepted into treatment by dialysis, thus the clinical demographics are changing [3–5]. The number of dialysis patients is dependent, at least partly, on the number of dialysis beds [6]. In Japan, Okinawa is an area of high incidence and prevalence of dialysis patients [1, 6]. Since 1971, we have registered all chronic dialysis patients residing in Okinawa and who survived at least one month on scheduled dialysis [4]. The prevalence and incidence of dialysis patients and the mean age at the start of dialysis increased linearly from 1971 to 1990. The present study extended the observation to 2000 and tested trends on the basis of predictions calculated from the 1971–1990 data. We also compared the Okinawa data with that of the Japanese Society for Dialysis Therapy (JSDT) registry [1] to examine geographic differences.

Survival rates for ESRD patients differ between countries and registries. Any comparison that involves separate registries or different countries must be approached with caution [7]. Analysis of long-term regional dialysis registry data is suitable for understanding the time-dependent changes in the demographics of chronic dialysis patients.

Key words: hemodialysis, peritoneal dialysis, end-stage renal disease, survival, comorbidity, diabetes mellitus, Japan and dialysis.

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METHODS

Data collection for the OKIDS registry

All chronic dialysis patients residing in Okinawa, Japan, who survived at least one month on scheduled dialysis were registered in the Okinawa Dialysis Study (OKIDS) registry [4]. Patients dying within one month of the start of dialysis were not included in the registry because it is unknown whether their renal function was improving or other medical conditions accounted for their rapid demise. Pertinent clinical information for the new dialysis patients and medical events in the prevalent dialysis patients were recorded via strict collaboration of physicians who are acknowledged herein. Records were updated at least twice a year for medical events such as death, renal transplantation, and patient transfer to outside Okinawa. If needed, other information was obtained through nurses, medical clerks, and the patients

themselves. All patients were followed up until a major medical event or to January 2001, and outcomes were verified by us. Since Okinawa is comprised of subtropical islands that are separated from mainland Japan, there is little migration of patients. The total population of Okinawa was 1.2 million in 1990 and 1.32 million in 2000, which is approximately 1.0% of the overall population of Japan. Several retrospective [4, 5, 8, 9] and prospective [10–12] studies based on the registry data have been reported.

The present study summarizes data from the past 30 years, 1971 to 2000. Patients with intermittent or continuous ambulatory peritoneal dialysis (CAPD) were included in the analysis, because CAPD patients comprise a very small fraction of the overall population, and they often switch dialysis modalities. Fewer than 100 CAPD patients have participated in OKIDS throughout the study period. Criteria for the differential diagnosis of ESRD were neither simple nor standardized. Therefore, the medical records were reviewed further, and patients were grouped into one of six disease categories. Chronic glomerulonephritis (CGN) was diagnosed when proteinuria and/or hematuria was noted before the onset of hypertension and renal failure. Nephrosclerosis (NScl) was diagnosed when hypertension and/or major vascular disease was documented before the onset of renal failure. DM nephropathy was diagnosed clinically by a long history of DM, presence of DM retinopathy, and the use of insulin [8]. Systemic lupus erythematosus (SLE) was diagnosed according to the criteria of the American Rheumatism Association [9]. Polycystic kidney disease (PKD) was diagnosed, after chart review, after the presence of multiple cysts and with a family history. A sixth category, "other" disease, was used for patients who did not fall into one of the above-mentioned disease categories. Predialysis comorbidities were confirmed by review of the medical charts and were grouped into six categories: atherosclerotic heart disease (ASHD), peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), malignancies (MAL), cerebrovascular disease (CVD), and "other."

The dialysis regimen has been described previously [4, 10]. The mean dialysis dose was around 18.0 $m^2 \times$ h/week. More than 90% of the patients were receiving dialysis at 3.5 or more hours per session. Dialyzer reuse does not usually occur in Japan, since the care providers are reluctant to reuse the dialyzer if doing so means they cannot receive government reimbursement [13]. Vascular access usually was created by a surgeon, and the arteriovenous (AV) fistula was the preferred access. In our region, we normally wait until the AV fistula has matured, and in the interim the patients are dialyzed with a temporary catheter. The target hematocrit has been set empirically between 30% and 35%, and more than 80% of the dialysis patients have been given erythropoietin [1]. By the end of 2000, there were 46 dialysis units in Okinawa: 9 in the public sector, 17 in private hospitals, and 20 in clinics. In the retrospective analysis for 1971 to 1990, there was a significant linear increase in the annual incidence, prevalence and mean age at the start of dialysis [4]. In the present study, we analyzed these population measures again and compared the actual data for 1991 to 2000 with the predicted values [4]. Twenty patients who were started on chronic dialysis therapy outside Okinawa during 1971 to 1990 became residents after January 1991 and are included in the present study.

