UNIVERSIDAD DE OVIEDO

PROGRAMA DE DOCTORADO EN INVESTIGACIÓN EN MEDICINA

Evaluación económica del tratamiento sustitutivo renal en España

Guillermo Villa Valdés

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RESUMEN DEL CONTENIDO DE TESIS DOCTORAL

1.- Título de la Tesis	
Español/Otro Idioma: **Evaluación económica del tratamiento sustitutivo renal en España**	Inglés: **Economic evaluation of renal replacement therapy in Spain**

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RESUMEN (en español)

La insuficiencia renal crónica (IRC) se define como la disminución del filtrado glomerular inferior a 60 ml/min/1,73 m^2 o como la presencia de daño renal persistente durante al menos 3 meses. En su etapa terminal (IRCT), el paciente con IRC requiere tratamiento sustitutivo renal (TSR). Las principales modalidades de TSR son la hemodiálisis (HD), la diálisis peritoneal (DP) y el trasplante renal (Tx). En 2010, la incidencia y prevalencia en España de pacientes en TSR fue de 119 y 1.033 casos por millón de población, respectivamente. Se estima que el coste del TSR en España representa entre el 1,6% y el 2,5% del gasto sanitario público. La evaluación de tecnologías sanitarias es un campo multidisciplinar que analiza las implicaciones médicas, sociales, éticas y económicas de la adopción de una nueva tecnología. En esta tesis doctoral, se presenta una evaluación económica del TSR en España. Se han analizado los costes del TSR para el Sistema Nacional de Salud (SNS) y se ha aproximado la carga de la IRCT para la sociedad. Se ha evaluado la eficiencia de intervenciones de aumento en la proporción de pacientes incidentes programados en diálisis y también de intervenciones de disminución en la proporción de pacientes que vuelven tardíamente a diálisis tras el fallo del injerto renal. En 2010, un 0,1% de la población española se encontraba en TSR. La mitad de esos pacientes eran portadores de un trasplante funcionante y un 45% de los pacientes estaba en HD, mientras que la DP tenía una prevalencia mucho menor. El trasplante es la modalidad de TSR menos costosa a partir del segundo año. Respecto a las modalidades de diálisis, la DP presenta menores costes directos e indirectos que la HD. Los pacientes incidentes programados en HD muestran un coste del acceso vascular inferior a los de los pacientes no programados y también unos costes indirectos menores. El TSR supone un coste anual agregado elevado para el SNS, de unos 1.400€ millones anuales (un 2,2% del gasto sanitario público en 2010). La carga de la IRCT para la sociedad española ronda los 1.800€ millones anuales. Casi la mitad de los pacientes españoles incidentes en diálisis son pacientes no programados. Un incremento en la proporción de pacientes programados proporcionaría un menor coste por paciente y mejores resultados en salud (intervención dominante) que la actual situación en España. Por su parte, un aumento en la proporción de pacientes incidentes programados en DP no sólo resultaría una intervención dominante, sino que sería un factor clave para lograr una reducción en la carga de la IRCT para la sociedad española. Tanto desde el punto de vista clínico, como desde un punto de vista de económico, las autoridades sanitarias deberían promover el inicio programado en diálisis y particularmente el inicio programado en DP. La práctica totalidad de los pacientes españoles que sufren fallo del injerto vuelven a diálisis de manera tardía. Además de una mayor morbilidad y mortalidad, estos pacientes presentan una mayor necesidad de fármacos y una mayor frecuencia de hospitalizaciones que los pacientes que vuelven a diálisis oportunamente. Si comparamos la situación actual en España con un escenario ideal en el que todos los pacientes con fallo del injerto vuelven de manera oportuna a diálisis, se incrementarían ligeramente los costes directos médicos debido a la mayor supervivencia alcanzada, pero se obtendrían mejores resultados en salud. Esta intervención resultaría eficiente si se consideran los umbrales frecuentemente aceptados. Si además se tuvieran en cuenta los costes indirectos, el inicio oportuno en diálisis tras el fallo del injerto resultaría una intervención dominante. Las autoridades sanitarias deberían promover, por tanto, la vuelta oportuna a diálisis tras el fallo del injerto, mediante la inclusión de recomendaciones específicas para este grupo de pacientes dentro de las guías existentes y proporcionando, además, una adecuada información al paciente.

RESUMEN (en inglés)

Chronic renal insufficiency (CRI) is defined as a decrease in the glomerular filtration rate below 60 ml/min/1.73 m^2 or the presence of persistent kidney damage for at least 3 months. In the terminal stage (TCRI), CRI patients require renal replacement therapy (RRT). The main RRT modalities are hemodialysis (HD), peritoneal dialysis (PD) and kidney transplantation (Tx). In

2010, the Spanish RRT incidence and prevalence figures were 119 and 1,033 cases per million population, respectively. The cost of RRT in Spain has been estimated at 1.6% to 2.5% of the public healthcare expenditure. Health technology assessment is a multi-disciplinary field that examines the medical, economic, social and ethical implications of the adoption of a new technology. In this doctoral dissertation, an economic assessment of RRT in Spain is presented. The costs of RRT have been analyzed both from the perspective of the National Health System (NHS) and the society. The efficiency of an increase in the proportion of programmed incident patients in dialysis has been evaluated. Finally, the efficiency of a decrease in the proportion of patients who are referred back to dialysis in a late manner after graft function loss has been assessed. In 2010, a 0.1% percent of the Spanish population was in RRT. Half of these patients had a functioning transplant and 45% of them were in HD, while PD presented a much lower prevalence. Kidney transplantation is the less costly RRT modality starting with the second year. Regarding dialysis modalities, PD shows lower direct and indirect costs than HD. Programmed incident patients in HD present also lower vascular access costs and indirect costs than non-programmed patients. The RRT program represents a high cost for the NHS, estimated at about 1,400€ million per year (a 2.2% of the public healthcare expenditure in 2010). The burden of TCRI for the Spanish society is estimated at about €1,800 million per year. Almost half of the Spanish incident patients in dialysis are non-programmed patients. An increase in the proportion of programmed patients would bring about lower per-patient costs and improved health outcomes (dominant intervention) compared to the current situation in Spain. Moreover, an increase in the proportion of incident programmed patients in PD would not only be a dominant intervention, but also a key factor in reducing the burden of TCRI for the Spanish society. Both from a clinical and from an economic perspective, Spanish health authorities should promote a programmed dialysis start and particularly a programmed start in PD. Almost all the Spanish patients undergoing graft function loss are referred back to dialysis in a late manner. These patients face increased morbidity and mortality risks, and show higher drug needs and hospitalization rates than timely referred patients. When compared to the current Spanish situation, timely dialysis referral would imply a moderate increase in direct medical costs due to increased survival rates. Improved health outcomes would be however

achieved. This intervention would be efficient if the usual thresholds were considered. If we further took into account indirect costs, timely dialysis referral after graft function loss would be a dominant intervention. Spanish health authorities should therefore promote the inclusion of specific recommendations for this group of patients within the existing clinical guidelines, also providing adequate information to the patient.

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Los directores de la tesis doctoral "Evaluación Económica del tratamiento sustitutivo renal en España" consideran idónea la presentación de esta tesis bajo la modalidad de compendio de publicaciones, tal y como se propuso originalmente en el Proyecto de Tesis Doctoral. Los trabajos que componen esta tesis han sido publicados en revistas de reconocido prestigio en el ámbito de la Nefrología (Nephrol Dial Trasplant y Perit Dial Int) y de los servicios sanitarios (BMC Health Serv Res).

Oviedo, a 15 de octubre de 2012.

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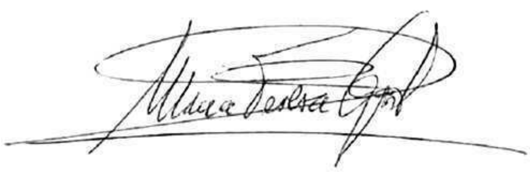

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2.- Tesis Doctoral
Título: **Evaluación económica del tratamiento sustitutivo renal en España**
Autor: **Guillermo Villa Valdés**
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2.- Publicaciones que formarán parte de la tesis y de las que es coautor

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CONTENIDOS

I. Introducción

La insuficiencia renal crónica (IRC) se define como la disminución del filtrado glomerular (FG) inferior a 60 ml/min/1,73 m^2 o como la presencia de daño renal persistente durante al menos 3 meses [1]. En su etapa terminal (IRCT), el paciente con insuficiencia renal requiere tratamiento sustitutivo renal (TSR). De acuerdo con los últimos datos publicados, en 2010, la incidencia y prevalencia de pacientes en TSR en España fue de 119 y 1.033 casos por millón de población (pmp), respectivamente [2]. España muestra una incidencia similar, pero una prevalencia ligeramente superior a la de otros países de su entorno [3,4].

Las principales modalidades de TSR son la hemodiálisis (HD), la diálisis peritoneal (DP) y el trasplante renal (Tx). El trasplante es el tratamiento de elección para el paciente con IRCT [5]. Sin embargo, el número de trasplantes que se pueden realizar viene limitado por la disponibilidad de órganos. España es el país con la tasa de donantes de órganos de cadáver más alta del mundo [4,6]. En 2010, se realizaron 2.225 trasplantes renales en nuestro país [2]. Se estima que, en ese mismo año, existían aproximadamente 50.000 pacientes prevalentes en TSR en España. De ellos, un 49% eran portadores de un trasplante renal funcionante, un 46% estaba en HD y sólo un 5% estaba en DP. Además, cada año, aproximadamente 6.000 nuevos pacientes inician TSR. Un 84% de estos pacientes inicia tratamiento en HD, por tan sólo un 13% de pacientes incidentes en DP y un 3% de pacientes trasplantados [2].

La detección precoz de la IRC es particularmente importante. Desde un punto de vista clínico, un diagnóstico temprano retrasa la progresión de la enfermedad y favorece el control de los factores de riesgo, como los eventos cardiovasculares [7]. Varias sociedades médicas, como la *United Kingdom Renal Association* [8], la *National Kidney Foundation* norteamericana [9], la Sociedad Española de Nefrología (SEN) [10] y la Sociedad Española de Medicina Familiar y Comunitaria (semFYC) [11] han elaborado recomendaciones sobre el diagnóstico y los objetivos terapéuticos que debe cumplir el paciente renal [1]. Estas sociedades han establecido protocolos de derivación del paciente al nefrólogo para su evaluación y seguimiento.

El seguimiento del paciente en servicios de nefrología posibilita la toma de decisiones informadas sobre la elección de la modalidad de diálisis. Las preferencias del paciente son un factor clave en la elección de la modalidad [12]. La falta de libertad del paciente a la hora de elegir su tratamiento se ha asociado con una reducción en su calidad de vida relacionada con la salud (CVRS), en particular en lo referente a la dimensión psicológica [13]. La información disponible para el paciente se ha asociado, además, con la elección de la DP sobre la HD [14-18]. Varios estudios han concluido que el coste de la HD es superior al de la DP [19-23], a pesar de que la CVRS del paciente en DP es al menos tan buena como la del paciente en HD [24,25] y de que su supervivencia parece mayor [2,26,27]. Un aumento en la proporción de pacientes que inician TSR en DP podría propiciar, por tanto, un menor coste económico para el Sistema Nacional de Salud (SNS) [28] y una menor carga para la sociedad.

