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Original article

Mortality trends among Japanese dialysis patients, 1988-2013: a joinpoint regression analysis

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Running head: Mortality trends in Japanese dialysis patients

Abstract

Background: Evaluation of mortality trends in dialysis patients is important for improving their prognoses. The present study aimed to examine temporal trends in deaths (all-cause, cardiovascular, noncardiovascular, and the five leading causes) among Japanese dialysis patients.

Methods: Mortality data were extracted from the Japanese Society of Dialysis Therapy registry. Age-standardized mortality rates were calculated by direct standardization against the 2013 dialysis population. Average annual percentage of change (APC) and the corresponding 95% confidence interval (CI) were computed for trends using joinpoint regression analysis.

Results: A total of 469,324 deaths occurred, of which 25.9% were from cardiac failure, 17.5% from infectious disease, 10.2% from cerebrovascular disorders, 8.6% from malignant tumors, and 5.6% from cardiac infarction. The joinpoint trend for all-cause mortality decreased significantly, by -3.7% (95%CI: -4.2 to -3.2) per year from 1988 through 2000, then decreased more gradually, by -1.4% (95%CI: -1.7 to -1.2) per year during 2000-2013. The improved mortality rates were mainly due to decreased deaths from cardiovascular disease, with mortality rates due to noncardiovascular disease outnumbering those of cardiovascular disease in the last decade. Among the top five causes of death, cardiac failure has shown a marked decrease in mortality rate. However, the rates due to infectious disease have remained stable during the study period (APC 0.1 (95%CI: -0.2 to 0.3)).

Conclusions: Significant progress has been made, particularly with regard to the decrease in age-standardized mortality rates. The risk of cardiovascular death has decreased, while the risk of death from infection remains unchanged for 25 years.

Key words: Dialysis, Epidemiology, Joinpoint regression, Registry, Secular trends

Short summary:

Using data from the Japanese Society of Dialysis Therapy registry, the present study demonstrated that the age-standardized all-cause mortality has decreased during the past 25 years, even though critical predictors of mortality such as diabetes and longer dialysis vintage have become increasingly prevalent in the Japanese dialysis population. The decreased mortality was mainly due to a decrease in cardiovascular disease, and the mortality rate from noncardiovascular disease has been higher than that from cardiovascular disease in the last decade. Furthermore, the risk of death from cardiac failure has markedly decreased, while the risk of death from infection remains unchanged for 25 years. These findings suggest that noncardiovascular death, especially in relation to infectious disease, is now an important target that should be addressed in order to improve survival among dialysis patients.

Introduction

Dialysis patients have lower survival rates compared to those in the general population (1-4). A large European study of incident dialysis patients found that age-adjusted risk of cardiovascular and noncardiovascular mortality was increased to a similar extent as compared with the general population (1). In a previous study (3), we analyzed cardiovascular and noncardiovascular mortality rates in Japanese dialysis patients as compared to those in the general Japanese population and found that differences in age-adjusted mortality rates for cardiovascular disease were similar to those for noncardiovascular diseases. These findings indicate that preventing both cardiovascular and noncardiovascular deaths could significantly increase survival rates among dialysis patients (1, 3).

Evaluation of mortality trends in dialysis patients is necessary in order to improve their prognoses and prioritize the various aspects of their care. To the best of our knowledge, however, no report to date has evaluated cardiovascular and noncardiovascular mortality trends in dialysis patients. Many years ago, cardiovascular disease was considered the main cause of death for dialysis patients (5), but recent progress with treating cardiovascular disease has likely led to changes in these trends. Furthermore, understanding recent changes in cause-specific mortality might shed some light on which cause of death is most closely associated with changes in mortality. A careful evaluation of these issues may help to establish future strategies to lower mortality rates in dialysis patients.

In the above context, the present study aimed to examine changes in all-cause, cardiovascular, and noncardiovascular mortality rates among Japanese dialysis patients at

the national level to define recent trends during 1988-2013. Because trends will vary by the cause of death, we also determined cause-specific mortality trends.

Subjects and Methods

Data sources and study population

We extracted mortality data for dialysis patients from the annual data reported by the Japanese Society for Dialysis Therapy Renal Data Registry (JRDR) Committee, from the period 1988-2013 (6-18). Details on the JRDR data collection techniques and the characteristics of this dialysis population are described elsewhere (19). Briefly, the Japanese Society for Dialysis Therapy (JSDT) began conducting annual questionnaire surveys of dialysis facilities throughout Japan in 1968. Since 1983, the JSDT has been compiling a computer-based registry. The questionnaires are filled out by staff members from each facility and sent back to the office of the Committee of the Renal Data Registry (JSDT-CRDR) to build a database and investigate national trends in dialysis care. Questionnaire response rates from patients exceed 98% every year, and several studies have been conducted using these data (3, 20). Details regarding the inception, limitations, validity, variables, and questionnaires used in the study are available online at the JSDT website (http://www.jsdt.or.jp). We used data from 1988 to 2013, because age categories were changed after the 1988 survey report.

