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Cause-Specific Excess Mortality Among Dialysis Patients: Comparison With the General Population in Japan

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Abstract: Despite significant therapeutic advances, mortality of dialysis patients remains unacceptably high. The aim of this study is to compare mortality and its causes in dialysis patients with those in the general Japanese population. We used data for 2008 and 2009 from the Japanese Society for Dialysis Therapy registry and a national Vital Statistics survey. Cardiovascular mortality was defined as death attributed to heart failure, cerebrovascular disorders, myocardial infarction, hyperkalemia/sudden death, and pulmonary thromboembolism. Non-cardiovascular mortality was defined as death attributed to infection, malignancies, cachexia/uremia, chronic hepatitis/cirrhosis, ileus, bleeding, suicide/refusal of treatment, and miscellaneous. We calculated standardized mortality ratios and age-adjusted mortality differences between dialysis patients and the general population for all-cause, cardiovascular versus non-cardiovascular, and cause-specific mortality. During the 2-year study period, there were 2 284 272 and 51 432 deaths out of 126 million people and 273 237 dialysis patients, respectively. The standardized mortality ratio for all-cause mortality was 4.6 (95% confidence interval, 4.6–4.7) for the dialysis patients compared to the general population. Age-adjusted mortality differences for cardiovascular and non-cardiovascular disease were 33.1 and 30.0 per 1000 person-years, respectively. The standardized mortality rate ratios were significant for all cause-specific mortality rates except accidental death. Our study revealed that excess mortality in dialysis patients compared to the general population in Japan is large, and differs according to age and cause of death. Cause-specific mortality studies should be planned to improve life expectancies of dialysis patients. **Key Words:** Dialysis, Excess mortality, General population, Standardized mortality ratio.

According to the Japanese Society for Dialysis Therapy (JSDT) registry, more than 25 000 dialysis patients die every year in Japan (1). Despite significant therapeutic advances, the annual crude mortality rate of dialysis patients has been approximately 9.5% since 1992, and was 9.8% in 2008 (1). The life expectancy of dialysis patients was approximately half that of the general population of the same sex and age, in all age ranges (2). These findings suggest that there is still significant room for improvement in life prognosis for dialysis patients.

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Evidence is accumulating that excess mortality in dialysis patients can be explained by both cardiovascular and non-cardiovascular causes (3,4). For example, European incident dialysis patients have 8.8- and 8.1-fold higher cardiovascular and non-cardiovascular mortality, respectively, than the general population (4). However, little is known about excess mortality of Japanese dialysis patients. In Japan, life expectancy at birth is now the longest in the world (5), and the incidence of cardiovascular disease is relatively low compared to the United States and Europe (6). To improve the prognosis of Japanese dialysis patients, it is necessary to determine the cardiovascular and non-cardiovascular mortality rates of dialysis patients compared to the Japanese general population. It is also necessary to determine cause-specific mortality rates because excess mortality will differ among causes of death.

The aim of this study is to compare mortality and its causes in dialysis patients with those in the general Japanese population.

PATIENTS AND METHODS

Data sources

We extracted mortality data of dialysis patients from the annual data reported by the JSDT Renal Data Registry Committee for 2008 and 2009, which included a total of 51 423 deaths (7,8). The details of the JSDT registry data collection techniques and the characteristics of this dialysis population have been described elsewhere (1). The JSDT registry collects data on medical history, treatment conditions, and outcomes of individual dialysis patients from dialysis facilities in Japan every year by questionnaire.

We obtained mortality data for the general population from a national survey. The National Vital Statistics Survey Form consists of five forms: Live Birth Form, Death Form, Fetal Death Form, Marriage Form, and Divorce Form. We used data from the Death Form, which is based on Notification of Death, and included a total of 2.28 million deaths for 2008 and 2009 (9,10).