Dialysis registry of the JSDT

The JSDT has had a standing committee responsible for statistics and investigation since 1983 [1]. The JSDT mails a survey every year at the end of November to the heads of all dialysis facilities on record. Details of survey method have been described previously [14, 15]. The latest report of the 1999 JSDT registry was used for the present study. In brief, as of December 31, 1999, a total of 3220 out of 3231 units (99.66%) have responded. The total number of dialysis patients was 197,213, up 6.4% ($N = 11{,}891$) from the prior year. The mean age of new dialysis patients was 63.4 years. The primary renal disease among the new dialysis patients in 1999 was DM nephropathy in 36.2%, followed by CGN in 33.6%. The mean Kt/V for those on dialysis three times per week was 1.33 (1.25 for men and 1.46 for women), and the mean dialysis session time was four hours (4.03 hours for men and 3.96 hours for women). The mean serum level of albumin was 3.88 g/dL for men and 3.82 g/dL for women. The mean body mass index of the new dialysis patients was 20.9 kg/m^2 for men and 20.2 kg/m^2 for women.

Statistical analysis

Annual incidence and prevalence data at each year-end were obtained from a government report and are expressed per million population. The observation period was calculated from the start of dialysis until the end of follow-up, death, renal transplantation, or transfer outside Okinawa, and is expressed in patient-years. One-way repeated measures analysis of variance (ANOVA) was used to compare the incidence and prevalence between groups. Kaplan-Meier survival curves were calculated. Patients were censored at the time of death, renal transplantation, transfer outside Okinawa, or January 2001. Multivariate Cox proportional hazards analysis was done to examine the relative risk of death by the start year of dialysis after adjusting for confounding variables such as age, sex, start year of dialysis, primary renal disease, and predialysis comorbidities. Data are expressed as mean (SD). All analyses were done using the SAS

Table 1. Clinical demographics of chronic dialysis patients in Okinawa, Japan (1971–2000)

Number of patients	5246
Men/women	2981/2265
Age at start of dialysis, years	
Men mean (SD)	53.6 (16.5)
range	1 to 101
Women mean (SD)	57.2 (17.6)
range	1 to 97
Primary renal disease	
Chronic glomerulonephritis	2461 (46.9%)
Diabetes mellitus	1603 (30.6%)
Nephrosclerosis	535 (10.2%)
Systemic lupus erythematosus	111 (2.1%)
Polycystic kidney disease	123 (2.3%)
Others	413 (7.9%)
Predialysis comorbid condition	
Atherosclerotic heart disease	206 (3.9%)
Chronic obstructive lung disease	71 (1.4%)
Cerebrovascular disease	296 (5.6%)
Peripheral vascular disease	90 (1.7%)
Malignancies	157 (3.0%)
Others	185 (3.5%)
Current status in January 2001	
Alive on dialysis	2840 (54.1%)
Died	2137 (40.7%)
Renal transplantation	208 (4.0%)
Transferred outside	61 (1.2%)

Table 2. Comparison of the number of patients (per million population) from 1991–2000 in Okinawa and JSDT

Year	General population *million*	Number of new dialysis patients		Number of prevalent dialysis patients	
		OKIDS	JSDT	OKIDS	JSDT
1991	1.22	190	169	1251	944
1992	1.23	208	181	1346	996
1993	1.24	228	191	1445	1076
1994	1.25	233	194	1562	1149
1995	1.26	224	210	1661	1230
1996	1.27	258	226	1760	1328
1997	1.28	295	229	1926	1395
1998	1.29	292	234	2071	1465
1999	1.30	315	249	2227	1557
2000	1.32	297	252	2320	1624

Abbreviations are: OKIDS, Okinawa Dialysis Study; JSDT, Japanese Society for Dialysis Therapy; NA, data not available.

