Premature mortality due to nephrotic syndrome and the trend in nephrotic syndrome mortality in Japan, 1995–2014

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Abstract

Background: This study analysed the trend in mortality from nephrotic syndrome in Japan from 1995 to 2013. Moreover, to better understand premature death from nephrotic syndrome, the average years of life lost due to nephrotic syndrome were estimated.

Methods: National death certificate data were evaluated. Age-standardised mortality rates from nephrotic syndrome were calculated by direct standardisation using the World Standard Population. Trends for average annual changes in percentages were determined by joinpoint regression analysis. Average years of life lost were estimated by dividing total years of life lost by the number of deaths from nephrotic syndrome. Years of life lost were estimated by the constant endpoint method, with 65 years as the endpoint. Average years of life lost due to malignant neoplasms, the leading cause of death in Japan, were estimated for comparison.

Results: There were 9945 deaths (4872 men and 5073 women) during the study period. The numbers of deaths and crude overall mortality rates increased, while age-standardised mortality rates continuously decreased, for both sexes. The annual percentage changes were ī 1.9% (95% confidence interval [CI], ī 2.3% to ī 1.4%) for men and ī 3.5% (95% CI, ī 4.1% to ī 2.9%) for women. The average years of life lost due to nephrotic syndrome decreased during the study period, but were greater than for patients who died of malignant neoplasm.

Conclusions: Mortality and premature mortality rates from nephrotic syndrome significantly decreased in Japan between 1995 and 2014. Despite these improvements, nephrotic syndrome patients Ò65 years of age still have a poor prognosis.

Keywords: epidemiology, Joinpoint regression, nephrotic syndrome, premature death, secular trends, years of life lost

Introduction

Nephrotic syndrome (NS) is characterised by heavy proteinuria with decreased serum protein concentration and is one of the best-known presentations of kidney disease in adults and children [1]. Relatively little is known, however, about the epidemiology of mortality from NS. Despite having a generally favourable prognosis, some patients with NS die from life-threatening complications, especially infections and thromboembolism [2]. Infection is one of the most frequent complications, especially in nephrotic children [3], whereas thromboembolism is frequent in adults, but less frequent in children, with NS [2, 4]. Current anticoagulant and thrombolytic agents may reduce the risk of thromboembolism-related deaths [2]. Immunosuppressive therapy may reduce the risk of infection-related mortality, because most infections are associated with active diseases [5].

To our knowledge, there are no detailed reports on mortality trends in patients with NS. Understanding recent trends in NS mortality may help evaluate the effects of recently developed treatments. Parallel to examining trends in NS mortality rates over time, assessing changes in NS-associated premature deaths (i.e. deaths occurring prior to a selected cut-off age) may help determine whether changes in premature death are consistent with changes in overall death from NS.

This study was designed to evaluate trends in NS mortality rates throughout Japan during the years 1995ï 2014. This study also evaluated two measures of premature death from NS: years of life lost (YLL) and average years of life lost (AYLL) [6, 7]. YLL, defined as the number of years of death from a disease prior to death in the absence of that disease, is a measure of disease burden on the general population. AYLL, defined as the average total YLL among deceased individuals, is a measure of disease burden to individual patients.

Materials and Methods

Study population

Mortality data for 5-year age groups during the period 1995ï 2014 were obtained from the Vital Statistics Bureau of Japan [8]. The Japanese Ministry of Health, Labour and Welfare is charged with overseeing the annual collection of vital statistics surveys to analyse vital events and obtain a basic population data source to support policy making on health, labour, and welfare under the Statistics Act of Japan [9]. This National Vital Statistics Survey Form consists of five forms: the Live Birth Form, the Death Form, the Fetal Death Form, the Marriage Form, and the Divorce Form. We used data from the Death Form, which is based on Notification of Death. These data provide yearly numbers of deaths from all causes in Japan. The procedures adhere to international standards for mortality statistics regarding the underlying cause of death, which is defined by the World Health Organization as the disease or injury that initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury, in accordance with the rules of the International Classification of Diseases (http://www.who.int/topics/mortality/en/). We have previously reported studies conducted using these data [10, 11].

Deaths caused by NS during this period were estimated using the International Classification of Diseases and Injuries (ICD), 10th Revision (ICD-10) codes N04. This classification includes NS with minor glomerular abnormality (N04.0); NS with focal and segmental glomerular lesions (N04.1); NS with diffuse membranous glomerulonephritis (N04.2); NS with diffuse mesangial proliferative glomerulonephritis (N04.3); NS with diffuse endocapillary proliferative glomerulonephritis (N04.4); NS with diffuse mesangiocapillary glomerulonephritis (N04.5); NS with dense deposit disease (N04.6); NS with diffuse crescentic glomerulonephritis (N04.7); NS with other morphologic changes (N04.8); and NS with unspecified morphologic changes (N04.9). The planned analyses did not include secondary nephrotic syndrome such as diabetic nephropathy and lupus nephritis. Data on the sex and age distribution of the overall Japanese population were obtained from population censuses [12, 13].