Recientemente, se han publicado varios estudios del coste de la diálisis en España [29-32]. Estos trabajos se han centrado fundamentalmente en el análisis retrospectivo de datos a nivel de paciente [30-32] o en la revisión de publicaciones oficiales y datos contables [29] procedentes de un único centro o de un número de centros limitado. El resto de los estudios de costes publicados en nuestro país tiene una antigüedad superior a los diez años [33]. Aunque no se conoce el coste real del TSR en España, se estima que éste representa entre el 1,6% y el 2,5% del gasto sanitario público [33]. Sin embargo, ninguno de los análisis de costes publicados hasta la fecha ha estimado los costes indirectos (pérdida de productividad laboral por mortalidad y morbilidad) [34] que supone la IRCT para la sociedad española.

El inicio tardío o no programado en diálisis tiene importantes implicaciones clínicas, tales como desnutrición, anemia, mayores tasas de morbilidad y mortalidad [35-41], y, como consecuencia, mayores costes [39,42-46]. De acuerdo con la literatura existente, sólo entre el 51% y el 54% de los pacientes españoles que inician diálisis son pacientes programados. Además, el inicio programado es menor entre los pacientes que inician HD (entre el 43% y el 53%) que entre los pacientes que inician DP (entre el 81% y el 90%) [17,39,47]. Un aumento en la proporción de pacientes que inician diálisis de manera programada podría propiciar, por tanto, mejores resultados en salud para el paciente renal, un menor coste económico para el SNS y una menor carga para la sociedad. Esta cuestión aún no ha sido estudiada en nuestro país, ni tampoco en otros países de nuestro entorno.

El trasplante renal es el tratamiento de elección para el paciente con IRCT [5]. En comparación con los pacientes que permanecen en diálisis y en lista de espera, los pacientes trasplantados muestran una mayor supervivencia [48], una mejor CVRS [49] y un menor consumo de recursos [50-54]. En los últimos años, la mejora en los tratamientos inmunosupresores ha permitido un aumento de la supervivencia de los injertos renales. La supervivencia a un año es superior al 90%, la supervivencia a 5 años es cercana 70% y la supervivencia a 10 años es inferior al 50% [55]. En los primeros meses, las causas más frecuentes de pérdida del injerto son el rechazo agudo, los problemas técnicos y el riñón no funcionante [56]. Las pérdidas tardías más frecuentes son debidas a la nefropatía crónica del trasplante y a la muerte con injerto funcionante [57]. Se estima que, tras el primer año, entre un 2% y un 4% de los pacientes trasplantados pierden su injerto. Cada año, por tanto, entre 500 y 1.000 pacientes españoles perderían su injerto y deberían volver a diálisis [2,58,59].

A pesar de la existencia de guías nacionales e internacionales de práctica clínica, no existe consenso sobre el momento más oportuno de vuelta a diálisis tras el fallo del injerto renal. Tanto la negativa del paciente a volver a diálisis, como la reticencia del clínico a asumir el fracaso del trasplante podrían justificar el hecho de que la mayoría de los pacientes españoles con fallo del injerto renal vuelvan tardíamente a diálisis. De acuerdo con las guías de práctica clínica, un paciente debería iniciar diálisis en dos situaciones [60-62]: (1) FG inferior a 15 ml/min/1,73 m^2 y presencia de síntomas (etapa 5 de la clasificación K/DOQI [63]) y (2) FG inferior a 6 ml/min/1,73 m^2, aún en ausencia de síntomas. Sin embargo, algunos estudios recientes recomiendan un inicio en diálisis más restrictivo, para FG entre 5 y 9 ml/min/1,73 m^2 [64]. Éste sería el caso de los pacientes con pérdida del injerto renal [65,66].

Además de una mayor morbilidad y mortalidad [65,67-72], los pacientes con pérdida del injerto renal presentan una mayor necesidad de fármacos, como eritropoyetina [73] y hierro intravenoso [74], y una mayor frecuencia de hospitalizaciones debidas a complicaciones [64]. Una reducción en la proporción de pacientes que vuelven tardíamente a diálisis tras el fallo del injerto podría propiciar, por tanto, mejores resultados en salud para el paciente renal y una mayor eficiencia en el uso de los recursos para el SNS y la sociedad. Este argumento aún no ha sido estudiado en nuestro país, ni tampoco en otros países de nuestro entorno.

La evaluación de tecnologías sanitarias (ETS) es un campo multidisciplinar que analiza las implicaciones médicas, sociales, éticas y económicas del desarrollo, uso y difusión de una nueva tecnología sanitaria [75]. La ETS es la comparación de al menos dos intervenciones en términos de sus costes y de sus resultados en salud [76]. En un entorno en el que los recursos son escasos y las necesidades sanitarias son ilimitadas, la ETS pretende servir de puente entre el desarrollo clínico y la toma de decisiones en el ámbito sanitario [77].

Existen dos paradigmas fundamentales de la evaluación económica [78,79]. El primero de ellos se relaciona con la economía del bienestar [80] y propugna que la decisión sobre asignación de recursos sanitarios debe evaluarse en los mismos términos que cualquier otra decisión social sobre asignación de recursos. Una determinada intervención se llevará a cabo si es capaz de producir una mejora neta del bienestar social [81], es decir, si las mejoras que proporciona compensan las posibles pérdidas de bienestar (criterio Kaldor-Hicks de potencial mejora de Pareto [82,83]). Bajo este paradigma, los resultados en salud deben expresarse en términos monetarios, lo que plantea serias dificultades de medición en la práctica y cierta controversia desde el punto de vista ético [84]. Este tipo de evaluación se conoce como análisis coste-beneficio y actualmente es poco frecuente en el ámbito de la salud [85-86]. El segundo paradigma se relaciona con la economía de la empresa y propugna una asignación de recursos basada en la optimización de una función objetivo que evalúa los resultados en salud proporcionados por una determinada intervención y que estará sujeta a una restricción presupuestaria [78]. El análisis coste efectividad (ACE) es el tipo de evaluación económica predominante bajo este segundo paradigma.

Existen múltiples maneras de medir resultados en salud [79]. Sin embargo, dada la necesidad de asignar recursos entre distintas patologías, el ACE se ha centrado principalmente en la utilización de una medida estándar de resultado: los años de vida ajustados por calidad (AVAC) [76]. Este tipo de evaluación económica se denomina frecuentemente análisis coste-utilidad [87]. Los AVAC son medidas de resultado que incorporan dos aspectos de la salud: la cantidad de vida y la CVRS del paciente [88,89].

Los AVAC se calculan multiplicando el número de años de vida ganados en una intervención por un índice denominado utilidad [76]. La utilidad recoge las preferencias sociales por los estados de salud a los que se enfrentará el paciente durante la evolución de su patología. Por convenio, las utilidades suelen medirse en una escala entre 0 (muerte o peor estado de salud imaginable) y 1 (salud perfecta o mejor estado de salud imaginable) [76,90]. Aunque existen distintos métodos para medir utilidades, en la ETS, se recomienda el uso de métodos indirectos basados en instrumentos genéricos (no asociados a una patología específica) de medición de CVRS [91,92]. Los cuestionarios SF-6D [93,94] y EQ-5D [95,96] son los más frecuentemente utilizados. Para estos dos instrumentos, se han desarrollado algoritmos que permiten transformar el estado de salud manifestado por un paciente individual (sus puntuaciones en el cuestionario) en utilidades sociales [97,98]. Para ello, una muestra suficientemente amplia y representativa de la población general debe valorar un subconjunto de todos los estados de salud posibles. Este subconjunto es definido habitualmente a partir de un diseño ortogonal y es valorado posteriormente utilizando diferentes técnicas de elección, como las loterías [99] o el método de la equivalencia temporal [87,88].

En el ACE, se calculan los costes y los resultados en salud de la nueva intervención y de una o más intervenciones ya existentes. Mediante la comparación de los costes y los resultados incrementales de la nueva intervención respecto a los tratamientos estándar (relación coste-efectividad incremental) [100] y teniendo en cuenta la disponibilidad a pagar del decisor por unidad de resultado incremental [91,101-103], se pueden tomar decisiones informadas sobre la adopción de nuevas intervenciones de una manera sistemática [78].

En esta tesis doctoral, se presenta una evaluación económica del TSR en España. En la primera publicación, se analizan los costes asociados al TSR para el SNS y se aproxima la carga de la IRCT para la sociedad. En la segunda publicación, se evalúa la eficiencia de intervenciones de aumento en la proporción de pacientes incidentes programados en diálisis. En la tercera y última publicación, se evalúa la eficiencia de intervenciones de disminución en la proporción de pacientes que vuelven tardíamente a diálisis tras el fallo del injerto renal. En la próxima sección, se describen en mayor detalle los principales objetivos de esta investigación.

II. Objetivos

Se han definido los siguientes objetivos de esta investigación:

Publicación 1. Análisis de costes del programa español de tratamiento sustitutivo renal

- Objetivo primario:
  - Analizar los costes directos para el SNS del programa español de TSR.
- Objetivos secundarios:
  - Analizar los costes indirectos de la IRCT para la sociedad española.
  - Aproximar la carga de la IRCT para la sociedad española.

Publicación 2. Análisis coste-efectividad del programa español de tratamiento sustitutivo renal

- Objetivo primario:
  - Evaluar la eficiencia (relación coste-utilidad incremental (RCUI)) de intervenciones de aumento en la proporción de pacientes incidentes programados en diálisis, desde una perspectiva social.
- Objetivo secundario:
  - Evaluar la eficiencia de intervenciones de aumento en la proporción de pacientes incidentes en DP, desde una perspectiva social.

Publicación 3. Análisis coste-efectividad de la vuelta oportuna a diálisis tras el fallo del trasplante renal en España

- Objetivo primario:
  - Evaluar la eficiencia (RCUI) de intervenciones de disminución en la proporción de pacientes que vuelven tardíamente a diálisis tras el fallo del injerto renal, desde la perspectiva del SNS.
- Objetivo secundario:

- Explorar la eficiencia de intervenciones de disminución en la proporción de pacientes que vuelven tardíamente a diálisis tras el fallo del injerto renal, desde una perspectiva social.

III. Publicación 1. Análisis de costes del programa español de tratamiento sustitutivo renal

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Cost analysis of the Spanish renal replacement therapy programme

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Abstract

Background. A cost analysis of the Spanish Renal Replacement Therapy (RRT) programme in the year 2010, for end-stage renal disease (ESRD) patients, was performed from the perspective of the Public Administration.
Methods. The costs associated with each RRT modality [hemodialysis (HD), peritoneal dialysis (PD) and kidney transplantation (Tx)] were analysed. The Spanish ESRD incidence and prevalence figures in the year 2010 were forecasted in order to enable the calculation of an aggregate cost for each modality. Costs were mainly computed based on a review of the existing literature and of the Official Bulletins of the Spanish Autonomous Communities. Data from Oblikue Consulting eSalud health care costs database and from several Spanish public sources were also employed.
Results. In the year 2010, the forecasted incidence figures for HD, PD and Tx were 5409, 822 and 2317 patients, respectively. The forecasted prevalence figures were 22 582, 2420 and 24 761 patients, respectively. The average annual per-patient costs (incidence and prevalence) were €2651 and €37 968 (HD), €1808 and €25 826 (PD) and €38 313 and €6283 (Tx). Indirect costs amounted to €8929 (HD), €7429 (PD) and €5483 (Tx). The economic impact of the Spanish RRT programme on the Public Administration budget was estimated at ~€1829 million (indirect costs included): €1327 (HD), €109 (PD) and €393 (Tx) million.
Conclusions. HD accounted for >70% of the aggregate costs of the Spanish RRT programme in 2010. From a costs minimization perspective, it would be preferable if the number of incident and prevalent patients in PD were increased.

