National and Sub-national Prevalence, Trend, and Burden of End Stage Renal Diseases (ESRD) in Iran 1990–2013; The Study Protocol

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Abstract

Background: End Stage Renal Diseases (ESRD) imposes a huge economic burden on the health system; however, there is a serious lack of data related to ESRD, especially at Sub-national level, in Iran. Calculating the burden of ESRD at National and Sub-national level provides an opportunity to apply cost-effective interventions for the purpose of prevention and treatment. The current study protocol aims to explain the general structure and methods that will be used in the burden of ESRD study in Iran from 1990 to 2013.

Methods: The prevalence, incidence, mortality and geographical and socioeconomic inequality trend of ESRD will be calculated through a comprehensive systematic review of published and unpublished data. Years of Life Lost due to premature mortality, and Years Lived with Disability and Disability-Adjusted Life Years (DALYs) will be quantified for ESRD by gender, age group, and province with their uncertainly intervals. "Spatio-Temporal" and "Bayesian multilevel autoregressive" will be applied to deal with data scarcity and misalignment problem which exist in the data sources.

Discussion: The findings of the burden of ESRD study will be useful to organize preventive, treatment also research priorities at national and sub-national levels in Iran. Better understanding of the magnitude of ESRD burden is essential to prevent the progression of chronic kidney diseases to the end stage phase which is considered as a devastating illness.

Keywords: Burden, chronic kidney disease, end stage renal disease, Iran, study profile

Introduction

End stage renal disease (ESRD) is a devastating illness associated with high cost of treatment, enormous disability, and low quality of life. Kidney damage is a structural or functional abnormality which gradually leads to chronic kidney disease (CKD).[1] One possible outcome of CKD is ESRD which is accompanied by signs and symptoms of renal failure and may consequently necessitate replacement therapy, including dialysis or renal transplantation. Since the annual mortality rate of patients under dialysis is high, dialysis and kidney transplantation are not optimal therapies.[2]

Moreover, the trend of morbidity from ESRD in developing countries is not consistent with that of developed countries. In industrialized countries, ESRD increases with age,[3,4] but in Nigeria as a developing country, the maximum prevalence is observed in the third or fifth decade of life; thus, it imposes a high economic burden.[5] In Iran, there are more than 24,000 ESRD patients and its trend has dramatically risen over the recent years.[6]

Furthermore, to prevent and control ESRD in Iran more efficiently, it is required to make decisions based on the conditions in each province. National and Sub-national Burden of Diseases study (NASBOD) provides a unique opportunity to assess mortality as well as years lived with disability (YLD) due to ESRD.[7] The burden of ESRD study will estimate the trend and burden of ESRD at national and sub-national levels in Iran from 1990 to 2013. The current study aims to describe the methodological framework of calculating the burden of ESRD in Iran.

Materials and Methods

The study of burden of chronic kidney diseases will be limited to stage five of CKD, namely End Stage Renal Disease (ESRD). ESRD is categorized into three subgroups with respect to the treatment approaches; hemodialysis, peritoneal dialysis and kidney transplantation. The prevalence, incidence, and measures including Years of Life Lost, Years Lived with Disability, and Disability Adjusted Life Years (DALYs) will be estimated. DALY will be reported by gender, age, and province from 1990 to 2013; furthermore, the uncertainty levels related to these estimations will be provided.

The executive part of the burden of ESRD study is constituted of a core team and a technical team. The core team will be responsible for providing standard definitions for measures, preparing

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the search protocol for systematic review, training all researchers, data gathering and hunting, data cleaning, applying statistical models, interpreting results, and preparing the reports. The technical team, which includes experts and knowledgeable persons in the field of nephrology and epidemiology who work on these specific diseases, will be responsible for preparing practical definitions of diseases and helping the core team to interpret the results. In order to provide all teams with the sufficient knowledge and to make them coordinated, some workshops were held based on their educational needs.

Since ESRD represents only the tip of an iceberg of CKD patients with different degrees of disease and as the majority of them are unknown, there is extremely limited access to data about CKD patients. Besides, the Transplantation Management Center of Ministry of Health has information only about ESRD patients who receive specific treatments. Therefore, the expert panel including nephrologists and epidemiologists selected ESRD based on the importance of disease, its incidence, its economic burden, and mainly the level of data availability. Although our main measure will be ESRD DALY, it will be possible to use other sources which have estimated the probability of CKD patients progressing to ESRD as a proxy to estimate the burden of all stages of CKD in Iran.

Data sources

Systematic review

In order to calculate the incidence and prevalence of ESRD at national and sub-national levels in Iran, the researchers will conduct a systematic review through a comprehensive approach. All related Medical subject heading terms (MeSH), Entry terms (PubMed thesaurus) and Emtree (the EMBASE thesaurus) will be searched in international databases (PubMed, ISI the Web of Science, and Scopus) and Iranian databases (IranMedex, Irandoc, and SID). Other data sources including congress abstracts, conference proceedings, theses, and reports published in related databases in Persian language will be assessed. We will also review the reference lists of the included articles to find other relevant articles. It is worth mentioning that the Persian terms for searching in Iranian search engines will be equivalent to their English counterparts and all probable combinations will be considered. The detail of search strategy is available in Table 1.

