Epidemiology of end-stage renal disease: International comparisons of renal replacement therapy

Francesco Paolo Schena
Division of Nephrology, Dialysis and Transplant, Department of Emergency and Organ Transplantation, University of Bari, Policlinico, Bari, Italy
Correspondence: Prof F. P. Schena, Division of Nephrology, Dialysis and Transplantation, Policlinico, Piazza Giulio Cesare 11, 70124 Bari, Italy

ABSTRACT

Epidemiology of renal replacement therapy: International comparisons of renal replacement therapy. Renal replacement therapy (RRT) remains the most important tool for all patients with end-stage renal disease (ESRD) in the world. Patients are usually listed in the national renal registries which report demographic data, incidence, prevalence and outcome. Differences in acceptance of the RRT, patient demographics, socioeconomic burdens and national health care legislation influence the validity of international comparisons of ESRD therapy. For this reason, the renal registries decided to organize an international collaborative study group, the International Federation of Renal Registries (IFRR), for improving the standardization of renal databases and for promoting international collaborative studies. Demographic data from renal registries in 1996 showed that approximately 1,000,000 of ESRD patients received RRT throughout the world and approximately 200,000 new patients started RRT. The different distribution of patients in the world is strongly influenced by the level of gross domestic product (GDP), since economical crisis may influence the number of patients starting RRT. The reported incidence and prevalence values of ESRD patients in RRT from the renal registries show these differences. The mortality rate of these patients is notably influenced by the percentage of enrolled diabetic RRT patients. Therefore, important differences in outcome of RRT depend on the underlying disease which is a determinant factor of prognosis. Other factors responsible for the outcome are represented by dialysis dose, type of membrane, erythropoietin and nutritional status.

Keywords: renal registries, incidence, prevalence, outcome measures

Renal replacement therapy (RRT) by hemodialysis, peritoneal dialysis, and renal transplantation became available in the 1960s; thereafter, a growing number of patients undergoing treatment of end-stage renal disease (ESRD) were listed in the renal registries. Dialysis continues to be the most frequent type of RRT because of the low rate of renal transplantation, strictly related to insufficient organ donation to meet demand. Renal transplantation is the best form of treatment for a limited number of ESRD patients.

Although the use of data from renal registries permits important observations on the health of the patients with ESRD, the extent and accuracy of the data collected vary widely. For this reason, Kjellstrand stated that international comparisons of data on ESRD patients and renal replacement therapy may not be valid because of the differences in acceptance of the treatment, patient demographics, socioeconomic burdens, and national health care legislation. Considering this important scientific bias, the renal registries decided to organize an international collaborative study group called the International Federation of Renal Registries (IFRR) to discuss different databases. The first meeting of the IFRR was held in 1997 during the 14th International Congress of Nephrology in Sydney, Australia, and the first report was published in the same year. Delegates from the Asian-Pacific Registry, Australian and New Zealand Dialysis and Transplant Registry (ANZDATA), Canadian Organ Replacement Registry (CORR), European Renal Association Registry (ERA-EDTA), Japanese Society for Dialysis Therapy (JSDT), Latin American Registry, and the United States Renal Data System Registry (USRDS) participate in the IFRR. The duties of the federation include the development of a dialogue between renal registries for the improvement and standardization of renal databases; the definition of a common terminology, the definition of a common methodology for analyzing data and finally the promotion of international collaborative studies.
DEMOGRAPHIC DATA

Table 1 shows the number of patients on RRT world-wide in 1996 and the number of new patients who started RRT for the first time. Data have been obtained from renal registries with >90% response rate (RR) from dialysis facilities, registries with <90% response rate, and from published papers (1999 pers. comm. from G. Lee, Asian-Pacific Registry; A. Disney, ANZDATA; S. Fenton, CORR; F. Berthoux, ERA-EDTA; K. Maeda, Japanese Society for Dialysis Therapy; N. Mazzuchi, Latin American Registry; and L. Agodoa, USRDS). For some countries the number of RRT patients has been estimated. In 1996, approximately 1,000,000 patients received RRT (dialysis or renal transplant) in the world and 200,000 new patients started RRT. There are several limitations to this estimate because in the international renal registries and in the countries with low gross domestic product (GDP), some factors such as demography of the population, socioeconomic structures, organization of health care systems, patient access to RRT, and the response rate of dialysis facilities to the questionnaire influence the estimation of RRT population. These limits were documented by Mazzuchi et al in the Latin American Registry4. The most important factor, for the renal registries, which influences the collection of annual data, is the response rate to the questionnaire.