Case definitions

Causes of death for both the dialysis patients and general population were followed by the JSDT definition using the 10th modified edition of the International Classification of Diseases (ICD-10) codes (11) (Appendix I). It is important to note that our analyses included the annual mortality due to a certain disease rather than the fatality rate, which is the ratio of deaths among patients presenting with a certain disease over a certain period of time.

Data analysis

We analyzed all-cause mortality first, then estimated cardiovascular and non-cardiovascular mortality, and finally calculated cause-specific mortality. We defined cardiovascular mortality as deaths attributed to heart failure, cerebrovascular disorder, myocardial infarction, hyperkalemia/sudden death, and pulmonary thromboembolism. We defined non-cardiovascular mortality as deaths from all other causes, that is, infection, malignancies, cachexia/uremia, chronic hepatitis/cirrhosis, ileus, bleeding, suicide/refusal of treatment, and miscellaneous. Accidental deaths and deaths with unknown causes were excluded from analysis.

The calculation methods have been described previously in detail (12). Briefly, we categorized both the dialysis patients and the general population into five age groups: 0–29, 30–44, 45–59, 60–74, and ≥75 years. Mortality rates were calculated by dividing the number of deaths by the number of person-years accumulated during the study period. We estimated the number of person-years during the study period as twice the population at the mid-point (13). We calculated the expected number of deaths by multiplying the total number of person-years during the study period by the corresponding age-specific mortality rate for the general population. Standardized mortality ratios (SMRs) were then calculated as the ratio between the observed and expected number of deaths. We calculated confidence intervals (CIs) for the SMRs using the normal approximation of the Poisson distribution. The SMR can be interpreted as the relative difference in the mortality rate among the dialysis patients compared with that of the general population. We calculated the age-adjusted mortality rate difference to determine whether there was excess mortality in dialysis patients compared with the general population on an absolute scale. We also calculated the percent difference in all-cause mortality to determine the contributions of cause-specific mortality to any differences observed in all-cause mortality (14).

RESULTS

During the 2-year study period, there were 2 284 272 and 51 423 deaths recorded out of 126 million people and 273 237 dialysis patients, respectively. The crude all-cause mortality rate was 9.06 and 94.10 per 1000 person years in the general population and the dialysis population, respectively (Table 1). The SMR for all-cause mortality was 4.6 (95% CI: 4.6–4.7) for the dialysis patients with respect to the general population.

The proportions of cardiovascular and non-cardiovascular mortality in dialysis patients were approximately 46% (21 155 of 45 847 known causes of death) and 53% (24 351 of 45 847 known causes of death), respectively. The SMRs for cardiovascular and non-cardiovascular diseases were 6.7 (95% CI: 6.9–7.1) and 3.1 (95% CI: 3.0–3.1) times higher in dialysis patients than in the general population. The age-adjusted mortality rate difference for cardiovascular diseases (33.1 per 1000 person-years) was similar to that for non-cardiovascular diseases (30.0 per 1000 person-years).

Standardized mortality ratios for cause-specific mortality were significantly higher for hyperkalemia/sudden death, bleeding, heart failure, pulmonary thromboembolism, chronic hepatitis/cirrhosis, infectious disease, cachexia/uremia, ileus, cerebrovascular

TABLE 1. *All-cause and cause-specific mortality among dialysis patients compared with the general population*