Statistical analyses

The actual numbers of deaths from NS were counted for each calendar year from 1995 to 2014. Age- and gender-specific mortality rates from NS in Japan were subsequently calculated by dividing the number of deaths from NS for each ageï gender category by the total number of people in that category in the general population. Confidence intervals (CI) were calculated using Poisson distribution. Age-standardised mortality rates (ASR) per 100 000 persons for each year were calculated using the direct method according to the World Standard Population.

Trends in ASR were analysed using the joinpoint regression model (Joinpoint Regression Software, ver. 4.0.4, May 2013; Statistical Methodology and Applications Branch, Surveillance Research Program of the US National Cancer Institute), as described [14, 15]. This analysis fits a series of straight lines on a log scale to the ASR, provides the annual percentage change (APC) in ASR, and detects the point in time (calendar years) at which trends change significantly. A joinpoint of zero indicates a straight line, and the optimal number of joinpoints was identified using the Monte Carlo permutation method [14]. The APC in ASR and the corresponding 95% CI for each time period were calculated and tested to determine a difference from the null hypothesis (i.e., no changes). A two-sided *P*-value <0.05 was considered statistically significant.

In addition to examining mortality rates from NS, YLL and AYLL were estimated to determine recent changes in premature deaths from NS. YLL was estimated using the constant end point method [16, 17]. In this method, YLL was tabulated by subtracting the age at death from the endpoint age, defined in this study as 65 years, because this age is often used to estimate YLL and is deemed retirement age. AYLL was estimated by dividing total YLL by the number of deaths from NS. For comparison, YLL and AYLL were estimated for deaths from malignant neoplasm. We chose malignant neoplasm for comparison for the following two reasons: 1) malignant neoplasm has been the leading cause of death in Japan since 1981; and 2) the underlying cause of death data are reported to capture approximately 90% deaths reported in death

certificates for malignant neoplasms [18]. Deaths from malignant neoplasm were determined using the ICD-10 codes C00ï C97.

For sensitivity analysis, YLL was estimated using the life table method [16, 17], because life expectancy in Japan is among the longest in the world. YLL was estimated by multiplying the yearly number of deaths by the number of years of life remaining according to the complete life tables reported by the Ministry of Health, Labour and Welfare every 5 years, for the years 1995, 2000, 2005, and 2010 [19]. Life expectancies at birth for men and women were 76.38 and 82.85 years, respectively, in 1995; 77.72 and 84.60 years, respectively, in 2000; 78.56 and 85.52 years, respectively, in 2005; and 79.55 and 86.30 years, respectively, in 2010.

The study was conducted according to the principles of 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 Institutional Review Board (IRB) at our University did not require IRB review in this study, because our analyses were secondary analyses using existing figures without any individual patient identifiers, which is not considered to be research involving human subjects and does not require IRB review.

Results

During the study period, 4872 men and 5073 women died of NS. The number of deaths from NS gradually increased over time, whereas age-specific rates gradually decreased in both sexes (Table 1). During each year, the age-specific rates of death from NS increased with age, steeply increasing among both men and women aged Ó80 years.

During the study period, crude overall mortality rates gradually increased, but ASRs significantly decreased, in both sexes (Figure). Between 1995 and 2014, the ASR per 100 000 person-years decreased 30.8% in men, from 0.26 to 0.18, and 44.4% in women, from 0.18 to 0.10 (Table 2). From 1995 to 2014, ASRs from NS decreased continuously, by ī 1.9% (95% CI: ī 2.3% to ī 1.4%, *P*<0.01) per year for men and by ī 3.5% (95% CI: ī 4.1% to ī 2.9%, *P*<0.01) per year for women.

Table 3 shows YLLs and AYLLs for the years 1995, 2000, 2005, and 2010 for men and women. During the study period, YLL due to NS gradually decreased, with lower YLL due to NS than due to malignant neoplasms in both sexes. Using the constant end point method and 65 years as the endpoint, however, AYLL due to NS was higher than AYLL due to malignant neoplasms in both sexes. The life table method of sensitivity analysis showed that AYLL due to NS was lower than AYLL due to malignant neoplasms in both sexes (Supplementary Table 1).