software (SAS, Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Over the 30-year period, 5246 patients (2981 men and 2265 women) were treated in Okinawa. The clinical demographics of the OKIDS registry patients are summarized in Table 1. The overall mean (SD) age at the start of dialysis was 55.1 (17.1) years and ranged from 1 to 101 years. Total observation was 28,431 patient-years. Comorbid conditions existed in 5.6% of patients for 1971 to 1980, 15.5% for 1981 to 1990, and 22.7% for 1991 to 2000. During the period of 1991 to 2000, the observed incidence and prevalence of dialysis patients were significantly higher ($P < 0.02$ for both) than predicted. The predicted incidence and prevalence of dialysis patients were from 183 and 1291 in 1991 to 266 and 2068 in 1999, respectively. In comparison to the JSDT data, both incidence and prevalence were significantly high in Okinawa ($P < 0.01$ for both; Table 2).

The mean age at the start of dialysis increased from 55.9 years in 1991 to 61.4 years in 1999, but the predicted ages for 1991 to 1999 were 58.0 years to 69.3 years and 58.2 years to 63.4 years (JSDT). The mean age of OKIDS SLE patients (37.9 years) and the mean age of OKIDS PKD patients (53.4 years) were lower than the mean ages of JSDT SLE patients (53.1 years), and JSDT PKD patients (58.0 years). With the exception of 1971 to 1980, there were significant sex differences in mean age at the start of dialysis. Men started dialysis earlier than women among patients with chronic glomerulonephritis, DM, nephrosclerosis, and "other" diseases. However, no sex differences in mean age at the start of dialysis were found among patients with SLE or PKD.

Changes in prevalence of dialysis patients in the three decades are shown according to age categories in Figure 1. For 1971 to 1980, there was no noticeable difference between age groups. However, the prevalence increased with age in the second and third ten-year periods. Changes in prevalence of dialysis patient are shown per primary renal disease in Figure 2. For 1971 to 1980, CGN was the main cause of ESRD. For 1981 to 1990, both CGN and DM contributed to the increase in the treatment rate. Between 1991 and 2000, DM and NScl contributed to the further increase. The contribution of CGN did not change remarkably between the second and third ten-year periods. However, the average age at the start of dialysis increased from 46.4 years in the second decade to 53.8 years in the third decade.

Survival curves by decades of starting dialysis are shown in Figure 3. The overall survival rate was 88.6% for one year, 66.5% for five years, 48.2% for ten years, and 29.3% for 20 years. Survival rates were significantly influenced by age at the start of dialysis (Fig. 4), predialysis comorbidities (Fig. 5), and primary renal diseases (Fig. 6). Effects of confounding variables such as start year, primary renal disease, and predialysis comorbidities are summarized in Table 3. Patients with PKD had comparable survival to patients with CGN.

Changes in the causes of death and mortality rates for each decade are shown in Figure 7. The overall death rate was 75.2 per 1,000 patient-years for the past 30 years. Cardiac death decreased sharply for 1981 to 1990, and a similar trend occurred for 1991 to 2000. For 1991 to 2000, deaths due to withdrawal from dialysis and infection increased slightly.