Causes of death	Dialysis patients		General population			Difference	
	Total No. deaths	Crude mortality rates†	Crude mortality rates†	Age-adjusted mortality rates†	Standardized mortality ratio‡ (95% CI)	Age-adjusted mortality rate difference†	% difference in all-cause mortality
Cardiovascular diseases	21 155	38.7	2.4	5.6	6.7 (6.9–7.1)	33.1	44.9
Heart failure	12 155	22.2	0.7	1.7	13.2 (13.0–13.4)	20.6	27.8
Cerebrovascular disorders	4 368	8.0	1.0	2.3	3.5 (3.4–3.6)	5.7	7.7
Myocardial infarction	2 097	3.8	0.6	1.4	2.7 (2.6–2.8)	2.4	3.3
Hyperkalemia/Sudden death	2 402	4.4	0.1	0.1	29.6 (28.4–30.8)	4.2	5.8
Pulmonary thromboembolism	133	0.2	0.0	0.0	7.9 (6.6–9.3)	0.2	0.3
Non-cardiovascular diseases	24 351	44.6	6.6	14.6	3.1 (3.0–3.1)	30.0	40.6
Infection	10 435	19.1	1.1	2.6	7.5 (7.3–7.6)	16.5	22.4
Bleeding	962	1.8	0.1	0.1	14.5 (13.6–15.5)	1.6	2.2
Malignancies	4 763	8.7	2.8	6.2	1.4 (1.4–1.4)	2.5	3.3
Cachexia/Uremia	1 458	2.7	0.2	0.4	7.5 (7.1–7.9)	2.3	3.1
Chronic hepatitis/Cirrhosis	626	1.1	0.1	0.1	7.8 (7.2–8.4)	1.0	1.4
Suicide/Refusal of treatment	480	0.9	0.2	0.3	2.9 (2.6–3.1)	0.6	0.8
Ileus	504	0.9	0.1	0.1	6.8 (6.2–7.4)	0.8	1.1
Miscellaneous§	5 123	9.4	2.9	4.1	2.3 (2.2–2.3)	5.3	7.2
Accidental death	341	0.6	0.0	0.6	1.0 (0.9–1.1)	0.0	0.0
Unknown	5 576	10.2	0.1	0.1	91.3 (88.9–93.7)	10.1	13.7
All-cause mortality	51 423	94.1	9.1	20.3	4.6 (4.6–4.7)	73.8	100.0

Numbers may not add up due to rounding. †Per 1000 person-years; ‡Standardized for age; §For details, refer to the Appendix; CI, confidence interval.

disorder, suicide/refusal of treatment, myocardial infarction, miscellaneous (ICD-10 codes in Appendix I), and malignancies, in descending order. Figure 1 shows cause-specific mortality among dialysis patients compared with the general population. Mortality rates were higher in the elderly than in young individuals. Notably, mortality rates for hyperkalemia/sudden death were higher even among younger dialysis patients. While other cause-specific mortality rates increased exponentially with age, the mortality rates of suicide/refusal of treatment almost plateaued between the ages of 45 and 74 in both the dialysis patients and general population. The mortality rates of chronic hepatitis/cirrhosis increased with age until 74 years old, and then slightly decreased. The mortality rate of accidental death was similar between the dialysis patients and the general population. Values in Figure 1 reflect mortality rates in dialysis patients compared with the general population in the 60–74-year-old group, since most dialysis patients in Japan belong to this age group. Mortality rates associated with hyperkalemia/sudden death and heart failure were markedly higher in dialysis patients compared with the general population, being 46- and 36-fold higher, respectively, in the 60–74-year-old group.

DISCUSSION

The present study showed that all-cause mortality among Japanese dialysis patients was approximately five-fold higher than in the general population. We also showed that the age-adjusted mortality rate difference for cardiovascular diseases was similar to that for non-cardiovascular diseases. These findings indicate that preventing both cardiovascular and non-cardiovascular deaths is important for decreasing all-cause mortality among Japanese dialysis patients. We also revealed that excess mortality in dialysis patients differed with cause of death. These results indicate that countermeasures against each cause of death are needed to improve prognosis of dialysis patients.