Keywords: cost analysis; end-stage renal disease; haemodialysis; kidney transplantation; peritoneal dialysis

Introduction

End-stage renal disease (ESRD) includes Stages 4 and 5 of the classification of the chronic kidney disease (CKD) proposed by the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines [1]. According to the ERA-EDTA registry, Spain shows a higher ESRD prevalence than other European countries. In regard to ESRD incidence, i.e. the patients who start in any renal replacement therapy (RRT) modality for the first time, Spanish figures are similar to those from other nearby countries [2]. Specifically, in 2009, an incidence of 129 and a prevalence of 1039 patients per million population were registered by the Spanish Society of Nephrology (SEN, Spanish acronym) [3].

Due to the serious health care and economic implications of CKD, early detection is particularly important. This would require greater collaboration between the primary care doctors and the nephrologists [4–6]. In 2008, the SEN and the Spanish Society of Family and Community Medicine (semFYC, Spanish acronym) published a consensus document on CKD, in which they recommended patients in ESRD to be referred to nephrology for evaluation and follow-up [7].

From a clinical perspective, a timely diagnosis favours the slowing of the progression of the disease, while at the same time increasing the ability to control risk factors, such as cardiovascular events [8]. Different studies have shown that a delayed referral of the patient to nephrology leads to worse results in terms of morbidity and mortality [9–12], as well as in economic terms [13–17]. Likewise, follow-up of patients in ESRD-specific units enables them to be informed on the different RRT modalities [haemodialysis (HD), peritoneal dialysis (PD) and kidney transplantation (Tx)] and gives them the opportunity to make a choice and to provide informed consent for the selected modality. Different studies have shown that the number of patients who prefer home-based dialysis increases when they have such information available to make a choice [18–21].

Various studies have also proven that the costs associated to Tx are lower than the costs associated with the rest of the

RRT modalities, starting with the second year, since the greatest proportion of the treatment costs are incurred during the first year (admittance, surgery, greater immunosuppressant doses, etc.) [22, 23]. On the other hand, several studies have concluded that HD therapy is more expensive than PD therapy in developed countries [24–27]. In Spain, different cost analyses have reached the same conclusion [28, 29].

Within the Spanish National Health System (SNS, Spanish acronym), RRT is free of charge for the patient, but the high impact of the RRT programme costs on the national budget needs to be considered. This study seeks to estimate the costs of providing RRT health care for the ESRD patients in Spain, from the perspective of the Public Administration. It is possible to estimate the global cost of treating all RRT patients in a nephrology unit and, based on that estimate, to calculate the average cost for a single patient [30]. This study, conversely, chooses to analyse the costs of the individual items, which are then added up to provide annual per-patient average figures as well as aggregate costs for each RRT modality. This approach constitutes a more realistic approximation of the cost, according to a rigorous methodology [31].

Materials and methods

A cost analysis of the Spanish RRT programme in the year 2010 was carried out from the perspective of the Public Administration. Direct (medical and nonmedical) and indirect costs were considered. Additionally, the incidence and prevalence figures of the different RRT modalities in the year 2010 were forecasted employing the nonparametric regression methodology proposed by Villa *et al.* [32] and using the publicly available data from the SEN [33] and the Spanish National Transplant Organization (ONT, Spanish acronym) [34] registries. Firstly, the original data from those registries were collected and weighted in order to account for the whole Spanish population. Secondly, linear trends were fitted by means of nonparametric quantile regressions (QR) with bootstrapped SE. QR is suitable in the case of tailed-distributed dependent variables and in the possible presence of outliers, since it predicts the conditional median of the response, instead of its conditional mean [ordinary least squares (OLS) approach]. The forecasted incidence and prevalence figures allowed the calculation of an aggregate cost for each RRT modality.

Costs, described below in detail, were estimated based on a systematic review of the existing literature and of the Official Bulletins of the Spanish Autonomous Communities. Data from Oblikue Consulting eSalud health care costs database [35] and from the Spanish National Statistics Institute (INE, Spanish acronym) [36] were also collected. Regarding the update of past costs to January 2010, either the general consumer price index (CPI) or the specific CPI for the medical sector was applied, both of them provided by the INE.

Direct medical costs

Vascular (HD) and peritoneal (PD) accesses

In order to estimate the cost of the vascular access, the average number of arteriovenous fistulas (AVF) performed was considered. The average number of intravenous catheters and the number of days of hospitalization were also taken into account [37]. Regarding the peritoneal access costs, a total cost including laboratory, personnel, surgical materials, health care materials, anesthesia, drugs and other costs was computed [38].

Training

Regarding PD, a distinction was made between training in a hotel, inpatient or outpatient mode [39]. A weighted average was computed from the percentage of patients who start in continuous ambulatory peritoneal dialysis (CAPD) (64%) or in ambulatory peritoneal dialysis (APD) (36%) [40]. Training costs included the costs of personnel, health care materials and drug consumption.

HD treatment session

Regarding hospital haemodialysis (HHD), the focus was placed on the patients who were considered a group at risk for the hepatitis C virus (HCV). Since these patients need to be isolated from the rest of patients, the way that nursing personnel takes care of them is different from that required for the rest of the unit. A weighted average was calculated based on the consideration that the prevalence of antibodies against the HCV in patients within the HD programme was 12% [39]. The cost of the HD treatment session included the costs of applying a bicarbonate-based solution. A weighted average cost was calculated based on the distribution observed [45% of the patients in HHD and 55% in incenter haemodialysis (ICHD)] [41].

PD treatment session

The cost of the treatment session was estimated assuming that half of the patients used a non-buffered glucose solution and that the remaining patients used a buffered one. Again, a weighted average was estimated from the proportion of patients in APD and CAPD.

Drug consumption

The immunosuppressant medication was considered for Tx and the recombinant human erythropoietin (rHuEPO) and the intravenous iron consumption was taken into account for HD and PD [42]. There is evidence that the residual renal function is better maintained in patients treated under PD compared to HD [43, 44]. In turn, a greater dose of rHuEPO is required for HD patients [45].

Vascular (HD) and peritoneal (PD) accesses complications

Regarding HD, the cost of a thrombosis was considered taking into account the various treatment options (surgical thrombectomy, mechanical or endovascular thrombolysis and pharmacomechancial thrombolysis) [46]. After thrombectomy or thrombolysis, a fistulography must be performed to detect any possible stenosis as the cause of the thrombosis. For the estimation of the average number of thrombosis that a single patient will suffer within a year, the type of vascular access was taken into account, since the frequency of complications differs depending on whether the access is an AVF, a catheter or a polytetrafluoroethylene (PTFE) prosthesis. Specifically, it was assumed that patients with AVF (81%) suffer ¼ thromboses per year, as compared to ½ thromboses suffered by catheterized patients (10%) and ½ suffered by patients with PTFE prostheses (9%) [47]. The costs stemming from the vascular access complications depend on whether a patient starts in HD as scheduled or unscheduled. This cost was already included within the vascular access costs, so the present cost refers to posterior complications. Regarding PD, one of the most frequent complications is peritonitis. It can be assumed, as a general rule, that ½ episodes will occur every year [48]. The costs derived from the PD access complications and the treatment of peritonitis included laboratory, personnel, health care material and drug consumption [38].

Nephrology general expenses, equipment depreciation, maintenance and external services

These costs were calculated using data from the SEN Costs Working Group [49]. In the case of HHD, they included general direction, administrative management, personnel costs, expenses related to the hospital structure and overhead, general maintenance expenses, purchasing and storage. For ICHD, they included administrative management, medical monitoring, use of specialized care, patient follow-up and checkups. In the case of PD, they included general direction, administrative management, personnel management and expenses related to the hospital structure.

Utilities

Utilities included telephone, water and electricity [50].

Kidney transplantation

The cost of the surgery was taken into account as well as the amount incurred by readmittance, revisions and medication for the first year. Additionally, the costs corresponding to the subsequent years were also considered [35].

Nonmedical direct costs

Transport

This information was gathered from Hospital Perpetuo Socorro, a public hospital in Alicante, Spain, where 41% of the patients were living within the metropolitan area and the remaining 59% used interurban public transport to get to the hospital. It was assumed that the average distance was 69 km. It was also considered that 62% of the patients went to the hospital by taxi, 24% by ambulance and 14% by their own vehicle [28].

Indirect costs

From a human capital perspective, the costs associated to the patient lost labor productivity due to ESRD morbidity and mortality were estimated [51]. These costs were determined based on the Spanish average salaries and unemployment rates, as well as on the retirement and mortality rates observed for each RRT modality. Those were the items for which reliable information was available, since other items, such as the patient lost domestic productivity or the caregiver lost leisure time, were very difficult to quantify objectively. The following sources of information were employed: the Spanish Salary Structure Survey (EES, Spanish acronym) from the INE and the Active Population Survey (EPA, Spanish acronym) from the INE and the Spanish National Institute of Social Security (INSS, Spanish acronym) [52]. In order to perform the calculations, it was considered that 28% of the patients in PD continued working, as compared to 13% of the patients in HD and 46% of the patients in kidney transplantation, according to the data from the Kidney Patients Information Unit of the Spanish Autonomous Community of the Basque Country.

Results

For the year 2010, an estimate was made of an incidence of 5409 (HD), 822 (PD) and 2317 (Tx) patients. The forecasted prevalence figures were 22 582, 2420 and 24 761 patients, respectively. Figures 1 and 2 show the registered data and the forecasted trends for the prevalence and incidence figures in the different RRT modalities in the period of 1996/2010.

Table 1 presents detailed information on the annual per-patient costs of the different RRT modalities, as well as average annual costs for HD, PD and Tx. Regarding HD, weighted average (ICHD and HHD) costs of €2651 (incidence) and €37 968 (prevalence) were obtained. The indirect costs amounted to €8929. In regard to PD, weighted average costs (CAPD and APD) amounted to €1808 (incidence) and €25 826 (prevalence), while the indirect costs added up to €7429. The estimated cost during the first year of kidney transplantation was €38 313, while it was only €6283 in the subsequent years. Kidney transplantation indirect costs amounted to €5483.

Table 2 presents the forecasted incidence and prevalence figures for the different RRT modalities. Based on this estimates as well as on the average annual costs for each modality, aggregate costs of €1077 (HD), €85 (PD) and €244 (Tx) million were estimated, if indirect costs were not included. These amounts increased up to €1327, €109 and €393 million, respectively, if indirect costs were included.

The total budgetary impact of the Spanish RRT programme for the Public Administration amounted to ~€1407 million (indirect costs not included) and €1829 million (indirect costs included). HD accounted for between 77% (indirect costs not included) and 73% (indirect cost included) of the aggregate costs of the Spanish RRT programme in 2010. The balance of costs was for Tx (between 17 and 21%) and PD (6%) patients.