No language restriction will be applied in the systematic review. From January 1990 to December 2013, all national and sub-national studies which reported data on ESRD will be included in the review. Studies with non-random sampling or studies which had been conducted in the specific groups will be excluded.

Reviewers will conduct title scans. If accepted, the article will be promoted to the next level. Abstracts will be reviewed independently by two researchers, and will be excluded if the article meets one or more of the exclusion criteria. Disagreements between researchers regarding abstract inclusion or exclusion will be resolved through consensus. The articles promoted after the abstract and title review will be assessed by a reviewer based on the full text to determine whether they should be included. If some information is needed to be clarified in the selected articles, the researchers will send emails to the corresponding authors.

Quality assessment

A quality assessment checklist will be designed and all the articles selected in the final step will be assessed by two independent reviewers. The sampling quality will be assessed in terms of response rate, sample size, and sampling method and the measurement quality will be measured in terms of type of measurement tools, calibration, and accuracy of measurement methods. Consequently, each article will obtain a specific score. Quality scores will be classified into three categories (excellent = 13–19, good = 6–12, and poor ≤5) and the fix effect of these scores will enter to the model.

Data extraction form will be designed by the technical team in order to extract all relevant data based on sex, age, year of study, scope (urban or rural) and scale of study (national, provincial, district, or community), prevalence, incidence, standard deviation, confidence interval (CI), and/or standard error (SE) of the ESRD.

National data sources

The Transplantation Management Center of Ministry of Health, which registers all patients with ESRD who undergo kidney transplantation, hemodialysis, and peritoneal dialysis, will be considered as another data source. All population-based studies and data of vital registration system will be used. In order to provide epidemiologic indicators of ESRD, we will use the data obtained from inpatient survey[8] which collected the causes of admission by sex, age and region from all existing hospitals in Iran from 1996 to 2011.

Table 1. Search strategy for ESRD.

Search strategy in PubMed/Medline	"chronic kidney disease," OR "chronic renal failure," OR "Disease, End-Stage Kidney" OR "Chronic Kidney Failure" OR "ESRD" OR "Renal failure, End-stage" OR "end-stage renal disease," OR "End-Stage Kidney Disease" OR "kidney transplantation" AND ("Iran"[Mesh] OR "Iran"[All Fields]) OR Iranian[All Fields] OR I.R.Iran[All Fields] OR "I.R Iran"[All Fields] OR ("Persia"[MeSH Terms] OR "Persia"[All Fields])) AND (("1985/01/01"[PDAT]: "2013/12/31"[PDAT]) AND "humans"[MeSH Terms])
Search strategy in ISI Web of science	Time span=1990-2013. Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH. Topic= ("chronic kidney disease," OR "chronic renal failure," "Disease, End-Stage Kidney" OR "Chronic Kidney Failure" OR "ESRD" OR "Renal failure, End-stage" OR "end-stage renal disease," OR "End-Stage Kidney Disease" OR "kidney transplantation") AND (("Iran" OR Iranian OR I.R.Iran OR "persia") OR Address= (Iran))
Search strategy in Scopus	(TITLE-ABS-KEY ("chronic kidney disease," OR "chronic renal failure," "Disease, End-Stage Kidney" OR "Chronic Kidney Failure" OR "ESRD" OR "Renal failure, End-stage" OR "end-stage renal disease," OR "End-Stage Kidney Disease" OR "kidney transplantation") AND (TITLE-ABS-KEY (Iran OR Iranian OR I.R.Iran OR Persia) OR (affil (Iran) AND pub year <2013

Because of the importance of mortality data in estimation of burden of diseases, the NASBOD team benefit from all available data sources, including death registry system of MOHME, to improve their estimations. Different methods will be applied to deal with incompleteness of death registry or inaccuracy of cause-specific mortality.[9]

Statistical and analytical methods

YLL will be calculated using age and ESRD specific mortality after correction for incompleteness and misclassification.[9–11] YLD will be calculated using estimates of incidence and duration of non-fatal ESRD for Iran, and disability weights for ESRD will be applied from the GBD study. Despite all efforts to capture available data sources entirely and to make a comprehensive search, one of the most predictable difficulties in data gathering process will be missing data. Particularly, in order to estimate DALYs at sub-national level, data are not available for sexes, every age group, and all provinces. Moreover, for some provinces which have been separated from each other in the given time period of the study, the problem of misalignment arises. In order to estimate uncertainty interval by sex, age, year, and province, the NASBOD team will benefit from two statistical models including multilevel autoregressive model and Spatio-temporal model. In order to confirm the model independency of estimations, two mentioned models will be applied.