Table 1 - RRT patients world-wide as of December 31, 1996.

The database of renal registries world-wide should validate the accuracy at the time of data collection, but four important, strictly-correlated factors may influence the quality of the data. First, the submission of the data may be mandatory and linked to the reimbursement of treatments performed in dialysis facilities. The USRDS registry works in this manner because Medicare only reimburses the cost of dialysis treatment after it receives patient data, which are then supplied to the USRDS. This system covers more than 93% of all patients treated for ESRD in the United States. Second, other registries work on the basis of voluntary submission of data. In such cases, only a few renal registries, such as the ANZDATA registry, CORR, and the Japanese Society for Dialysis Therapy receive data from more than 90% of all dialysis facilities. Other voluntary national and international registries have a response rate to the questionnaire of the dialysis centers lower than 90%. For these reasons some registries are an under-representation of patients receiving RRT. Third, in addition to the quantity and quality of the therapy, access to the different forms of RRT is partly dependent on the health care system of the country. This explains why in some areas of the world in which the GDP is low, a low percentage of subjects with ESRD receives RRT. On the other hand, in some countries with a high GDP, renal transplantation is less frequent because organ donation is low due to religious or social problems. Such variables cannot be easily adjusted for in most statistical analyses.

Finally, reports from the renal registries include ESRD patients receiving RRT—either dialysis or renal transplantation—by the first day of treatment. However, this is not consistent from registry to registry; for instance, the registry of the Japanese Society for Dialysis Therapy includes only dialyzed patients, while the USRDS registry considers all ESRD patients treated with RRT by the 91st day because the Medicare system does not achieve complete reporting of patients data before day 90. Thus, patients who die before this time (early mortality within 90 days) are not accounted for by the USRDS. In addition, in all renal registries world-wide, patients who die of ESRD before receiving RRT are not included, and data from the registries consequently do not express the true epidemiology of ESRD in those countries.

INCIDENCE

Incidence represents the number of persons diagnosed with ESRD in a specific population in a given time period, usually a year. It is a useful measure for medical and epidemiological research that examines the causes of the disease and the differences in how subpopulations are affected by these causes. The annual incidence rate of treated ESRD patients is expressed by the number of patients beginning RRT related to the annual general population at the beginning of the year. It is expressed as a number of patients per million of population (pmp) per year. There is a bias of the incidence among the renal registries because not all patients with ESRD are included, as was mentioned in the discussion of demography above. In addition, the incidence of ESRD does not take into account those patients not treated; therefore it does not measure the overall occurrence of ESRD.

The incidence of ESRD patients on RRT continues to increase world-wide. By considering the incidence rates of the four national renal registries with more than 90% of response rate to the questionnaire during these last four years (1994–1997), the number of new patients pmp listed in USRDS and Japanese Registries is higher than in ANZDATA and CORR. The mean annual percentage of increase is 7.6% of incidence rate in USRDS and 3.2–3.7% in the other three
registries Figure 1. The rates of newly treated ESRD patients vary from registry to registry and may reflect differences in acceptance and referral patterns among countries. The likelihood of acceptance into RRT program is influenced by many factors such as age, gender, distance of home from dialysis facility, employment and transplantation program. The acceptance rates for incident patients continues to increase in industrialized countries but not in those with low GDP. In fact, in 1998 a reduction in incidence of new RRT patients was reported in some Asian countries (Singapore and Taiwan) as a result of the economic crisis in these areas of the world Figure 2. A growing proportion of the RRT population is over the age of 74 years5. About half of the new patients are over the normal retirement age, and over the last decade there has been at least a four-fold increase in the number of patients entering dialysis over the age of 74 years5. A growing proportion of the RRT population is over the age of 85 years. The pros and cons of RRT in patients over 80 years of age are continuously discussed6. However, elderly patients must be informed about the treatments offered. Specific recommendations will help them to decide whether to accept treatment, and the final decision must be the patient’s alone, with no pressure to make choices on the grounds of financial limitations.