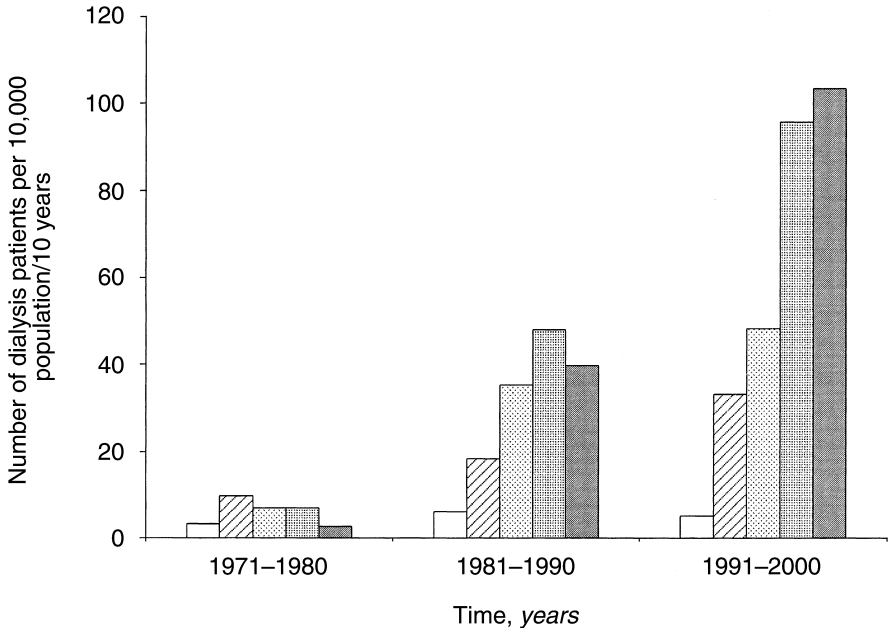

Fig. 1. Prevalence of chronic dialysis patient per 10,000 population shown by age categories for three 10-year periods. Symbols for the age ranges are: (□) ≤39; (▨) 40 to 49; (▩) 50 to 59; (■) 60 to 69; (■) ≥70.

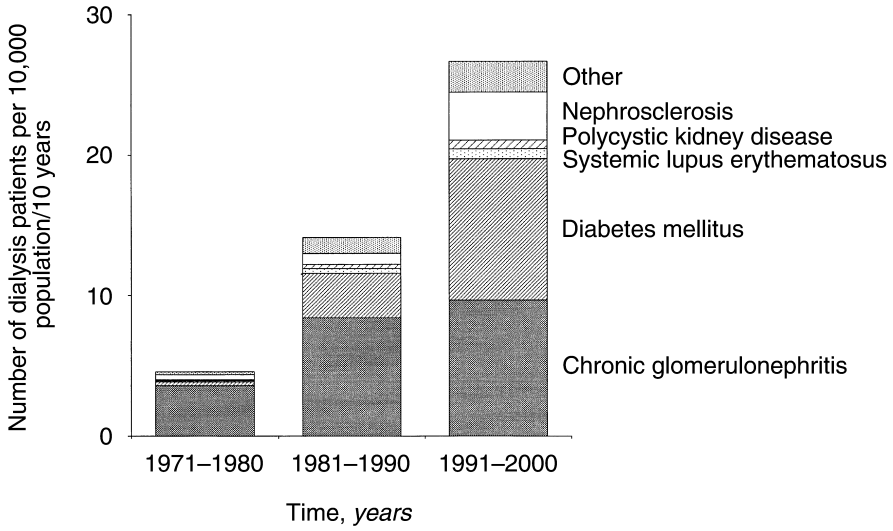

Fig. 2. Prevalence of chronic dialysis patient per 10,000 population shown by primary renal disease for 10-year periods.

DISCUSSION

The present study documents clinical demographic changes traced through over three decades via a regional dialysis registry. The incidence and prevalence of chronic dialysis patients increased more than expected. Usami et al showed the number of available dialysis beds to be correlated with the number of dialysis patients, but this was not considered a causative factor [6]; in fact, there are more dialysis units per capita in Okinawa (35.1 per million population) in comparison to the JSDT data (25.4 per million population) [1]. However, this does not necessarily mean that the criteria for initiating dialysis are subject to change. Actually, the mean serum creatinine values at the start of dialysis decreased only slightly from 14.3 mg/dL during 1971 to 1981 to 12.0 mg/dL for 1988 to 1990 [16]. This subtle decrease in incident creatinine values may be explained by a concurrent increase in the number of older and sicker patients [17]. Given the low rate of renal transplantation (6.5 to 9.1 per 1000 patient-years during the study period) and CAPD (Table 1), the present study fairly accurately shows the overall changes in hemodialysis therapy for the past three decades in Okinawa, Japan.

The reasons why the incidence of ESRD has increased so rapidly are not clear, but several possibilities exist. First, the low birth weight (less than 2500 grams) rate

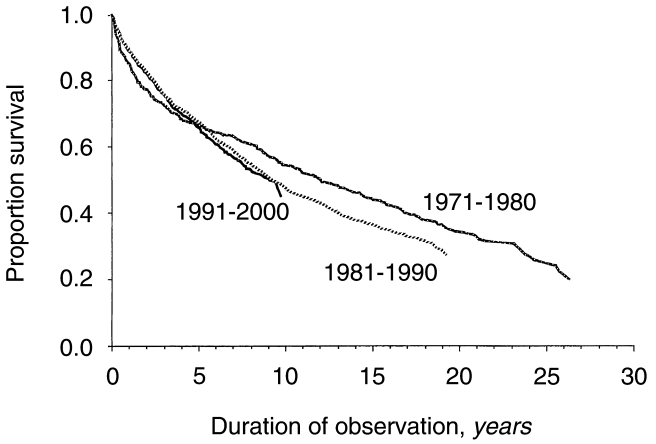

Fig. 3. Survival curves, calculated by the Kaplan-Meier method, by the start year of dialysis.