Several characteristic findings of the cause-specific excess death should be discussed. Mortality due to hyperkalemia/sudden death was extremely high among dialysis patients compared to the general population, even among younger dialysis patients. This suggests that we should place a high priority on preventing these deaths, especially among young patients. However, the diagnosis of hyperkalemia is not completely reliable. Postmortem examination of 35 sudden death cases in chronic dialysis patients showed that dissecting aortic aneurysm was the most common cause of sudden death, followed by cerebral

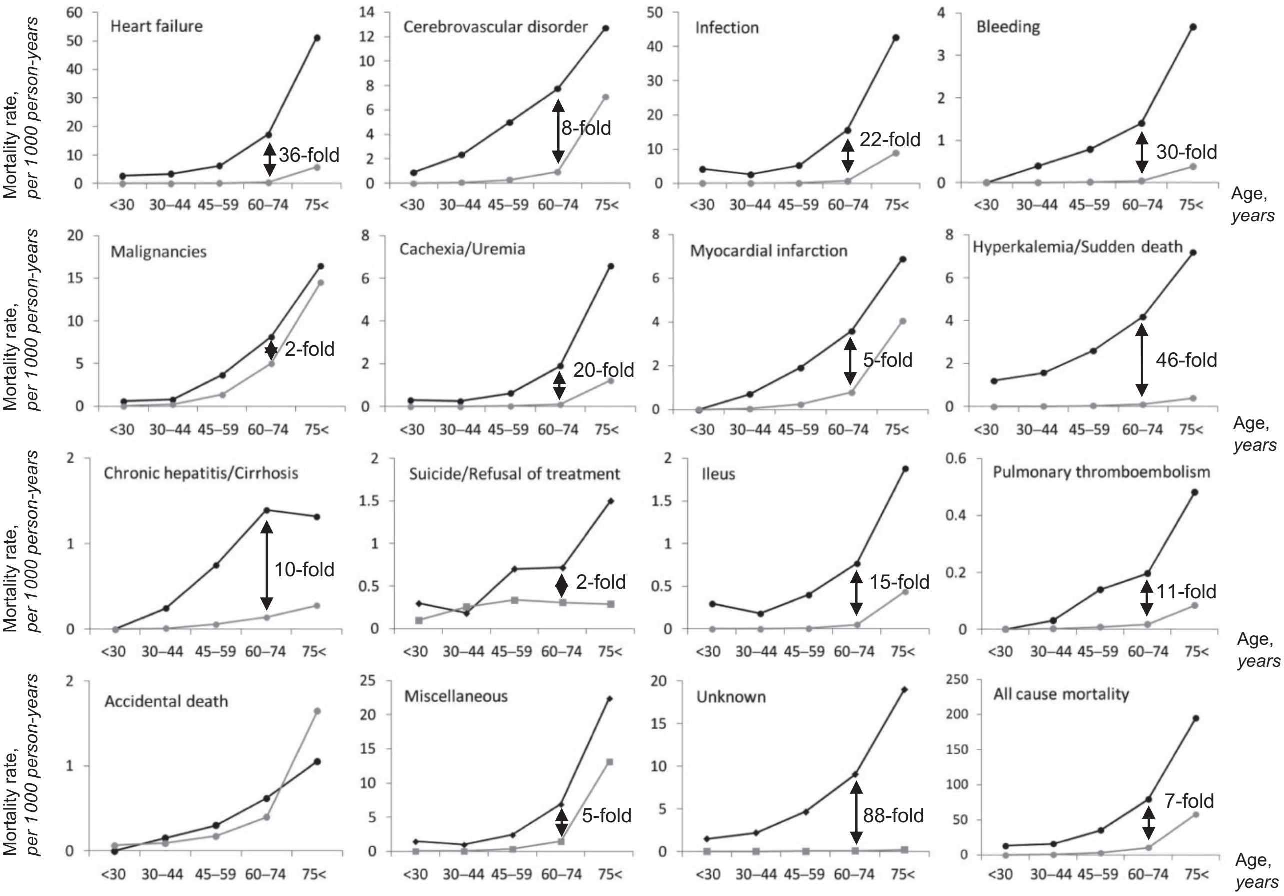

FIG. 1. Cause-specific excess mortality among dialysis patients (black line) compared with the general population (gray line). The data are stratified by age. Numbers reflect the ratios of mortality rates in dialysis patients compared with the general population in the 60–74-year-old age group, since most dialysis patients in Japan belong to this age group.

hemorrhage, acute subdural hematoma, acute myocardial infarction, cerebral infarction, and subarachnoid hemorrhage (15). Thus, some cases of sudden death might be due to cardiovascular diseases rather than hyperkalemia. Further detailed study is needed to prevent sudden death among dialysis patients, especially among younger dialysis patients.