Discussion

A cost analysis of the Spanish RRT programme, for the year 2010 and from the perspective of the Public

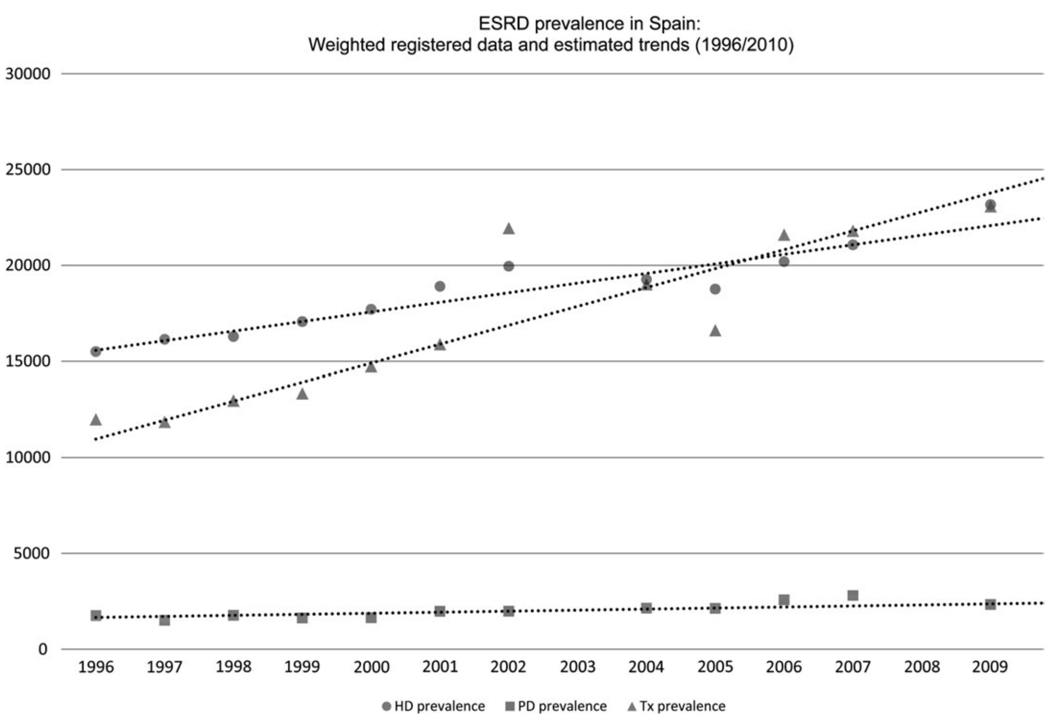

Fig. 1. ESRD prevalence in Spain: weighted registered data and estimated trends (1996/2010).

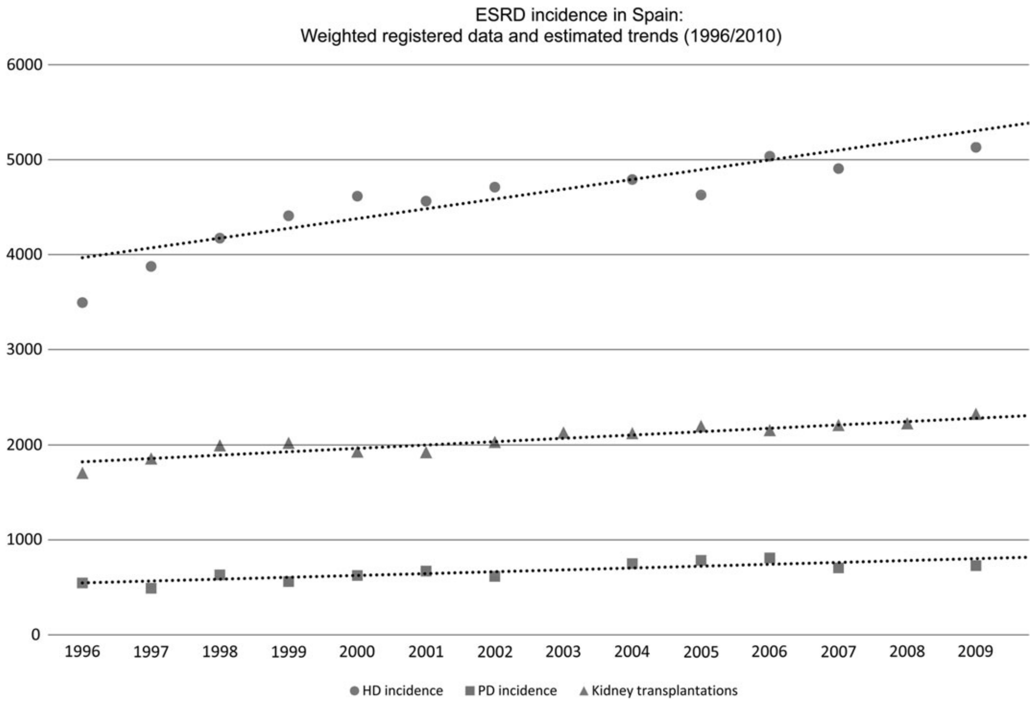

Fig. 2. ESRD incidence in Spain: weighted registered data and estimated trends (1996/2010).

Table 1. Annual per-patient costs[a]

	ICHD	HHD	HD (weighted average)	CAPD	APD	PD (weighted average)	Tx
Medical direct costs							
Scheduled vascular access	928	928	928				
Unscheduled vascular access	4595	4595	4595				
Peritoneal access				808	808	808	
Training				681	1568	1000	
Kidney transplantation (first year)							38 313
Average incidence costs			2651			1808	38 313
Kidney transplantation (subsequent years)							6283
Treatment session	20 376	30 084	24 745	17 081	25 306	20 042	
Equipment depreciation		1084	488	209	209	209	
Utilities		274	123	37	37	37	
Nephrology general expenses	1977	5492	3559	1955	2860	2281	
Equipment maintenance		610	275				
External services		919	414	165	165	165	
Drug consumption	2975	2975	2975	2975	2975	2975	
Access complications	311	311	311	117	117	117	
Nonmedical direct costs							
Transport	5079	5079	5079				
Average prevalence costs			37 968			25 826	6283
Indirect costs							
Lost labor productivity due to mortality	904	904	904	518	518	518	124
Lost labor productivity due to morbidity	8025	8025	8025	6911	6911	6911	5359
Average indirect costs			8929			7429	5483

[a]Tx, kidney transplantation.

Administration, has been carried out. It was concluded (indirect costs included) that 73% of the aggregate RRT costs in 2010 came from patients in HD, 21% of the costs were associated to patients in kidney transplantation and only ~6% of the costs were due to patients in PD.

The higher costs of HD are explained by the greater proportion of patients in this modality, as well as by the higher average cost estimated. This finding is in agreement with previous research [24–26, 28, 29]. Our results are similar to the ones obtained in a study by Hernandez-Jaras *et al.* [30], in which the average annual per-patient cost in HD (updated to 2010) was €37 438, as compared to €37 968 in this article, despite both studies do not perform costing on the same elements nor use the same methods.

Table 2. Annual incidence, prevalence and aggregate costs in 2010[a]

	HD	PD	Tx
Forecasted incidence (patients)	5409	822	2317
Forecasted prevalence (patients)	22 582	2420	24 761
Annual incidence costs (in €)	2651	1808	38 313
Annual prevalence costs (in €)	37 968	25 826	6283
Annual indirect costs (in €)	8929	7429	5483
Aggregate costs (in million €) (indirect costs not included)	1077	85	244
Aggregate costs (%) (indirect costs not included)	77	6	17
Aggregate costs (in million €) (indirect costs included)	1327	109	393
Aggregate costs (%) (indirect costs included)	73	6	21

[a]Tx, kidney transplantation.

Additionally, in accordance with other studies, our research estimated a greater cost for HHD, as compared to ICHD, as well as a greater cost for APD as compared to CAPD [25, 28]. On the other hand, this study confirms that, starting in the second year, kidney transplantation presents a lower annual per-patient cost compared to the dialysis modalities. This finding also agrees with the evidence from previous studies [22, 23].

As mentioned in this paper, the number of patients who prefer PD over HD increases when patients have information about the different dialysis modalities available prior to choosing [18–21]. Nevertheless, the Spanish incidence and prevalence figures in HD are far higher than those in PD. If it is also considered that HD is the most costly modality for the Public Administration, it seems logical to think that, both from the perspective of the patients' rights to choose the therapy for which they are best suited, as well as from the economic benefits to the society, it would be preferable if the number of incident and prevalent patients in PD were increased. As a continuation of this research, a cost-effectiveness analysis of the different RRT modalities might contribute to confirm and extend the findings presented in here.

It is important to highlight that the dialysis modality chosen depends heavily on the progression of the pathology at the time of referral to nephrology, since early detection allows the patient to be informed about the treatment options. The timing for dialysis initiation is critical for the patients, so they can be educated, have appropriate peritoneal or vascular accesses performed early and start in RRT as scheduled, unlike what happens to patients referred to nephrology in a delayed manner, who, in many cases, must have urgent dialysis performed.

As mentioned earlier, RRT in Spain is free of charge for the patient, but it causes high health care costs for the Public Administration. This study estimates and compares the costs of the different Spanish RRT programme modalities. It is important to point out that the established therapeutic model in a country is a consequence of a decision which is not only based on clinical criteria but also on economic criteria. De Vecchi *et al.* [27] compared the costs of different RRT modalities in countries with different types of funding mechanisms. They concluded that PD is the least costly technique from the perspective of publicly funded health care systems. So, home-based dialysis is more predominant in countries with public funding as compared to countries with predominant private health care systems. This finding leads to the conclusion that the health care financing model of a country might influence the use of the various RRT modalities [31].

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Conflict of interest statement. None declared.

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IV. Publicación 2. Análisis coste-efectividad del programa español de tratamiento sustitutivo renal

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COST-EFFECTIVENESS ANALYSIS OF THE SPANISH RENAL REPLACEMENT THERAPY PROGRAM

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♦ ***Background:*** **We undertook a cost-effectiveness analysis of the Spanish Renal Replacement Therapy (RRT) program for end-stage renal disease patients from a societal perspective. The current Spanish situation was compared with several hypothetical scenarios.**

♦ ***Methods:*** **A Markov chain model was used as a foundation for simulations of the Spanish RRT program in three temporal horizons (5, 10, and 15 years). The current situation (scenario 1) was compared with three different scenarios: increased proportion of overall scheduled (planned) incident patients (scenario 2); constant proportion of overall scheduled incident patients, but increased proportion of scheduled incident patients on peritoneal dialysis (PD), resulting in a lower proportion of scheduled incident patients on hemodialysis (HD) (scenario 3); and increased overall proportion of scheduled incident patients together with increased scheduled incidence of patients on PD (scenario 4).**

♦ ***Results:*** **The incremental cost-effectiveness ratios (ICERs) of scenarios 2, 3, and 4, when compared with scenario 1, were estimated to be, respectively, –€83 150, –€354 977, and –€235 886 per incremental quality-adjusted life year (ΔQALY), evidencing both moderate cost savings and slight effectiveness gains. The net health benefits that would accrue to society were estimated to be, respectively, 0.0045, 0.0211, and 0.0219 ΔQALYs considering a willingness-to-pay threshold of €35 000/ΔQALY.**

♦ ***Conclusions:*** **Scenario 1, the current Spanish situation, was dominated by all the proposed scenarios. Interestingly, scenarios 3 and 4 showed the best results in terms of cost-effectiveness. From a cost-effectiveness perspective, an increase in the overall scheduled incidence of RRT, and particularly that of PD, should be promoted.**

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At the end of 2010 in Spain, more than 55 000 patients diagnosed with end-stage renal disease (ESRD) were receiving renal replacement therapy (RRT), representing an incidence of 137 patients [hemodialysis (HD): 85%; peritoneal dialysis (PD): 13%; kidney transplantation (Tx): 2%] and a prevalence of 1079 patients (HD: 45%; PD: 5%; Tx: 50%) per million population. The economic impact of the RRT program on Spanish society was estimated to be about €1 829 million that same year (1).