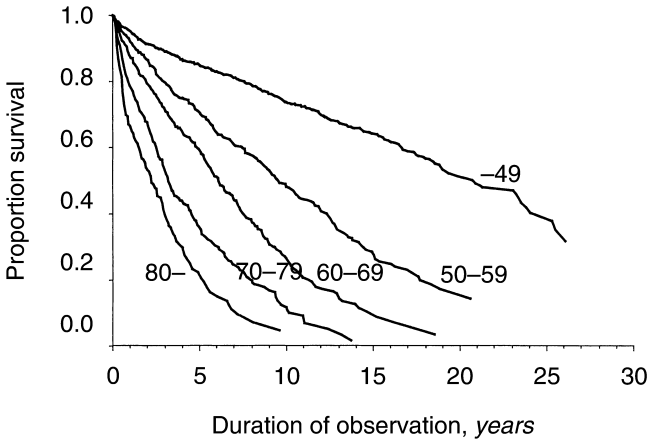

Fig. 4. Survival curves, calculated by the Kaplan-Meier method, by age at the start of dialysis.

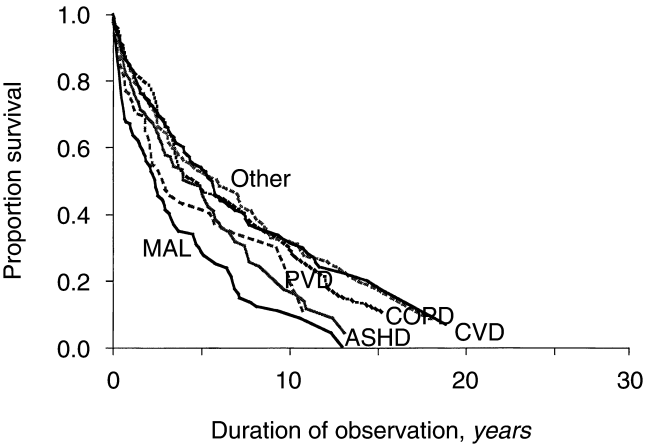

Fig. 5. Survival curves, calculated by the Kaplan-Meier method, by predialysis comorbidities. Abbreviations are: MAL, malignancies; ASHD, atherosclerotic heart disease; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; CVD, cerebrovascular disease.

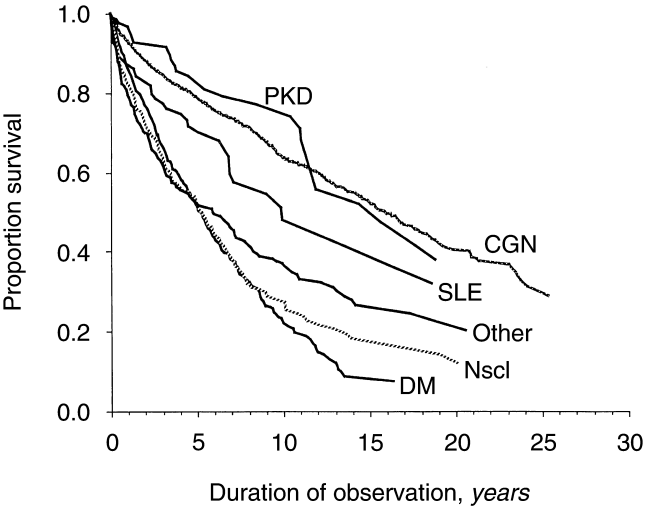

Fig. 6. Survival curves, calculated by the Kaplan-Meier method, by primary renal disease. Abbreviations are: PKD, polycystic kidney disease; CGN, chronic glomerulonephritis; SLE, systemic lupus erythematosus; Nscl, nephrosclerosis; DM, diabetes mellitus.