In this study, dialysis patients had a 190% higher rate of suicide/refusal of treatment than the general population. This rate is unacceptably high given that the suicide rate in the Japanese general population is the eighth highest in the world and the highest among developed countries (16). Published information regarding suicide in dialysis patients is scarce. Patients with end-stage renal disease have an 84% higher rate of suicide compared with the general population in the United States (17). Our study did not distinguish between suicide and refusal of treatment, but the suicide rate in the Japanese dialysis population might be high because untreated depression is the leading cause of suicide among the general population, and dialysis patients with depression have been underdiagnosed and undertreated in Japan (18). This issue also requires further detailed investigation.

We found that mortality rates of chronic hepatitis/cirrhosis slightly decreased after age 75, while other cause-specific mortality rates increased after age 75. There are several possible explanations for this observation. First, patients with chronic hepatitis/cirrhosis might rarely survive after age 75. This speculation is consistent with the finding that hepatitis C virus (HCV) infection is the most common cause of chronic liver disease in dialysis patients, and anti-HCV-positive patients on dialysis have an increased risk of mortality compared with anti-HCV-negative patients (19). Second, patients with chronic hepatitis/cirrhosis over age 75 might die from other causes, because dialysis patients have many competing mortality risks. A prospective cohort study showed that cardiovascular disease, cerebrovascular disease, infection, and cancer account for 65% of the mortality among anti-HCV-positive patients (20). Third, the mortality rate of chronic hepatitis/cirrhosis might decrease because prevalence of the anti-HCV antibody decreases after age 75 (2). Fourth, patients over age 75 might not have a rapidly progressive course of liver cirrhosis. However, it remains controversial whether dialysis patients have a rapid progression to liver cirrhosis compared with the general population (21). Further detailed studies that focus on chronic hepatitis should be planned.

Mortality due to accidental death was similar between dialysis patients and the general population in this study. Japan experiences many different natural disasters, such as earthquakes, tsunamis, and floods. For example, the Iwate-Miyagi Nairiku Earthquake in July 2008, the heavy rainfall disasters in August 2008, the Chugoku-Kyushu-Hokubu Heavy Rainfall in July 2009, and the Shizuoka Earthquake in August 2009 occurred during the study period. These findings suggest that Japanese disaster relief activity would protect dialysis patients against mortality from these natural disasters. In fact, when the Great East Japan Earthquake occurred on 11 March 2011, many physicians and networks in Japan worked together to successfully transfer many dialysis patients (22,23). However, since our study period had relatively little human suffering caused by the natural disasters, we must re-evaluate this issue.

The study had some limitations that should be noted. First, we could not separate deaths among dialysis patients from the national data that we used as a reference group. However, the magnitude of this problem is negligible because these deaths represent <3% of all national deaths. Second, we only adjusted the SMRs for age. We lacked sufficient data to evaluate the number of patients stratified by gender, dialysis vintage, or dialysis modality. Life expectancies are higher for females than for males in the general population. Similarly, life expectancies are higher for females than for males in all age ranges of the dialysis population (2). More precise analysis is needed. Finally, we could not confirm the validity of diagnoses listed as cause of death. In addition, there was a large proportion of "Unknown" causes of death among the dialysis patients. Some studies have reported that death certificates and registry reports provide differing causes of death for patients with end-stage renal disease (24,25). Concordance assessment is needed in Japan to develop a clear epidemiological picture among dialysis patients.

Despite these limitations, this study has several strengths. Our study used data from a national Vital Statistics survey and a nationwide survey of Japanese dialysis facilities. Both surveys are an almost complete national census. In addition, we comprehensively evaluated cause-specific excess mortality among Japanese dialysis patients compared to the general population. In addition, as far as we know, this is the first report about the risk of accidental death among dialysis patients in comparison with the general population. Finally, our findings provide valuable data on unresolved issues concerning cause-specific excess mortality among Japanese dialysis patients.