The choice of dialysis modality depends largely on the patients, because they choose the modality that best satisfies their needs. The information available to patients is a determining factor in their choice, and information availability has been associated with an increase in the preference for PD over HD (2). Provision of information about treatment alternatives is considered to be highly relevant to patients, because a lack of freedom at the time that the RRT modality is chosen reduces health related quality of life (HRQoL), particularly in the psychological dimension (3). Nevertheless, no significant differences in clinical outcome have been detected in a comparison of those two alternatives (4).

It has been observed that the larger proportion of patients on HD might be a result of a lack of information provided to patients (5). Consequently, the importance of early detection of renal disease should be emphasized. Early referral of ESRD patients to nephrologists allows those patients to make a more informed decision about the RRT modality that they will receive. Furthermore, it

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helps to delay progression of the pathology, reducing morbidity and facilitating clinical follow-up (6–13)—and as a result also reducing costs (1).

Several organizations—such as the U.K. Renal Association, the U.S. National Kidney Foundation, the Spanish Society of Nephrology (SEN) (2), and the Spanish Society of Family and Community Medicine (14)—have issued recommendations related to the diagnosis of ESRD and the therapeutic objectives that should be established. These organizations recommend referral to nephrologists for patient evaluation and follow-up. As has already been mentioned, late referral of patients to nephrologists has important economic consequences, given that a non-scheduled (non-planned or urgent) start to RRT turns out to be more costly than a scheduled (planned or elective) start (1).

As mentioned earlier, a scheduled dialysis start has been associated with greater choice of PD over HD [relative risks of 2.09 and 1.68 computed from data presented by Marrón and colleagues (5,15)]. According to the existing literature, between 51% and 54% of the dialysis starts in Spanish patients (omitting Tx) are scheduled. Scheduled starts in patients starting HD range between 43% and 53%, and those in patients starting PD range between 81% and 90% (5,15,16).

As for the total cost of the RRT program in Spain, it should be mentioned that, according to a recent estimate carried out by Villa *et al.* (1), most of the estimated costs in the year 2010 were attributable to HD (73%); only small percentages were attributable to PD (6%) and to Tx (21%). According to the authors, this cost distribution is a consequence of both the larger number of patients treated with HD and the higher estimated average cost of that modality. The authors concluded that, from a cost minimization perspective, it would be favorable to increase the number of patients on PD.

In the present study, we aimed to determine whether better clinical and economic outcomes could be obtained by increasing the proportion of scheduled patients (those eligible for a planned start) in the Spanish RRT program, using various scenarios simulated in three temporal horizons (5, 10, and 15 years). In the first simulation, the overall proportion of scheduled incident patients was increased. In the second simulation, the proportion of scheduled incident patients on PD was increased, keeping the overall scheduled incidence constant. Finally, in the third simulation, the preceding two scenarios were combined. Our overall objective was to conduct a cost-effectiveness analysis of the Spanish RRT program for ESRD patients from a societal perspective. Using a Markov chain model we were able to compare the current Spanish situation with our hypothetical scenarios.

METHODS

We developed a Markov chain model for the Spanish RRT program. Markov models are useful for representing random processes that evolve over time; they are therefore suited to modeling the progression of chronic diseases. A specific disease is structured as a chain of various health states, in which movements between the states over given time periods ("cycles") occur with a given probability ("transition probability"). Estimates of costs and health outcomes are attached to each state in the model. By running the model over a large number of cycles (the "temporal horizon"), long-term costs and health outcomes associated with a disease are obtained (see Briggs and Sculpher (17) for a detailed introduction to Markov modeling).

In our particular case, four health states [HD, PD, Tx, Death (D)] were defined, with the chance of bidirectional transitions between all the states except D, which is an absorbent state. The model simulated progression of renal pathology in three temporal horizons (5, 10, and 15 years). Based on the opinion of an expert panel, 4 scenarios were considered:

- Scenario 1: A model that reflects the current situation of the Spanish RRT program.
- Scenario 2: A model with an increased overall proportion of scheduled incident patients (to 75% from 57%).
- Scenario 3: A model in which the overall proportion of scheduled incident patients was held constant (at 57%), but in which the relative proportion of scheduled incident patients on PD was increased (to 30% from 10% of all incident patients). As a consequence, the proportion of incident patients on HD decreased.
- Scenario 4: A model that combined scenarios 2 and 3. The overall proportion of scheduled incident patients was increased (to 75% from 57%), and the proportion of scheduled incident patients on PD was also increased (to 30% from 10% of all incident patients).

The simulation was set to start at the beginning of 2010, using data from a recent forecast of ESRD incidence and prevalence figures at the end of 2009 in Spain (1). The initial prevalence was distributed among the RRT modalities according to the proportions observed in that forecast: HD, 46%; PD, 5%; and Tx, 49%. Based on those data, the future prevalence in each cycle (1 year) and state was determined by the application of a transition probabilities matrix (TPM).

It was estimated that the number of incident patients grows at a constant rate of 2% with respect to the previous cycle and also that the initial incidence is distributed among the RRT modalities according to the proportions observed in the forecast: HD, 86%; PD, 13%; and Tx, 1%. According to Ortega *et al.* (16), 53% of Spanish incident patients on HD are scheduled. Moreover, based on expert panel opinion and on the existing literature (5,15), it was assumed that 10% of all incident patients are scheduled and started on PD, accounting for 83% of the incident patients on PD. Incident patients on Tx were always regarded as scheduled. Based on those percentages, it was possible to derive the overall proportion of scheduled incident patients. On the whole, it was estimated that 57% of incident patients on any RRT modality were scheduled.

The TPM determines the likelihood of patient flows between the defined health states from year to year (Figure 1). The TPM parameters were estimated based mainly on data recorded by the SEN registry. Exceptions included the probabilities of remaining on HD and on PD (18) and of making a transition from Tx to HD or to PD (19). Compared with non-scheduled patients, the scheduled patients on HD appear to have a lesser risk of death (relative risk: 0.39) (16). Mortality rates for HD were therefore computed as weighted averages of the mortality rates associated with scheduled and non-scheduled patients. The model also included a kidney Tx queue, ensuring that future transitions to Tx do not exceed the number of available organs (maximum of 4000 kidney transplantations annually, according to the expert panel).

The predictive validity of the TPM was checked by comparing the simulated data with the data available in the SEN registry for the period 1996 – 2009. An accumulated squared prediction error close to 5% was observed throughout that entire period, meaning that the predictive power of the matrix was considered to be very high, encompassing almost 95% of all variations registered in the prevalence. There was also evidence of a stable trend between the data taken from the SEN registry and the predictions provided by the model, further validating the established TPM (Figure 2).

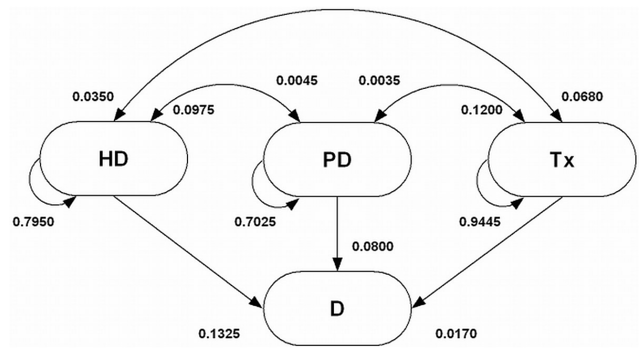

Figure 1 — Transition probabilities. HD = hemodialysis; PD = peritoneal dialysis; Tx = kidney transplantation; D = death.

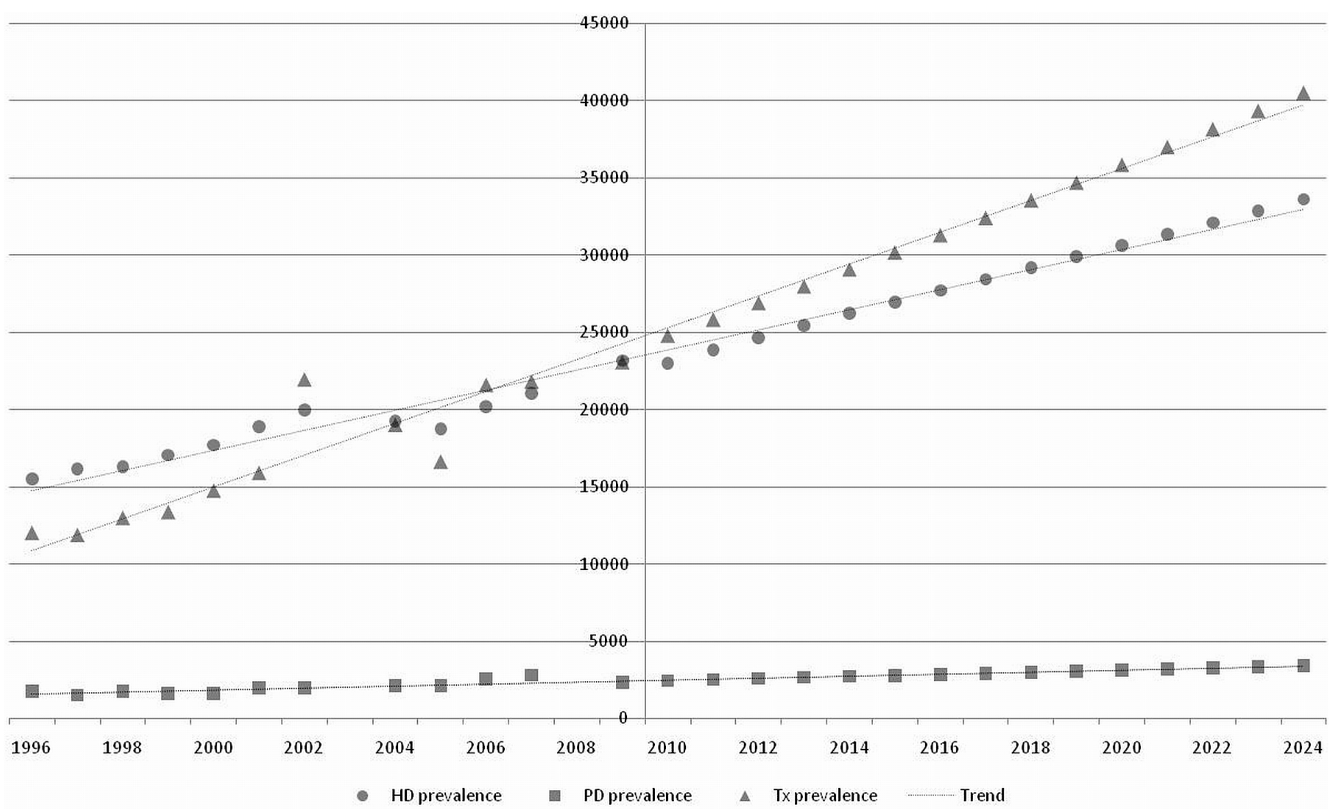

Figure 2 — Prevalence of end-stage renal disease in Spain. Weighted registry data (1996 – 2009), model forecast (2010 – 2024), and trends. HD = hemodialysis; PD = peritoneal dialysis; Tx = kidney transplantation.