Spatio-temporal model

Spatio-temporal Bayesian hierarchical modeling with conditional autoregressive prior for spatial random effects[12] will be applied to deal with the mentioned data scarcity. In the model, there is one main assumption that nearby areas are more connected to each other than distant zones. Based on this assumption, estimations of levels with insufficient data will be improved through borrowing information from neighboring areas which have a more complete data set. Additionally, spatio-temporal misalignment modeling will be applied to combine discordant areas between various data sources or through years.

Bayesian Autoregressive Multilevel model

The model has a hierarchical framework in which observations are nested in district, province, sub-region, region, and national levels, respectively.[10] The hierarchical nature allows higher levels to borrow information from lower levels based on the amount of data accessibility. In addition, units in one level may borrow data from each other. Some important components will be considered in the model, including nonlinearity associated with age and variation over time, heterogeneity among data sources, linear time trend, and covariate effects. In fact, in both Bayesian framework models Markov Chain Monte Carlo simulation will be used to perform a statistical inference.

Moreover, another challenge is the difference in the classification of measures; regression models allow a cross walk between categorical and continuous variables.

Ethical considerations

The ethical committee of Tehran University of Medical Sciences declared ethical approval; moreover, all articles which are included in the review will be cited in all published results of our study. The permission for the publication of results depends on funder's approval.

Discussion

Despite the fact that ESRD is a distressing complication with high burden on patients as well as their families, there is a serious lack of data in Iran. It is noticeable that ESRD can increase the risk of cardiovascular mortality as well as many disabilities and medical expenditures.[13] The dearth of evidence makes it difficult to identify the national and sub-national priorities. The burden of ESRD study, as a sub-component of NASBOD, will provide effective evidence for policy makers and will present the pattern of geographical inequality among different provinces in Iran.

The Global Burden of Diseases Studies were conducted at regional and national levels from 1990 to 2010 and the used methodologies, datasets and models improved through these series of studies.[14,15] GBD 2010 estimated 291 diseases, 67 risk factors, 1167 sequels in 187 countries and 21 regions by sex and age groups.[14,16,17] The 2010 GBD study estimated 6158 DALYs for acute glomerulonephritis for all ages as well as 81657 DALYs for CKD in Iran. They estimated these numbers at national level as well as did not consider ESRD separately.

There are some countries around the world which have assessed the burden of CKD and ESRD. For instance, Canada calculated the economic burden of ESRD[18] and measured direct (direct health care costs) and indirect costs including lost productivity which is due to premature mortality and morbidity caused by ESRD. One of the studies assessed the burden of ESRD in Australia and New Zealand[19] and compared the prevalence of ESRD and its related mortality between the citizens of each country. They used data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry and reported that mortality and prevalence of ESRD in indigenous people were higher than non-indigenous ones.

The first burden of diseases study[20] in Iran was conducted at national level and in six selected provinces in 2003. Nafar, et al.,[21] calculated DALYs due to CKD in 2004 using national data registries, data from transplantation management database of Ministry of Health, and results of published papers. The study used disability weight (DW) of ESRD and acute glomerulonephritis from GBD study 2000. These studies were not conducted at Subnational level and did not calculate the uncertainly intervals for their estimations.

In fact, one decade after the first burden study, it is extremely useful to run NASBOD by applying sophisticated methodological approaches and collecting as much data as available. Besides, it can provide sub-national estimations and detect the trend of socioeconomic status and geographical inequality that can be considered as other benefits of the burden of ESRD study. In comparison with the mentioned national studies, the burden of ESRD study will provide more accurate data points with confidence intervals and will use the DW of GBD 2010 which can be used appropriately later on by nephrologists and policy makers. Additionally, to keep pace with the current GBD estimations around the world, it seems inevitable to conduct the ESRD burden study.

The burden of ESRD study will have some limitations. First, although many efforts will be carried out to achieve all the available data, there is a significant data scarcity, especially at sub-national levels. Second, heterogeneity among different data sources, different sampling methods, as well as the diversity in provincial registries leads to higher levels of uncertainly. Another limitation is the misalignment problem which we will try to solve by apply-

ing statistical models. The NASBOD team will try to deal with these limitations.

The results of the burden of ESRD study would be helpful to fill the information gap which exists in the Iranian health system regarding the trend of CKD prevalence, incidence, and mortality. Additionally, the trend analysis and geographical and socioeconomic inequality patterns provide conclusive evidences to apply policies properly and set-up necessary services at sub-national level. Moreover, the nature of progressive CKD to ESRD and large number of young patients justify the need for the data from the burden of ESRD study with regard to designing effective preventive approaches and consequently decreasing the burden of ESRD substantially.

Authors' Contribution

General designing of paper: Tahereh Hassannia, Atefeh Noori, Farshad Farzadfar, Shohreh Naderimagham

Designing of models: Farshad Farzadfar, Tahereh Hassannia, Atefeh Noori

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All authors have read and approved the content and the authorship of the final version of the submitted manuscript.

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