in Okinawa has been as high as 7.4% to 9.3%, which is higher than the national average of 5.7%. Low birth weight has been linked to later development of hypertension and renal failure [18]. Second, patients do not always comply with their medical treatments. Our previous study screened a cohort and found that those who were screened and found to be at risk of developing ESRD were not treated accordingly [19, 20]. Data from USRDS indicated that only 42% had permanent vascular access attempted before ESRD treatment [21]. Therefore, late referral to a nephrologist is considered common not only in Okinawa but also worldwide [22]; however, whether progression of kidney disease is indeed slowed by the nephrologist's intervention remains to be determined [23]. Third, the incidence of DM has increased rapidly. More than one-third of the new dialysis patients were started because of DM, mostly non-insulin dependent DM. Okinawa reverted to Japan in 1972 after U.S. military rule that began at the end of World War II. Since then, the people of Okinawa have undergone a marked change in lifestyle and dietary habits. An increase in DM nephropathy has been reported recently in indigenous populations [24, 25].

The mean age at the start of dialysis was lower in the OKIDS patients than in the JSDT patients. In particular, the OKIDS patients with SLE and PKD were significantly younger than their JSDT counterparts. There were no sex differences in mean age at start of dialysis among patients with PKD. In contrast, Ishikawa et al showed that mean age at start of dialysis was younger in JSDT men than in JSDT women [26]. Konoshita et al showed that patients with PKD homozygous for the

Table 3. Results of the multivariate Cox proportional hazards analysis for the prognosis of chronic dialysis patients

	Adjusted[a] hazards ratio	95% CI	*P* value
Sex			
Women	1.000		
Men	1.141	1.046–1.245	0.0028
Start year of dialysis			
1971–1980	1.000		
1981–1990	0.743	0.650–0.862	<0.0001
1991–2000	0.721	0.659–0.790	<0.0001
Age at start of dialysis *years*			
0–49	1.000		
50–59	2.587	2.252–2.972	<0.0001
60–69	2.066	1.926–2.217	<0.0001
70–79	1.955	1.853–2.063	<0.0001
≥80	1.799	1.706–1.897	<0.0001
Primary renal disease			
Chronic glomerulonephritis	1.000		
Diabetes mellitus	2.225	1.985–2.495	<0.0001
Polycystic kidney disease	0.869	0.724–1.043	NS
Systemic lupus erythematosus	1.328	1.220–1.445	<0.0001
Nephrosclerosis	1.054	1.021–1.088	0.0013
Other	1.151	1.092–1.214	<0.0001
Predialysis comorbid condition			
None	1.000		
Atherosclerotic heart disease	1.549	1.272–1.886	<0.0001
Chronic obstructive pulmonary disease	1.181	1.011–1.380	0.0364
Peripheral vascular disease	1.214	1.104–1.335	<0.0001
Malignancies	1.198	1.141–1.258	<0.0001
Cerebrovascular disease	1.038	1.008–1.068	0.0122
Other	1.125	1.079–1.172	<0.0001

[a] Adjusted for variables in this table; NS denotes not significant

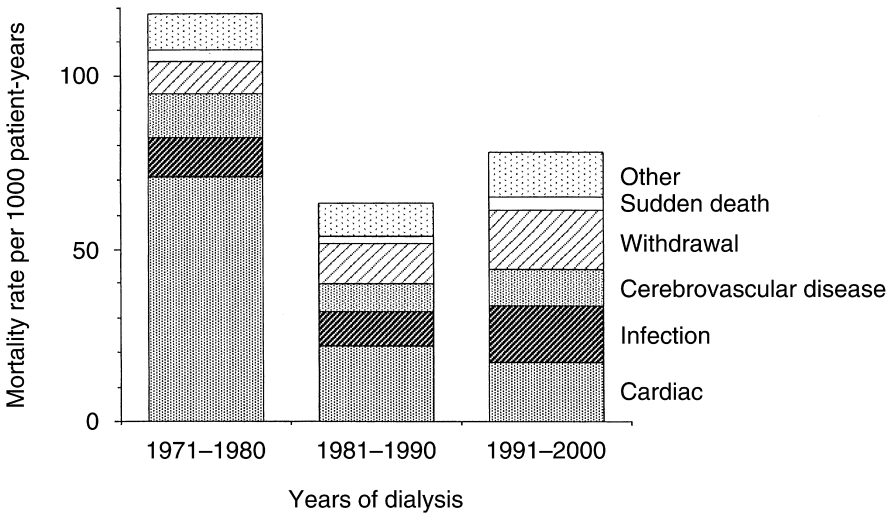

Fig. 7. Causes of death and mortality rates for each decade. Mortality rate is expressed as the number of deaths per 1000 patient-years.