To obtain information about clinical effectiveness, expressed in quality-adjusted life years (QALYs), we conducted a literature review. That review was complemented with data from a proprietary database obtained from the Sanitary Research Fund Project 96/1327, which was funded by the Spanish Ministry of Health. Health utilities were assigned values on a scale from 0 (worst state or death) to 1 (optimal or perfect health). The utilities were calculated based on the Project 96/1327 database, whose content was drawn from administration of the SF-36 health questionnaire. Using the methodology proposed by Rebollo *et al.* (20) and implemented in Spain, SF-36 HRQoL scores were converted into SF-6D health utilities. No statistically significant differences in means were found between the HD and PD utilities (0.69) at the 95% confidence level. The Tx utility (0.81) was significantly higher in comparison with the other two modalities. Those findings accord with results from previous studies (21,22). As for the possible difference in effectiveness between continuous ambulatory PD (CAPD) and automated PD (APD), we decided, based on the review carried out by Rabindranath *et al.* (23), not to perform individualized analyses for those modalities.

For each RRT modality, QALYs were defined as the product of the survival rate in a cycle and the health utility associated with the particular modality. As stated, the attributed costs were gathered from a previous study (1). Direct and indirect costs were both included from a societal perspective. Table 1 shows the costs (in euros at January 2010) and the health utilities considered in the model. Costs and health utilities were both discounted at a 3.5% rate. With regard to the cost-effectiveness comparisons, incremental cost-effectiveness ratios (ICERs) and net health benefits (NHBs), assuming a willingness-to-pay threshold of €35 000 per incremental QALY (ΔQALY), were both computed.

To evaluate the robustness of the results, a univariate sensitivity analysis was carried out. In addition, focusing on scenario 4, a bivariate "worst case" sensitivity analysis was conducted, in which the costs of PD were increased by 10%, and the utility of PD was decreased by the same percentage.

TABLE 1
Model Parameters: Costs and Health Utilities

Parameter	HD	PD	Tx
Scheduled incidence cost (€)	928	1 808	38 313
Non-scheduled incidence cost (€)	4 595	1 808	
Transition cost (€)	928	1 808	38 313
Prevalence cost (€)	37 968	25 826	6 283
Indirect cost (€)	8 929	7 429	5 483
Health utilities	0.69	0.69	0.81

HD = hemodialysis; PD = peritoneal dialysis; Tx = kidney transplantation.

RESULTS

Aiming for concision and unless otherwise stated, all results mentioned in this section relate to the long-term temporal horizon (15 years). Although our findings are consistent across the three temporal horizons considered, the interested reader can find detailed results of all simulations in Tables 2 and 3. Moreover, "discounted average per-patient (if applicable) annual" figures are simply called "average" figures.

SIMULATED PREVALENCE, INCIDENCE, AND TRANSITIONS

Compared with scenario 1, the average prevalence of HD remains almost constant in scenario 2 (29 880 and 30 006 respectively), but the prevalence of PD (3 099 vs 3 436) and Tx (34 108 vs 34 551) increases. In scenarios 3 and 4, the average prevalence of HD falls off (27 005 and 27 583 respectively), and once again, the average prevalence of PD (5 803 and 5 683) and Tx (35 157 and 35 414) increase.

Because the prevalence of PD is higher and, furthermore, because PD patients have a higher probability of receiving a graft than HD patients do (0.12 vs 0.07), in all 3 scenarios, more transitions to Tx also occur. In scenario 2, the transitions to PD remain constant compared with those in scenario 1; in scenarios 3 and 4, those transitions fall off. The fall-off is mainly the result of the reduction in the prevalence of HD. Furthermore, in scenario 4 (compared with scenario 3), the number of patients on PD declines because more scheduled incident patients are on Tx and HD, and in relative terms, the scheduled incidence of the patients on PD represents a lower proportion than is present in scenario 3. The number of transitions to Tx never exceed the maximum number of available organs as defined by the expert panel.

COST ANALYSIS

Compared with scenario 1 (€24 448), average costs fall off moderately in scenarios 2 (€24 337), 3 (€23 774), and 4 (€23 780), an effect attributable to the increase in the prevalence of both PD and Tx, combined with the significant fall-off in HD. Compared with the current situation, scenarios 3 and 4 imply annual cost savings of €32 million and €18 million respectively. However, scenario 2 suggests added costs of €10 million, because

TABLE 2
Average Annual Figures, 15-Year Horizon

	Overall	HD	PD	Tx
Scenario 1				
Prevalence	67 087	29 880	3 099	34 108
Incidence	7 434	6 364	962	108
Survival rate	0.8571	0.8109	0.8637	0.9053
Total cost (€ millions)	1 657	1 213	98	346
Per-patient cost (€)	24 448	36 417	25 971	11 244
Per-patient QALYs	0.5317	0.4627	0.4907	0.6117
Scenario 2				
Prevalence	67 993	30 006	3 436	34 551
Incidence	7 434	6 157	1 137	141
Survival rate	0.8588	0.8143	0.8633	0.9046
Total cost (€ millions)	1 666	1 206	109	351
Per-patient cost (€)	24 337	36 314	25 981	11 277
Per-patient QALYs	0.5330	0.4649	0.4907	0.6117
Scenario 3				
Prevalence	67 965	27 005	5 803	35 157
Incidence	7 434	4 933	2 394	108
Survival rate	0.8588	0.8082	0.8624	0.9037
Total cost (€ millions)	1 625	1 073	194	357
Per-patient cost (€)	23 774	36 444	26 023	11 316
Per-patient QALYs	0.5336	0.4613	0.4907	0.6117
Scenario 4				
Prevalence	68 679	27 583	5 683	35 414
Incidence	7 434	4 967	2 327	141
Survival rate	0.8601	0.8123	0.8623	0.9034
Total cost (€ millions)	1 639	1 088	190	360
Per-patient cost (€)	23 780	36 325	26 022	11 335
Per-patient QALYs	0.5345	0.4638	0.4907	0.6117

HD = hemodialysis; PD = peritoneal dialysis; Tx = kidney transplantation; QALY = quality-adjusted life year.

the reduction in the total cost of HD does not offset the larger costs observed in PD and Tx, caused by a higher incidence in those modalities and also by higher overall survival.

An increase in the average cost of HD is observed in scenario 3 compared with scenario 1 (€36 444 vs €36 417). In scenario 3, the proportion of scheduled incident HD patients is lower. In scenario 2, the opposite situation occurs, leading to the average cost of HD being lower (€36 314). In scenario 4, the average cost of HD is lower again (€36 325), because the cost increase observed in scenario 3 is offset by the cost reduction observed in scenario 2.

As for the average cost of PD, a slight increase compared with the cost in scenario 1 (€25 971) is observed in scenarios 2 (€25 981), 3 (€26 023), and 4 (€26 022). Those cost increases are caused by the higher relative proportion of incident PD patients. Incident patients present larger costs derived from creation of the peritoneal access and delivery of training. Likewise, the current average cost of Tx (€11 244) is observed to increase in scenarios 2 (€11 277), 3 (€11 316), and 4 (€11 335), a result of the higher proportion of incident patients on that modality, presenting larger costs.

EFFECTIVENESS ANALYSIS

Compared with scenario 1 (0.8571), scenarios 2 (0.8588), 3 (0.8588), and 4 (0.8601) evidence a slight increase in the discounted survival rate, providing 0.5317, 0.5330, 0.5336, and 0.5345 discounted QALYs respectively. With regard to the therapeutic modalities, greater effectiveness of Tx compared with

TABLE 3
Cost-Effectiveness Results for Three Temporal Horizons

	ICER	NHB	Overall Average cost	Overall QALYs	HD Average cost	HD QALYs	PD Average cost	PD QALYs	Tx Average cost	Tx QALYs
Scenario 1										
15 Years			24 448	0.5317	36 417	0.4627	25 971	0.4907	11 244	0.6117
10 Years			27 596	0.5750	39 449	0.5011	28 131	0.5315	12 228	0.6626
5 Years			29 116	0.6234	42 842	0.5441	30 547	0.5771	13 336	0.7194
Scenario 2										
15 Years	−83 150	0.0045	24 337	0.5330	36 314	0.4649	25 981	0.4907	11 277	0.6117
10 Years	−76 993	0.0045	27 489	0.5764	39 336	0.5035	28 146	0.5315	12 265	0.6626
5 Years	−71 565	0.0045	29 010	0.6249	42 717	0.5567	30 573	0.5771	13 375	0.7194
Scenario 3										
15 Years	−354 977	0.0211	23 774	0.5336	36 444	0.4613	26 023	0.4907	11 316	0.6117
10 Years	−372 050	0.0193	26 977	0.5767	39 474	0.5096	28 209	0.5315	12 310	0.6626
5 Years	−504 913	0.0164	28 580	0.6244	42 856	0.5425	30 690	0.5771	13 413	0.7194
Scenario 4										
15 Years	−235 886	0.0219	23 780	0.5345	36 325	0.4638	26 022	0.4907	11 335	0.6117
10 Years	−229 076	0.0204	26 976	0.5777	39 346	0.5024	28 207	0.5315	12 333	0.6626
5 Years	−238 238	0.0180	28 566	0.6257	42 718	0.5555	30 686	0.5771	13 439	0.7194

ICER = incremental cost-effectiveness ratio; NHB = net health benefit; HD = hemodialysis; PD = peritoneal dialysis; Tx = kidney transplantation; QALY = quality-adjusted life year.

HD and PD is observed. Barely any differences separated the latter modalities, basically because the health utility was considered to be the same (0.69) in both cases. Even so, the effectiveness of PD is somewhat greater in all scenarios because of the greater survival of patients on the PD modality. The average effectiveness for PD and Tx does not vary between the scenarios, because in no scenario did the survival rate vary. Conversely, the average effectiveness of HD varies because the rate of survival varies as the proportion of scheduled and non-scheduled incident patients on the HD modality changes.

COST-EFFECTIVENESS ANALYSIS

The ICERs of scenarios 2, 3, and 4, when compared with scenario 1, were estimated as −€83 150, −€354 977, and −€235 886 per ΔQALY respectively, demonstrating both moderate cost savings and slight effectiveness gains. The NHBs accruing to society were estimated at 0.0045, 0.0211, and 0.0219 ΔQALYs respectively, considering a willingness-to-pay threshold of €35 000/ΔQALY. Scenario 1 is therefore dominated by all the other scenarios proposed. Interestingly, scenarios 3 and 4 show the best results in terms of cost-effectiveness.

SENSITIVITY ANALYSIS

In the univariate sensitivity analysis, the ICERs resulting from scenarios 2 and 3 did not change significantly, despite application of variation rates of ±10% in each of the parameters individually. Focusing on scenario 4, the univariate sensitivity analysis reflected a possible impact on the results from changes in the utility and costs of PD.