Our present study analyses used existing data without any individual patient identifiers. The study was conducted in accordance with the guidelines set by the Declaration of Helsinki, Japanese privacy protection laws, and Ethical Guidelines for Medical and Health Research Involving Human Subjects (published by the Ministry of Education, Science and Culture, and the Ministry of Health, Labour and Welfare in 2015). The protocol was approved by the ethics committee of Niigata University (No. 2286).

Outcome measurement

Cause of death was defined according to the JRDR coding systems and categorized according to the JRDR categories. Notably, the classification codes for the causes of death differed between the 2003 and 2010 surveys (8, 15). Details on these revisions are outlined in the 2010 survey report (15). Briefly, the classification was first changed in the 2003 survey to comply with the tenth revision of the International Classification of Diseases (ICD-10). In the 2010 survey, the classification was modified partially to reflect more appropriately the actual status of dialysis patients in Japan while retaining consistency with the conventional classification employed in the 2003 survey. Specifically, key changes included the removal of acute pancreatitis from the list of infectious diseases (categorized into other causes), and the removal of other neoplasm from the list of cachexia/uremia (categorized into malignant tumor).

Statistical analyses

We analyzed the trend for all-cause mortality first, then those for cardiovascular and noncardiovascular mortality, followed by cause-specific mortality trends. We defined cardiovascular mortality as deaths attributed to cardiac failure, cerebrovascular disorders, cardiac infarction, hyperkalemia/sudden death, and pulmonary thromboembolism, according to a previous report (3).We defined noncardiovascular mortality as death from all other causes; namely, infectious disease, malignant tumors, cachexia/uremia, chronic hepatitis/cirrhosis, ileus, bleeding, suicide/refusal of treatment, and miscellaneous (3). Accidental deaths and those with unknown causes were not included in either cardiovascular or noncardiovascular mortality.

We calculated two types of mortality rates (per 1,000 person-years); namely, crude and age-standardized. Crude mortality rates were calculated by dividing the number of deaths by the number of person-years accumulated every year. Unadjusted age-specific rates were calculated by dividing the number of deaths by the number of person-years accumulated every year for the following age groups: <15, 15-29, 30-44, 45-59, 60-74, 75-89, and 90+ (years). We estimated the number of person-years as the mid-point of the population for each year (3, 20, 21) using the following equation: the number of person-years in year X = {(the number of prevalent dialysis patients at the end of year (X-1) + (the number of prevalent dialysis patients at the end of year X)} / 2. Age-standardized mortality rates (ASRs) and their standard errors were then calculated using the direct method (22). We used the population of Japanese patients on dialysis as of December 31, 2013 as the standard population. Trends in ASRs were then analyzed using the joinpoint regression model (Joinpoint Regression Software, Version 4.0.4 - May 2013; Statistical Methodology and Applications Branch, Surveillance Research Program of the US National Cancer Institute), according to the method proposed by Kim et al. (23). This analysis fits a series of straight lines on a log scale to the ASRs, provides the annual percentage change (APC) in ASRs, and detects the point in time when significant changes in a trend occur. The zero joinpoint represents a straight line and the optimal number of joinpoints was identified using the Monte-Carlo permutation method (23). The APC in ASRs for each time period and the corresponding 95% confidence interval (CI) were estimated and then tested to determine whether the data deviated from the null hypothesis of no changes. Two-tailed $P < 0.05$ was considered statistically significant.

Results

Study population

Table 1 shows age and sex distributions of all dialysis patients in Japan from 1988 to 2013. The number of dialysis patients, especially older ones, continuously increased. The number of those aged 90 years or older between 2008 and 2012 is roughly 50 times higher than that between 1988 and 1992. The proportion of male patients has been predominant and has increased continuously.

The proportion of patients with a long dialysis vintage increased gradually (Supplementary Table 1). In 2013, 4.2% of patients had dialysis vintages longer than 25 years. During this period, hemodialysis gained in popularity over peritoneal dialysis in Japan. Primary disease of end-stage kidney disease (ESKD) changed dramatically between 1988 and 2013. Chronic glomerulonephritis, which was the leading cause of ESKD in 1988, has been decreasing continuously, while the proportion of patients with diabetic nephropathy and nephrosclerosis has increased to the point that diabetic nephropathy is now the leading cause of ESKD in Japan. The proportion of patients with polycystic kidney disease has remained constant, around 3.2-3.5% between 1988 and 2013.