PREVALENCE

Prevalence represents the number of persons in a specific population who have ESRD at a given point. Both incidence rates of the disease and the survival rates influence it. The prevalence includes patients who are new and those who are continuing RRT for ESRD. The prevalence rate per million population is the prevalence count divided by the population size in million on either a particular date (point prevalence) or during an interval of time (period prevalence). Point prevalence indicates the number of alive treated patients on a particular date, usually December 31 of the year. It is the most common definition of prevalence used by the renal registries. Point prevalence is a useful measure for public health research, since it measures the overall burden of the disease on the health care delivery system. Period prevalence differs from the above term because it counts the number of patients receiving RRT anytime during a particular interval of time, such as a calendar year. It is the sum of the point prevalence on the first day of the year plus the incidence during the year. It is used less often than point prevalence. Period prevalence is a useful measure for cost analysis, since it indicates the total burden of the disease over the course of the year. Its rate is related to the annual general population count preferably in the middle of the year and is expressed as number of patients per million population (pmp). For simplicity both incidence and prevalence are referred as rates. These two terms are adjusted to age, gender and other conditions. The Japanese registry records the highest mean prevalence rates (7.4%) during the last four years (1994–1998) followed by the USRDS, CORR and ANZDATA Figure 4. This may be due to a better survival among ESRD patients and low transplant activity in Japan7.
In other registries where incidence rates of ESRD patients in RRT are similar, in addition to patient demographics and transplant activity, a similar prevalence of ESRD is observed [Figures 5, 6 and 7].

**Figure 5.**
Asian Pacific Registry prevalence data. (A) Overall prevalence. (B) Prevalence rates from selected countries (response rate > 90%).

**Figure 6.**
Latin American Registry prevalence data. (A) Overall prevalence. (B) Prevalence rates from selected countries (response rate > 90%).

**Figure 7.**
ERA-EDTA Registry prevalence data. (A) Overall prevalence. (B) Prevalence rates from 15 countries of the European Union (response rate = 89%).

**OUTCOME MEASURES**

Outcome research is a rapidly evolving field that incorporates epidemiology, health service research, health economics and psychometrics. The outcome measures have evolved from simple dichotomous ones such as survival or occurrence of a clinical event to patient-oriented measures such as satisfaction, quality of life and functional status. The outcome measures, listed by Epstein and Sherwood, are grouped into three important areas: clinical, characterized by clinical events, physiologic and metabolic measures and mortality; economic, including direct and indirect medical measures; and humanistic, in which symptoms, quality of life, functional status and patient satisfaction are included.

The choice of outcome measures depends on the priorities of those examining the data. Clinicians are more interested in clinical and humanistic outcomes whereas patients may be preferentially interested in humanistic measures. Health plan administrators are more interested in economic ones. Current renal registry management programs include a mixture of all measures.

The mortality rate is an important outcome measure to characterize the impact of RRT on the ESRD patient population in the national and international renal registries. The crude annual mortality rate is expressed by the number of deaths divided by the product of the number of ESRD patients and the time on treatment during the year (patient-years). It is expressed by the number of deaths per 100 patient-years at risk. Death rates can be adjusted for age categories, time spent on RRT and mortality of general population (standardized mortality ratio).

Difference in mortality rate could be due to differences in enrollment criteria or type of treatment. It can be adjusted among prevalent patients and differences in mortality could reflect innovations in treatment that affect all patients being treated in that year. Because large differences exist between countries on the acceptance of ESRD patients it is difficult to interpret observed differences in mortality rates. For dialysis patients factors influencing the mortality rate are represented by the type of disease causing ESRD, utilization of treatment modalities, different health care system and delivery. The USRDS registry excludes from some analyses dialysis-unrelated deaths caused by AIDS, accidents unrelated to treatment, and street drug overdoses. These exclusions make the death rate more useful as a norm for evaluating the care given to ESRD patients. The adjusted annual death rates for all dialysis patients and for all ESRD patients, prevalent at any time during each year, decreased progressively from 1989 to 1996 in USRDS registry but remains higher than that of other renal registries.