Quantification of changes in an ICER resulting from variation in a single parameter is not very reliable because the interactions of the various parameters are not taken into account. To test the robustness of the model, a bivariate "worst case" sensitivity analysis was carried out within scenario 4. The costs and utilities of PD were both modified: PD utilities were lowered by 10%, and PD costs were incremented by 10%. Gains in QALYs (0.5294 vs 0.5289) and cost savings (€24 053 vs €24 592) were both still observed in comparison with scenario 1.

DISCUSSION

In the present study, the Spanish RRT program was simulated in three temporal horizons (5, 10, and 15 years). In light of the current situation (scenario 1), three hypothetical scenarios were compared in terms of cost-effectiveness: an increased overall proportion of scheduled incident patients (scenario 2); a constant overall proportion of scheduled incident patients, but an increased proportion of scheduled incident patients on PD (scenario 3); and an increased overall proportion of scheduled incident patients combined with an increased proportion of scheduled incident patients on PD (scenario 4).

With regard to costs, the average costs are moderately lower in scenario 2 than in scenario 1. However, this decrease in the average cost does not completely offset the costs derived from the increase in the number of prevalent patients. Compared with scenario 1, scenarios 3 and 4 both show cost savings in average and in total terms alike. In both the latter scenarios, survival increases, but a decrease in the average cost offsets the total cost derived from the larger prevalence. With regard to effectiveness, scenarios 2, 3, and 4 provide more QALYs (even though the gains are modest) than does the alternative of taking no action to change the current situation.

The cost-effectiveness indicators show that scenarios 3 and 4 are the most efficient options, dominating scenarios 1 and 2.Therefore, if the number of scheduled incident patients were to be increased, and if patients were to be allowed to receive PD therapy, not only would a greater number of QALYs be obtained, but the intervention would bring about a lower cost than that obtained with the policies currently being followed. In this way, society would obtain a more efficient distribution of the resources invested to treat renal disease.

The importance of early detection and early referral to a nephrologist in ESRD has also been emphasized (6–13), because early detection and referral present an advantage both for the HRQoL of patients and for the economic costs. Similarly, early detection and referral give the patient the opportunity to become informed about the various treatment modalities—a situation that would be expected to increase the number of patients choosing PD (4).

CONCLUSIONS

In the cost analysis carried out by Villa *et al.* (1), the authors concluded that, from a cost-minimization perspective, it would be favorable to increase the number of incident patients on PD. In the present work, in which the costs and the effectiveness of the various RRT modalities have both been considered, a result favorable to PD has also been observed. Given that the NHB is positive, society should assume the costs of introducing the proposed scenarios, considering a willingness-to-pay threshold of €35 000/ΔQALY.

DISCLOSURES

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Cost-effectiveness analysis of timely dialysis referral after renal transplant failure in Spain

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Abstract

Background: A cost-effectiveness analysis of timely dialysis referral after renal transplant failure was undertaken from the perspective of the Public Administration. The current Spanish situation, where all the patients undergoing graft function loss are referred back to dialysis in a late manner, was compared to an ideal scenario where all the patients are timely referred.

Methods: A Markov model was developed in which six health states were defined: hemodialysis, peritoneal dialysis, kidney transplantation, late referral hemodialysis, late referral peritoneal dialysis and death. The model carried out a simulation of the progression of renal disease for a hypothetical cohort of 1,000 patients aged 40, who were observed in a lifetime temporal horizon of 45 years. In depth sensitivity analyses were performed in order to ensure the robustness of the results obtained.

Results: Considering a discount rate of 3 %, timely referral showed an incremental cost of 211 €, compared to late referral. This cost increase was however a consequence of the incremental survival observed. The incremental effectiveness was 0.0087 quality-adjusted life years (QALY). When comparing both scenarios, an incremental cost-effectiveness ratio of 24,390 €/QALY was obtained, meaning that timely dialysis referral might be an efficient alternative if a willingness-to-pay threshold of 45,000 €/QALY is considered. This result proved to be independent of the proportion of late referral patients observed. The acceptance probability of timely referral was 61.90 %, while late referral was acceptable in 38.10 % of the simulations. If we however restrict the analysis to those situations not involving any loss of effectiveness, the acceptance probability of timely referral was 70.10 %, increasing twofold that of late referral (29.90 %).

Conclusions: Timely dialysis referral after graft function loss might be an efficient alternative in Spain, improving both patients' survival rates and health-related quality of life at an affordable cost. Spanish Public Health authorities might therefore promote the inclusion of specific recommendations for this group of patients within the existing clinical guidelines.

Keywords: Chronic kidney disease, Cost-effectiveness analysis, Timely dialysis referral, Graft function loss, Kidney transplantation, Late dialysis referral, Markov models, Renal replacement therapy, Transplant failure

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Background

Kidney transplantation is the treatment of choice for Chronic Kidney Disease (CKD) [1]. In the last decades, the progressive improvement of immunosuppressant drugs has led to an increase in the survival of renal grafts. It has been shown that the one-year survival rate of a renal graft is above 90%. The five-year survival rate is nevertheless around 70% and survival after ten years is below 50% [2]. Every year, therefore, many patients experience graft function loss, being referred back to dialysis. In a recent study carried out by Villa et al., it is estimated that around 4% of the Spanish patients in kidney transplantation would be referred back to dialysis every year, adding up to almost 1,000 patients in 2010 [3].

Despite the existence of a number of clinical practice guidelines, both at the national and the international levels, there is no consensus on the right timing for dialysis referral after graft function loss. Both the reticence of clinicians to assume transplant failure and the reluctance of patients to restart dialysis might be among the causes of late dialysis referral. Moreover, kidney transplantation management and research have traditionally focused on immunosuppressant therapy and on the management of complications, rather than on the condition of patients restarting dialysis.

Following the international recommendations, there are two situations in which patients should start Renal Replacement Therapy (RRT) [4-6]: (1) Glomerular Filtration Rate (GFR) below 15 ml/min/1.73 m^2 (i.e. Stage 5 of CKD) and presence of uremic complications; and (2) GFR below 6 ml/min/1.73 m^2, even in the absence of symptoms. In the case of elder patients or in the presence of comorbidities, it is however recommended an early RRT start, even though GFR is above 15 ml/min/1.73 m^2 and there is absence of symptoms. Recent studies propose however that dialysis initiation is justified at GFR levels from 5 to 9 ml/min/1.73 m^2 if accompanied by symptoms [7].

Arias et al. found that patients experiencing graft function loss presented GFR of 9 ml/min/1.73 m^2 at the time of hemodialysis restart, with 78 % of the patients showing GFR of less than 10 ml/min/1.73 m^2 [8]. Likewise, Gill et al. found GFR of 8.4 ml/min/1.73 m^2 for a similar group of patients [9]. In both cases, GFR was below the current recommendations. Late dialysis referral usually involves a non-scheduled (non-programmed, non-planned or urgent) dialysis restart, what has important clinical [10,11] and economic [3,12] implications, such as higher undernourishment, worse anemic control, higher morbidity and mortality rates, and consequently larger costs. Furthermore, patients undergoing graft function loss show higher recombinant human erythropoietin (rHuEPO) [13] and intravenous iron (IV) [14] needs, experience higher hospitalization rates due to access complications [7] and face increased morbidity and mortality risks [8,15-20]. Because of that, a timely dialysis restart would be advisable for these patients as soon as they reach Stage 5 of CKD.

This article studies the health outcomes and the economic implications of late dialysis referral after graft function loss. A cost-effectiveness analysis of timely dialysis referral after renal transplant failure is undertaken for the first time in Spain. The current Spanish situation is compared to an ideal scenario in which all the patients undergoing graft function loss are referred back to dialysis in a timely manner.

Methods

A Markov chain model was programmed using Stata 10 data analysis software. Markov models are useful to represent random processes which evolve over time. They are suited to modeling the progression of chronic diseases. A specific disease is described as a chain of different health states, and movements between those states over discrete time periods ("cycles") occur with a given probability ("transition probability"). Estimates of health outcomes and costs are attached to each state in the model. By running the model over a large number of cycles ("temporal horizon"), the long-term health outcomes and costs associated with the disease are computed (see [21] for a detailed introduction to Markov modeling).

In our particular case, six health states were defined: HD: hemodialysis; PD: peritoneal dialysis; Tx: kidney transplantation; LRHD: late referral hemodialysis; LRPD: late referral peritoneal dialysis; and D: death. The model carried out a simulation of the progression of renal disease for a hypothetical cohort of 1,000 patients aged 40, the most frequent age for RRT initiation according to expert judgment, who were observed in a lifetime temporal horizon of 45 years. The model parameters and their supporting references are presented in Table 1.

Transition probabilities determine the likelihood of patient flows between the health states defined from cycle (a year) to cycle (Figure 1). Transition probabilities were based on a recent study [3], with the exception of age-dependent mortality probabilities, which were computed using data from the Spanish Society of Nephrology (SEN, Spanish acronym) registry [22] and assuming that late referral patients had a one-year survival rate of 73% [23]. All the model transitions were half-cycle corrected [24].

Based on the opinion of an expert panel of three clinicians, two alternative scenarios were considered:

- Scenario L. All the patients are referred back to dialysis (both to HD and PD) in a late manner after graft function loss (transition probabilities: Tx to HD: 0.0000; Tx to PD: 0.0000; Tx to LRHD: 0.0350;

Table 1 Model parameters

	Global	HD	PD	Tx	LRHD	LRPD	D	References
Direct medical costs: first-year		2,545 €	1,819 €	36,772 €	6,627 €	3,748 €	0 €	Villa et al. (2011) [12] and this study
Direct medical costs: prevalence		31,912 €	24,996 €	6,030 €	31,912 €	24,996 €	0 €	Villa et al. (2011) [12] and this study
Health utilities		0.69	0.69	0.81	0.53	0.53	0.00	Villa et al. (2012) [3] and Laupacis et al. (1996) [25]
Transition probabilities from/to HD, PD, LRHD, LRPD, Tx	See Figure 1							Villa et al. (2011) [3]
Age-dependent transition probabilities to D								SEN (2008) [22], Kaplan et al. (2002) [23] and this study
Starting cohort (patients)	1,000							Arbitrary
Starting age (years)	40							Expert panel opinion
Time horizon (years)	45							Expert panel opinion
WTPT (€/QALY)	45,000							De Cock et al. (2007) [26]
Discount rate	3 %							López-Bastida et al. (2010) [27]

HD: hemodialysis.
PD: peritoneal dialysis.
Tx: kidney transplantation.
LRHD: late referral hemodialysis.
LRPD: late referral peritoneal dialysis.
D: death.
WTPT: willingness-to-pay treshold.
QALY: quality-adjusted life year.