Mortality trends

A total of 469,324 deaths occurred during the study period: 46.3% from cardiovascular and 44.0% from noncardiovascular disease (Supplementary Table 2). Cardiac failure, infectious disease, cerebrovascular disorders, malignant tumors, and

cardiac infarction account for 25.9%, 17.5%, 10.2%, 8.6%, and 5.6%, respectively, of all deaths.

The crude rates for all-cause mortality increased from 84.5 per 1,000 person-years in 1988 to 96.3 in 2013 (14.0% increase). However, the ASR from all-cause deaths significantly decreased during the same period (Figure 1 and Table 3). The improved mortality rate was mainly due to decreased deaths from cardiovascular disease. Between 1988 and 2013, the age-standardized mortality per 1,000 person-years decreased, from 184.0 to 97.0 for all-cause (47.3% reduction), from 106.9 to 39.9 for cardiovascular (62.7% reduction), and from 70.4 to 46.0 for non-cardiovascular diseases (34.7% reduction). The ASR from cardiovascular disease decreased continuously from 1988 by -5.6% (95%CI; -6.6 to -4.5) per year, and then by -2.5% (95%CI; -3.0 to -2.0) per year during 1999-2013. The ASR from noncardiovascular disease also continued to decrease, but at a lower rate than that observed for cardiovascular mortality. Therefore, the ASR from non-cardiovascular disease has been higher than that from cardiovascular disease in the last decade. Although the ASR from unknown causes increased by 7.4% (95%CI: 5.5 to 9.4) per year from 1988 to 2008, the ASR from cardiovascular disease decreased to a greater extent.

Among the top five causes of death, ASR from cardiac failure has decreased markedly, while the ASR from infectious disease has remained stable during the study period (APC 0.1 (95%CI: -0.2 to 0.3)) (Figure 3). ASR from cerebrovascular disorders decreased significantly since 1990. With regard to ASR from malignant tumors, there was one joinpoint at 1998: ASRs decreased by -2.9% (95%CI: -4.4 to -1.5) per year from 1988 to 1998, and then stabilized (APC 0.01 (95%CI: -0.4 to 0.4)) (Figure 4). For the

ASR from cardiac infarction, there were two joinpoints: the rates were stable from 1988 to 2001 (APC -0.7 (95%CI: -2.4 to 0.9)), and then decreased significantly by -12.1% (95%CI: -17.7 to 6.1) per year from 2001 to 2006. Afterwards, the trend was stable from 2006 to 2013 (APC -0.5 (95%CI: -3.2 to 2.4)).

Discussion

This study revealed that the ASR from all-cause mortality has decreased during the past 25 years, even though critical predictors of mortality such as diabetes and longer dialysis vintage have become increasingly prevalent in the dialysis population. The improved ASR was mainly due to cardiovascular disease, and the ASR from noncardiovascular disease has been higher than that from cardiovascular disease in the last decade. Furthermore, ASR from infectious disease, the most common cause of noncardiovascular death, was stable during the study period, although ASR from cardiac failure, the most common cause of cardiovascular death, was greatly improved. These findings suggest that noncardiovascular death, especially in relation to infectious disease, is now an important target worth considering in order to improve poor survival rates among dialysis patients.

Survival rates among those on dialysis therapy have increased in several countries. According to the 2014 Annual Data Report by the United States Renal Data System (USRDS), all-cause mortality rates among ESKD patients showed a continuous decline from 1985 to 2012, after adjusting for age, sex, race, and primary diagnosis (24). Data from the European Renal Association-European Dialysis and Transplant Association Registry (ERA-EDTA) show that adjusted patient survival with renal replacement therapy (RRT) continued to improve from 1988 through 2007, after adjusting for age, sex, country, and primary renal disease (25). While the risk of cardiovascular disease has decreased, the risk of death from malignancies has increased in the older population (25). Data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) reveal that survival rates among patients on dialysis in Australia and New Zealand have

increased during the past 15 years, after adjusting for time-varying dialysis modality and comorbid conditions, demographics, initial state/country of treatment, late referral for nephrology care, primary kidney disease, and kidney function at dialysis inception (26). Survival of Korean patients initiating dialysis from 2005 to 2008 also improved over time, after adjusting for age, sex, type of Healthcare Security System, dialysis modality, and modified Charlson Comorbidity Index (27). Taiwan is the only country where the dialysis mortality has shown a recent increase; however, this reports crude mortality. Although first-year crude mortality decreased in all age groups from 1990 to 1994, it increased sharply in 1995, when the National Health Insurance provided free access and total coverage of medical expenses for dialysis therapy, and continued to increase in the 64-75 and >75 years age groups in 2001 (28). This recent increase in crude mortality rate was suggested to be associated with the increase in elderly ESKD or diabetic patients with multiple complications, who were not covered by medical insurance prior to establishment of the National Health Insurance (28). Our data support the claim that survival rates for patients on dialysis therapy have increased in Japan despite an increase in the number of elderly or diabetic patients.