D allele of the ACE gene are at increased risk for developing ESRD at an early age [27]. In this regard, it is possible that the ACE genotype differs in Okinawa, since analysis of HLA gene polymorphism suggests a gene flow from Okinawa to mainland Japan [28].

The overall survival rate among chronic dialysis patients in Okinawa has been good at 48.2% in 10 years. Cardiac death remained a leading cause of death, but it decreased significantly (Fig. 7). The exact reasons for the positive outcomes are not certain; however, we speculate that more emphasis on salt restriction and blood pressure control, the introduction of erythropoietin, and access to better cardiac care are contributing factors. According to the JSDT registry, the ten-year survival rate for chronic dialysis patients who started dialysis after 1983 was 0.490 in Okinawa, whereas the national average was 0.423 [1]. In general, Japanese people live longer than those of other countries [29], and Okinawa is the region

of Japan where the overall population's lifespan is the longest, particularly for women. The annual incidence of acute myocardial infarction and stroke death is reported at 31 and 137 per 100,000 population in Okinawa [30]. Therefore, survival rates in dialysis patients may reflect that of the Okinawa population in general. We showed the prevalence of hospitalization to be 13% by a cross-sectional study in 1997 [31]. The leading causes of hospitalization were stroke, infection, and cardiac disease. Social causes without major medical reasons accounted for about 18% of the total hospitalizations. If any of these patients had received social support from a spouse, family member, or community members, they could have undergone chronic dialysis therapy as out-patients.

There are some limitations to the present study. Both the OKIDS and JSDT data were provided voluntarily from the participating facilities. Studies looking at the reliability and validity of the JSDT data are currently underway. Although neither registry is likely to be perfect, the OKIDS registry is supplemented with additional information obtained directly from service providers. The USRDS collected data from billing information of the Health Care Financing Administration (HCFA) [32], an entirely different source than the OKIDS and JSDT sources.

Significant regional differences in clinical demographics exist in Japan [1, 6]. There are distinct environmental and socioeconomic conditions and lifestyles within the country that may affect the incidence of ESRD. The income per capita in Okinawa is among the lowest in Japan. Therefore, the OKIDS data is probably not representative of Japan as a whole. Geographic heterogeneity and variability among nations and within nations have been increasingly recognized [33].

The influence of the various treatment modalities and dialysis regimens on patient survival was not analyzed in this study. Dialysis techniques are slowly changing in Japan. The mean 4.30 session hours of dialysis in 1991 decreased to 4.00 hours in 1999 [1], and CAPD patients comprised less than 5% of the dialysis population in Okinawa as in Japan [1]. However, a meta-analysis of outcome studies between hemodialysis and CAPD was inconclusive [34].

Finally, our explanation for the rapid increase in the incidence of chronic dialysis remains speculative. The people of Okinawa greatly respect the elderly. Elderly persons on dialysis receive a lot of support from neighbors and family members. We believe such cultural attitudes toward the elderly and the sick, as well as public support for dialysis therapy may account for the high incidence of dialysis patients. In Japan, the health care system, consisting primarily of the Social Health Insurance Organization and the Government Health Insurance Organization, covers 100% of the population [13]. The standard per month reimbursements for outpatient hemodialysis treatment are similar between Japan (¥442,056) and the United States ($3,683.4) [13].

Renal transplantation rates remained low during the three decades, but the reasons are not clear. Given the greater age at the start of dialysis and the difficulty in obtaining a graft, xenotransplantation may be a hopeful alternative. If current trends continue, there will be 400 new dialysis patients and 4000 prevalent dialysis patients per million population in Okinawa, surpassing the average worldwide trends [35].

The incidence and prevalence of chronic dialysis patients increased faster than expected during the past ten years in Okinawa, Japan. Despite the increase in elderly patients and patients with multiple comorbid conditions, the survival rates among dialysis patents did not decline significantly. In fact, the prognosis of diabetic dialysis patients has improved significantly [36]. The social and economic burden of chronic dialysis therapy is increasing. The social system may become hard pressed to continue covering these associated costs over the next decade. More efforts for early detection and treatment of those who are at risk of developing ESRD are needed to decrease the number of dialysis patients.

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