Discussion

Using data from death certificates, we determined that age-standardised mortality rates from NS have continuously decreased in both sexes in Japan between 1995 and 2014. Although YLL due to NS, a measure of the burden of NS to the population as a whole, was lower than YLL due to malignant neoplasms, AYLL due to NS, a measure of the burden of NS to individual patients, was higher than AYLL due to malignant neoplasms, as determined using the constant method and with age 65 years as the endpoint. These findings suggest that mortality rates from NS improved over the two decades of the study. Nevertheless, individual patients with NS aged Ò65 years have a poor prognosis.

We found that the number of deaths from NS and crude overall mortality rates from NS gradually increased during the study period (1995ï 2014). These increases appear to be consequences of an aging population. The age-specific mortality rates from NS increase with age, and Japan has one of the most rapidly ageing populations in the world, with the proportion of the general Japanese population aged Ó65 years increasing from 14.6% in 1995 to 25.1% in 2014.

Additionally, we found that age-standardised mortality rates from NS have continuously decreased in both sexes in Japan between 1995 and 2014. A retrospective analysis from the United States found that the estimated mortality from NS in people aged 0ï 17 years was lower than in previous reports and remained stable from 2000 to 2006 [20]. Therefore, the improvement in NS mortality rates may not be limited to Japan, but may also be the trend in other countries.

While the exact reasons for the improvement in NS mortality rates cannot be determined precisely from our data, there are several possible explanations for this observation. First, newly developed anticoagulant and thrombolytic agents [2], as well as progress in immunosuppressive therapy, may reduce the risks of life-threatening complications in patients with NS, thereby reducing mortality rates. Second, reduced mortality rates in the general population may result in reduced mortality rates among patients with NS, because life expectancies in the general population may influence the lifespan of people with diseases. For example, a cross-sectional, multinational study showed that national mortality rates among dialysis patients

strongly correlated with national mortality rates in the general population [21]. Indeed, the trend in mortality rates among Japanese dialysis patients has improved over the last 25 years [15].

Use of the constant end point method revealed that AYLL from NS was greater than AYLL from malignant neoplasms in both men and women. However, the life table method showed that AYLL from NS was greater than AYLL from malignant neoplasms in both sexes. These findings suggest that patients with NS who were Ò65 years old have a shorter average lifespan compared with similarly aged patients with malignant neoplasms, while patients with NS who were >65 years old have a longer average lifespan compared with similarly aged patients with malignant neoplasms. Therefore, NS is still associated with a worse prognosis for individual patients aged Ò65 years, even compared with patients with malignant neoplasm, which is the leading cause of death in Japan.

This study had several limitations. First, renal biopsy findings and clinical information confirming a diagnosis of NS were not available. Thus, the death certificate data used in this study may have been inaccurate, despite our use of ICD-10 codes to determine that NS was the underlying cause of death. Furthermore, classification of patients with NS with other than the ICD-10 code N04 would have resulted in an underestimate of the true mortality rate from NS. Second, although our study reported mortality rates, it did not report case fatality rates, defined as the rate of death among patients presenting with a particular condition. We were therefore unable to determine whether reductions in mortality rates were a result of a decrease in the incidence of NS and/or a decrease in the fatality rate from NS.

To our knowledge, this is the first study to report the mortality trends from NS at a national level. Understanding recent trends in NS mortality rates is fundamental to assessing the effectiveness of disease control programs. Furthermore, this is the first study to report YLL and AYLL, measures of premature death from NS. YLL and AYLL depend on the age at death and the number of deaths at each age, and may resolve some of the mismatch of the disease impact derived from using the number of deaths alone [22]. Compared with the mortality risk that weighs all deaths equally, YLL and AYLL are more informative indicators for quantifying premature deaths [23]. Determining the trends in premature death from NS may help determine

whether these trends are consistent with trends in mortality rates. These considerations may help in the development of future strategies to prevent premature deaths in patients with NS.

Conclusions

Mortality rates from NS continuously decreased in both sexes in Japan between 1995 and 2014. Although YLL for NS, a measure of the burden of NS on the population as a whole, was lower than YLL for malignant neoplasms, AYLL for NS, a measure of the burden of NS on individual patients, was higher than AYLL for malignant neoplasms, as determined using the constant method and with age 65 years as the endpoint. Although suggesting that mortality in NS patients has improved over the past two decades, these findings show that NS patients aged Ò65 years have a poor prognosis.

Compliance with Ethical Standards

Disclosure of potential conflicts of interest

All the authors have declared no competing interest.

Research involving Human Participants and/or Animals

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Obtaining consent to participate are not required because the current analyses used existing national data without any individual patient data.

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Legends to figures

Figure Crude and age-standardised mortality rates for nephrotic syndrome by sex from 1995 to 2014 in Japan

Open (men) and filled (women) squares and circles represent the crude and age-standardised rates, respectively. The reference population was the World Standard Population. Lines are fitted rates based on joinpoint analysis.