While the exact reasons for increased survival in the dialysis population cannot be determined precisely from our data, there are several possible explanations for this observation. First, increased survival rates among the general population would lead to increased survival among patients on dialysis, given the strong correlation that has been reported between national mortality rates among dialysis patients and those in the general population (29). Second, progress in dialysis treatment and evidence-based guidelines has likely influenced mortality in a profound manner, because it has certainly changed during

the study period. Among several changes, anemia management certainly contributed to lower mortality rates, which were mainly due to the decreases in deaths from cardiovascular disease; in particular, a steep downward trend in mortality from cardiac failure was noted from 1988 to 1998. The market introduction of recombinant human erythropoietin analogs in 1990 contributed to lower rates of anemia. Evidence-based guidelines may also contribute to lower mortality. For example, the first edition of the guidelines for secondary prevention of myocardial infarction in Japan was published in 2000 and updated later (30). Those may have lowered the mortality rates from cardiac infarction from 2001 to 2006. We are unsure of how to explain the decreased mortality rates from malignant tumors from 1988 to 1998. Further research is warranted to determine the causes of the observed trends and factors that may modify risk in mortality rates in the dialysis population.

Interestingly, the risk of death from infectious disease has remained constant for 25 years, even though several new classes of antibiotics were introduced in Japan during the study period. For example, levofloxacin, a broad-spectrum antibiotic of the fluoroquinolone drug class, was introduced as a tablet in 1993 and as an intravenous injection in 2010. Linezolid, the first available member of the oxazolidinones (a new antibiotic class), was introduced as a tablet and as an intravenous injection in 2001. The influence of new drugs may have relatively small effects on the mortality risk for infectious diseases. The interaction of three pivotal factors (host immunity, virulence of pathogens, and the dialysis procedure per se) might be strongly associated with infection among dialysis patients (31). This finding should be validated in other dialysis registries, because infection is one of the most prominent causes of noncardiovascular death, which

now account for more than 50% of mortality in dialysis patients, according to renal registries in Europe, the USA, and Japan (4).

This study has several strengths. A major strength is its long duration of 25 years, which allowed us to appreciate fully the changes in various parameters over time. Furthermore, data were extracted from a nationwide survey conducted at Japanese dialysis facilities. Thus, the findings should be broadly generalizable to the Japanese dialysis population. Several issues should be considered when interpreting our data. First, as we lacked individual patient data, we were not able to adjust for potential confounders such as sex, dialysis vintage, and primary cause of ESKD. As the survival advantage that women have over men in the general population is markedly diminished in hemodialysis patients (32, 33), sex seemed unlikely to exert a major impact on the results. Increased dialysis vintage could account for the higher mortality rates, and may cause a different impact on cause-specific mortality (34). However, the proportion of patients with a long dialysis vintage was small. Second, misclassifications may occur with regard to the cause of death, since classification of the cause of death in patients with CKD as either cardiovascular or noncardiovascular is not always clear-cut (4). In clinical practice, the cause of death can be multifactorial, with overlap between cardiovascular and noncardiovascular components (4). In addition, the validity of the cause of death as reported on the JSDT registry has not been studied. Some studies have reported that death certificates and registry reports provide differing causes of death for patients with end-stage renal disease (35, 36). Furthermore, the coding system to denote the cause of death changed during the study period. However, the five main causes of death examined in this study were affected little by these changes, because the definition of the five main

causes did not change greatly. Regardless, this would not affect our findings pertaining to all-cause mortality, which is immune to changes in disease classification.

In conclusion, according to mortality data from the JRDR between 1988 and 2013, age-standardized mortality rates were greatly decreased. The risk of cardiovascular death has decreased as well, while the risk of death from infection remained unchanged for 25 years.

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Transparency Declaration

None to declare.