The crude mortality rate in ANZDATA in these last three years remained approximately 14% in dialysis patients and 7% in all ESRD patients (A. Disney. ANZDATA, personal communication, 1999) and ranged about 9% of dialysis patients in the Japanese Registry. Marcelli et al stated in a recent paper that for international studies, it is necessary to develop a common standard data collection instrument in all ESRD registries including the recording of comorbid conditions and their severity. Other factors responsible for the death rate among ESRD patients are represented by the dose of dialysis, shift from cellulose to synthetic membranes, administration of erythropoietsin dose, dialysis facility differences, mode of dialysis therapy, hypertension, cardiovascular diseases, Ca-P metabolism, and malnutrition.
Important differences in outcome of RRT patients depend on the underlying disease, which is a determinant factor of prognosis. It is well known that diabetes reduces the survival of ESRD patients; the prognosis is particularly severe for elderly patients. Some large differences exist among countries in the utilization of dialysis modalities and in acceptance of patients, particularly for diabetics and elderly subjects. Therefore, it is difficult to interpret observed differences in mortality rates among registries. A valid comparison of data in national registries should be attempted for the primary diagnosis. The USRDS registry in the last report showed an increased number of incident ESRD patients with diabetes receiving RRT in comparison with other countries. For this reason, diabetes was the most common cause of ESRD in the United States in 1996, whereas glomerulonephritis was the primary cause of ESRD in other registries’ patients. Nevertheless, an increased incident number of diabetic patients has been evidenced in the last four years in all national and international registries. The relatively high risk of death of these patients is further increased by their poor nutritional status and by factors related to their predialysis care. In fact, a prospective study on enrolled hemodialysis patients evidenced that at the start of dialysis diabetic patients had more left ventricular hypertrophy, ischemic heart disease and cardiac failure than non-diabetics. These findings suggest that these events in the predialytic life should be notably reduced.

FUTURE COLLABORATIVE STUDIES

A few years ago the USRDS started a prospective observational study that produced very important preliminary results. A substantial fraction of patients had had impaired nutrition for a prolonged period before starting dialysis; many reported nausea or vomiting for 3 or more months. These data strongly suggest a need for appropriate medical care of the patients before ESRD treatment, including early referral to nephrologist for patients with ESRD. Patients receiving peritoneal dialysis were younger than those treated by hemodialysis, and comorbid conditions were more prevalent among hemodialysis patients. In addition, the residual renal function among peritoneal dialysis patients was higher than hemodialysis patients. Poor compliance to RRT was registered by 10% of dialysis patients who skipped at least one session, 15% who shortened at least one session, 12% of CAPD patients who missed one exchange per week and 6% of APD patients who skipped or shortened treatment. Medication use was represented by a phosphate binder containing calcium. Vitamin D was administered more frequently among HD treated than PD treated patients. Finally, considering the quality of life, the patient-reported general health was slightly better for peritoneal than hemodialysis patients. Patient-reported general health tended to decrease with age. Non-diabetics had better health than diabetic hemodialysis patients. The majority of patients were retired or disabled. One-half of patients were driven by someone and one quarter drove themselves. After this study, in collaboration with Amgen, the University Renal Research and Education Association (URREA) located in Ann Arbor, Michigan, USA organized three important international dialysis outcomes and practice patterns studies (DOPPS) in three continents of the world. The US-DOPPS involves 160 dialysis facilities as a national representative sample of US. The I-DOPPS randomly selected 100 dialysis facilities in five European countries (France, Germany, Italy, Spain and the United Kingdom); 20 in each country. The Japan-DOPPS recruited 60 dialysis facilities in Japan as a national representative sample. These three observational and prospective studies follow a common design, protocol and analysis of the data for comparing practice patterns and their effects on patient outcomes. These studies should lead to improve the general health of hemodialysis patients throughout the world. The randomized choice of dialysis facilities and the accurate instruction of the nursing staff and physicians participating in the study will eliminate bias normally present in the collection of data from retrospective studies. Therefore, the adequate data collection methodology and the accuracy of information will give important insights on RRT in the world. Future collaborations among registries with more than 90% of response rate of the questionnaire from the dialysis facilities are well accepted for prospective clinical studies.

Table 2 - The most common diseases responsible for ESRD in the renal registries (1996).
REFERENCES


22. United States Renal Data System: 1999 Annual Data Report. XII: International Comparisons of ESRD therapy 1999 Bethesda, MD, USRDS,


24. United States Renal Data System: 1996 Annual Data Report. The USRDS dialysis,

ACKNOWLEDGMENTS

I am indebted to the members of the International Federation of Renal Registries for their help: L. Agodoa (United States Renal Data System); A. Disney (Australian and New Zealand Dialysis and Transplant Registry); S. Fenton (Canadian Organ Replacement Registry); K. Maeda (Japan Society of Dialysis Therapy); G. Lee (Asian Pacific Registry); F. Berthoux (ERA-EDTA Registry); N. Mazzuchi (Latin-American Renal Registry).