CONCLUSIONS

Our study revealed that excess mortality in dialysis patients compared to the general population in Japan is large, and differs according to age and cause of death. Cause-specific mortality studies should be planned to improve life expectancies of dialysis patients.

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APPENDIX I

List of diseases and related ICD-10 codes

Causes of death	
Heart failure	Pulmonary heart disease (I27) Pericarditis (I30–I32) Endocarditis and valvular disorder (I33–I39) Conduction blockage (I44–I45) Arrhythmia (I47–I49) Cardiac failure (I50) Lung edema (J81)
Cerebrovascular disorders	Subarachnoid hemorrhage (I60), Intracerebral hemorrhage (I61), Cerebral infarction (I63) Other cerebrovascular diseases (I62, I64–I69)
Myocardial infarction	Ischemic heart disease (I20–I25) Myocarditis (I40–I41) Cardiomyopathy (I42–I43)
Hyperkalemia/Sudden death	Hyperkalemia (E87) Cardiac arrest (sudden death) (I46)
Pulmonary thromboembolism	Lung embolism (I26)
Infection	Tuberculosis (A15–A19) Septicemia (A40–A41) Acute viral hepatitis (B15.9, B16.1, B16.9, B17) Fulminant viral hepatitis (B15.0, B16.0, B16.2, K72.0) Human immunodeficiency virus (HIV) infection (B20–B24) Other infectious diseases (A00–A09, A20-39, A42–A99, B00–B09, B25–B99, G00–G09) Influenza (J10–J11) Pneumonia (J12–J18), Peritonitis (K65)

APPENDIX I *Continued*

Causes of death	
Malignancies	Malignant neoplasms of digestive organs (C00–C26)
	Malignant neoplasms of respiratory organs (C30–C39)
	Malignant neoplasms of bone and cartilage (C40–C41)
	Malignant neoplasms of skin and soft tissue (C43–C49)
	Malignant neoplasms of breast (C50)
	Malignant neoplasms of female genital organs (C51–C58)
	Malignant neoplasm of kidney (C64)
	Malignant neoplasms of urinary tract and male genital organs (C60–C63, C65–C68)
	Malignant neoplasms of eye, brain, and central nervous system (C69–C72)
	Malignant neoplasms of internal glands (C73–C75)
	Malignant neoplasms of lymphoid and hematopoietic tissue (C81–C96, D45–D47)
	Other neoplasms and cachexia (C76–C80, C97, D00–D44, D48)
Cachexia/Uremia	Uremia (N18)
	Cachexia (R64)
	Dementia (syndrome) (F01, F03)
Chronic hepatitis/Cirrhosis	Hepatic fibrosis and cirrhosis (K74)
Ileus	Intestinal hematogenous disorder (K55)
	Ileus (K56)
Bleeding	Gastrointestinal bleeding (K92)
Suicide/Refusal of treatment	Suicide (X60–X84)
	Refusal of treatment (dialysis refusal) (Z531, Z532)
Accidental death	Disaster and accidental death (V01–X59, X85–Y36)
Miscellaneous	Dialysis encephalopathy (F02.8)
	Gallbladder and biliary tract diseases (K80–K83)
	Acute pancreatitis (K85)
	Other (B18–B19, D50–D89, E00–E874, E876–E90, F04–F99, G10–G99, H00, 95, I00–I15, I28, I51–I52, I70–I99, J00–J06, J20–J80, J82-99, K00–K52, K57–K63, K66–K71, K721–K73, K75–K77, K86–K87, K90–K91, K93, L00–L99, M00–M99, N00–N17, N188–N99, O00–O99, P00–P96, Q00–Q99, R00–R63, R65–R94, S00–S99, T00–T98)
Unknown	Undetermined (R95–R99)