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Table 1. Age and sex distributions of dialysis patients in Japan (1988-2013) by 5-year period (1988-2012) and in 2013 (the standard population)

Years	1988-1992	1993-1997	1998-2002	2003-2007	2008-2012	2013
Total number of patients (N)	500 224	763 583	998 318	1 220 878	1 441 962	306 925
Age group (N (%))						
< 15 yrs	745 (0.1)	1 060 (0.1)	742 (0.1)	507 (0.0)	510 (0.0)	116 (0.0)
15 – 29	15 657 (3.1)	17 488 (2.3)	15 123 (1.5)	10 138 (0.8)	6 897 (0.5)	1 121 (0.4)
30 – 44	10 431 (20.9)	97 649 (12.8)	85 940 (8.6)	82 351 (6.7)	79 554 (5.5)	15 071 (4.9)
45 – 59	190 770 (38.1)	283 477 (37.1)	330 372 (33.1)	340 044 (27.9)	302 316 (21.0)	56 950 (18.6)
60 – 74	149 629 (29.9)	278 543 (36.5)	407 326 (40.8)	524 726 (43.0)	656 641 (45.5)	140 772 (45.9)
75 – 89	36 947 (7.4)	82 437 (10.8)	152 445 (15.3)	252 348 (20.7)	377 670 (26.2)	88 147 (28.7)
≥ 90	398 (0.1)	1 540 (0.2)	4 524 (0.5)	10 473 (0.9)	18 337 (1.3)	4 736 (1.5)
Missing	1 767 (0.4)	1 419 (0.2)	1 846 (0.2)	291 (0.0)	37 (0.0)	12 (0.0)
Sex						
Men (%)	59.2	59.3	59.9	60.9	62.3	63.5
N missing	457	447	534	284	1	0

Table 2. Annual percentage change (APC) and its 95% confidence interval (CI) in age-standardized mortality rates (ASR) according to joinpoint regression analysis (1988-2013)

	1988 ASR	2013 ASR	1st period trend			2nd period trend			3rd period trend		
			period	APC (95% CI)	*P* value	period	APC (95% CI)	*P* value	period	APC (95% CI)	*P* value
All-cause	184.0	97.0	1988-2000	-3.7 (-4.2 to -3.2)	<0.01	2000-2013	-1.4 (-1.7 to -1.2)	<0.01			
Cardiovascular	106.9	39.9	1988-1999	-5.6 (-6.6 to -4.5)	<0.01	1999-2013	-2.5 (-3.0 to -2.0)	<0.01			
Noncardiovascular	70.4	46.0	1988-1998	-2.3 (-3.2 to -1.5)	<0.01	1998-2013	-1.1 (-1.4 to -0.9)	<0.01			
Unknown causes	3.0	10.5	1988-2008	7.4 (5.5 to 9.4)	<0.01	2008-2013	-0.1 (-5.5 to 5.6)	1.0			
Accidental deaths	0.5	0.5	1988-2013	-1.7 (-2.9 to -0.4)	<0.01						
Cause-specific											
Cardiac failure	72.9	26.0	1988-1998	-8.3 (-9.9 to -6.7)	<0.01	1998-2013	-1.2 (-1.7 to -0.6)	<0.01			
Infectious disease	24.0	20.2	1988-2013	0.1 (-0.2 to 0.3)	0.6						
Cerebrovascular disorders	17.4	6.9	1988-1990	8.3 (-10.9 to 31.6)	0.4	1990-2013	-4.4 (-4.7 to -4.2)	<0.01			
Malignant tumors	11.7	9.1	1988-1998	-2.9 (-4.4 to -1.5)	<0.01	1998-2013	0.01 (-0.4 to 0.4)	1.0			
Cardiac infarction	9.7	4.1	1988-2001	-0.7 (-2.4 to 0.9)	0.3	2001-2006	-12.1 (-17.7 to -6.1)	<0.01	2006-2013	-0.5 (-3.2 to 2.4)	0.7

ASRs per 1000 person-years according to the 2013 population of Japanese dialysis patients

Figure legends

Figure 1. Crude and age-standardized rates for all-cause mortality, 1988-2013.

Open and filled circles represent the crude and age-standardized rates, respectively. The reference population was the 2013 population of Japanese dialysis patients. Lines are fitted rates based on joinpoint analysis.

Figure 2. Age-standardized mortality rates for cardiovascular disease, noncardiovascular disease, and unknown causes, 1988-2013.

Data markers represent observed rates; lines are fitted rates based on joinpoint analysis.

Figure 3. Age-standardized mortality rates from cardiac failure, infectious disease, and cerebrovascular disorders, 1988-2013.

Data markers represent observed rates; lines are fitted rates based on joinpoint analysis.

Figure 4. Age-standardized mortality rates from malignant tumors and cardiac infarction, 1988-2013.

Data markers represent observed rates; lines are fitted rates based on joinpoint analysis.