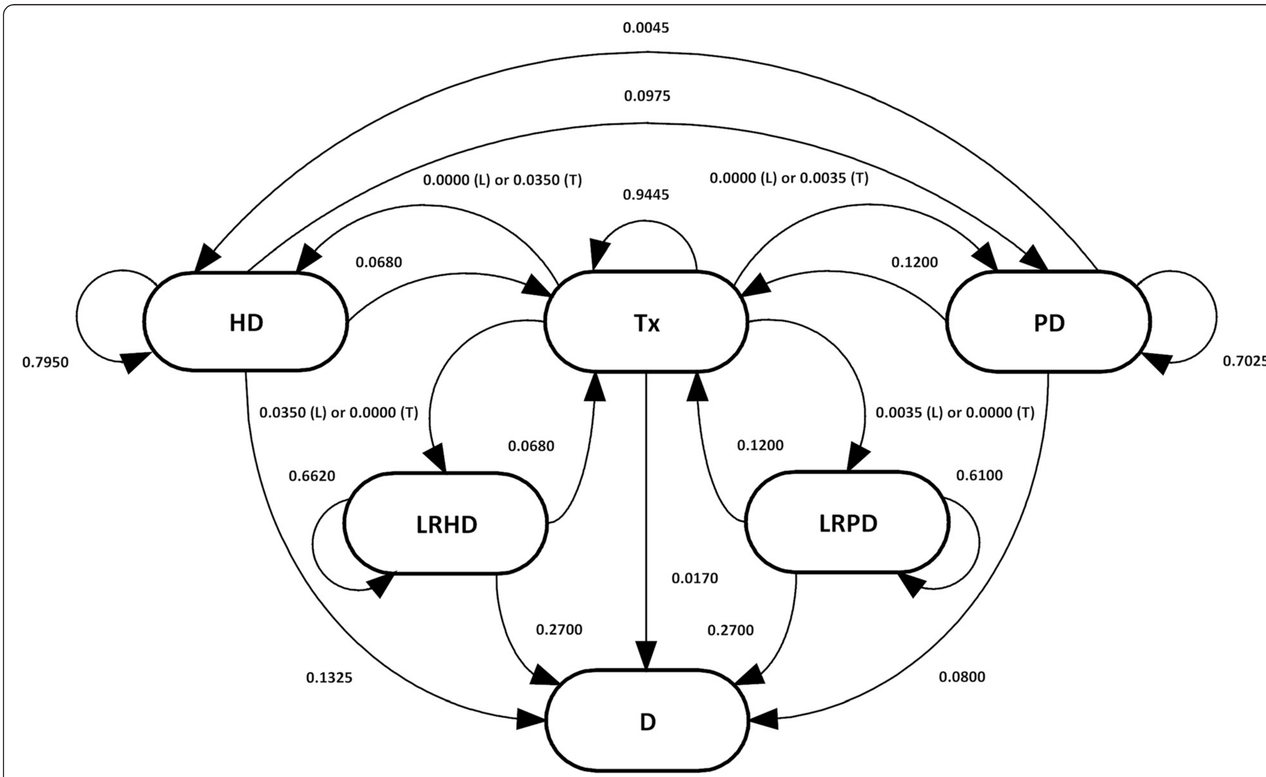

Figure 1 Transition probabilities. HD: hemodialysis. PD: peritoneal dialysis. Tx: kidney transplantation. LRHD: late referral hemodialysis. LRPD: late referral peritoneal dialysis. D: death. T: Scenario T. L: Scenario L.

Tx to LRPD: 0.0035). Scenario L represents the current Spanish situation, according to the expert panel opinion.

- Scenario T. All the patients are referred back to dialysis in a timely manner after graft function loss (transition probabilities: Tx to HD: 0.0350; Tx to PD: 0.0035; Tx to LRHD: 0.0000; Tx to LRPD: 0.0000). Scenario T represents an ideal situation.

Following a Public Administration perspective, direct medical costs (in January 2012 €), including the costs of the vascular (HD) or peritoneal (PD) accesses; access complications; delivery of training; treatment session; kidney transplantation; drug consumption; equipment depreciation and maintenance; Nephrology Service general expenses; utilities; and external services, were considered. HD, PD and Tx transition and prevalence costs were collected from a recent study. Transition (incidence or first-year) costs include the costs of the vascular access (HD), the costs of the peritoneal access and training (PD), and the costs of transplantation surgery (Tx).

LRHD and LRPD costs were based on that same methodology [12], but taking into account some considerations. It was considered that LRHD patients required a higher (Δ97%) number of days of hospitalization due to access complications than HD patients did [7]. It was further considered that, during the first year, LRHD and LRPD patients showed higher (Δ69 %) rHuEPO [13] and higher (Δ47%) IV [14] needs than HD and PD patients did. Moreover, both LRHD and LRPD patients were considered as non-scheduled (i.e. they start dialysis in a non-planned, non-programmed or urgent form). Per-patient annual transition costs were: 2,545 € (HD) < 6,627 € (LRHD) and 1,819 € (PD) < 3,748 € (LRPD).

Effectiveness was expressed in terms of quality-adjusted life years (QALY). QALY were defined as the survival rate in a cycle times the health utility associated with a given health state. Health utilities were assigned values on a scale from 0 (the worst health state or death) to 1 (the optimal or perfect health state). Utilities were obtained from the existing literature [3,25]. Regarding LRHD and LRPD utilities, we considered the average (first year) post-transplant "good dialysis state" utility reported by Laupacis et al. [25]. This study has been cited by a number of relevant studies for similar purposes [28-31]. This estimate presents however some limitations. First, patients (and not the society) were asked to evaluate hypothetical health states using the time trade-off method. Second, health states evaluated were not based on generic quality of life instruments.

Both costs and health utilities were applied a 3% discount rate [27]. As for the cost-effectiveness comparisons, the incremental cost-effectiveness ratio (ICER) was computed and a willingness-to-pay threshold (WTPT) of 45,000 €/QALY [26] was assumed.

For the purpose of contrasting the robustness of the results, univariate and probabilistic (Monte Carlo simulation) sensitivity analyses were carried out. In the univariate case, each single model parameter was changed (a 10% increase or decrease) at a time and a new ICER was computed. In the probabilistic case, 1,000 new ICER were computed by changing all the model parameters simultaneously. Beta distributions were assumed for the

Table 2 Results: Scenario L vs Scenario T

	Scenario L	Scenario T	Comparative
Deterministic analysis			
Per-patient annual cost	5,793 €	6,217 €	425 €
Per-patient annual cost (discount rate 3 %)	4,564 €	4,775 €	211 €
Per-patient annual QALY	0.2250	0.243	0.0176
Per-patient annual QALY (discount rate 3 %)	0.1594	0.1682	0.0087
ICER			24,135 €
ICER (discount rate: 3 %)			24,390 €
Probabilistic analysis (3 % discount rate)			
Per-patient annual cost (95 % confidence interval)	4,591 € (3,926 €; 5,422 €)	4,771 € (4,073 €; 5,630 €)	180 € (−898 €; 1,305 €)
Per-patient annual QALY (95 % confidence interval)	0.1594 (0.1372; 0.1815)	0.1682 (0.1446; 0.1947)	0.0088 (−0.0245; 0.0431)
Dominant	20.20 %	27.80 %	7.60 %
Efficient (higher effectiveness)	3.20 %	27.60 %	24.40 %
Efficient (lower cost)	14.70 %	6.50 %	−8.20 %
Acceptable	38.10 %	61.90 %	23.80 %
Acceptable (without loss of effectiveness)	29.90 %	70.10 %	40.20 %

ICER: incremental cost-effectiveness ratio.

transition probabilities, normal distributions were assumed for the health utilities, log-normal distributions were assumed for the costs and a uniform distribution was assumed for the discount rate [32]. Due to data unavailability and when required, standard deviations were assumed to be a 10% of the mean values. The cost-effectiveness plane and the confidence ellipse (95% confidence level) were developed. The probabilities of accepting the two scenarios proposed as a function of the WTPT (acceptability curves) were also computed.

Results

Cost-effectiveness results are shown in Table 2. Per-patient annual costs and QALY are presented for both scenarios, as well as comparative measures between them.

Considering a discount rate of 3%, Scenario T showed an incremental average (per-patient and year) cost of 211 €, compared to Scenario L. This average cost increase was however due to the incremental average survival observed in Scenario T. The incremental effectiveness was 0.0087 QALY. When comparing both scenarios, an ICER of 24,390 €/QALY was obtained, meaning that Scenario T is an efficient alternative if we consider a WTPT of 45,000 €/QALY.

The univariate sensitivity analysis showed that model results were robust. The ICER did not change significantly when alternative discount rates of 0% (24,135 €/QALY) or 5% (24,405 €/QALY) were considered. Only three model parameters caused absolute value changes in the ICER exceeding a 10% threshold: HD and LRHD prevalence costs, and HD utilities (Figure 2). A maximum ICER of 29,869 €/QALY, yet below the WTPT, was obtained by increasing the prevalence cost of HD in a 10%. Finally, a 10% increase in the utility of LRHD patients caused a 6.01% increase in the ICER, meaning that the influence of this parameter on the results is limited.

In this study, two extreme situations were considered in which either all the patients were referred back to dialysis in a late manner (Scenario L) or all of them were timely referred (Scenario T). A univariate sensitivity analysis was conducted on the proportion of patients who were referred back to dialysis in a late manner. As expected, it was concluded that the higher the proportion of late referral patients considered, the lower the ICER obtained. The ICER was furthermore below the WTPT for any proportion of late referral patients, ranging from 24,428 €/QALY (proportion of late referral patients equal to 0.01) to 24,390 €/QALY (Scenario L). Timely dialysis referral was therefore an efficient alternative for any proportion of late referral patients observed.

The probabilistic sensitivity analysis (Table 2, Figure 3) showed that, given a WTPT of 45,000 €/QALY, Scenario T was a dominant alternative in 27.80%, efficient with higher effectiveness in 27.60% and efficient with lower costs in 6.50% of the simulations. In contrast, Scenario L was a dominant alternative in 20.20%, efficient with lower cost in 14.70% and efficient with higher effectiveness in 3.20% of the simulations. The acceptance probability of Scenario T was 61.90%, while Scenario L was acceptable in 38.10% of the simulations. If we however restrict the analysis to those situations not involving any loss of effectiveness (i.e. situations of dominance and efficiency with higher effectiveness), the acceptance probability of Scenario T was 70.10%, doubling that of Scenario L (29.90%). Figure 4 shows the acceptability curves of the two scenarios considered for any WTPT ranging from 0 €/QALY to 90,000 €/QALY.

Discussion

This study presented a cost-effectiveness analysis of timely dialysis referral after renal transplant failure in Spain from the perspective of the Public Administration. Late dialysis referral after graft function loss usually involves a non-scheduled dialysis restart that has important clinical and economic implications, such as higher undernourishment, worse anemic control, higher morbidity and mortality rates, and consequently larger costs incurred. The health outcomes and the economic resources associated with late dialysis referral after graft function loss were discussed and quantified.

A Markov chain model was developed and the current Spanish situation, where the great majority of patients are referred back to dialysis in a late manner, was compared to an ideal scenario in which all the patients undergoing graft function loss were timely referred. In depth sensitivity analyses were performed in order to ensure the robustness of the results obtained.

LRHD and LRPD patients presented lower survival rates and health utilities, and higher transition and prevalence costs than HD and PD patients did. Assuming a WTPT of 45,000 €/QALY, timely dialysis referral might be an efficient alternative when compared to the current Spanish situation. This result proved to be independent of the proportion of late referral patients considered, since the ICER was below the WTPT for any proportion of late referral patients.

Timely dialysis referral implied a moderate increase in total costs. This cost increase was nevertheless caused by the increased survival rates observed in the timely referral scenario, since all the prevalent patients require a lifelong treatment. In real life, the additional costs associated with starting dialysis 6 or 12 months earlier might also contribute to a cost increase. Simulations were rerun only considering those situations not involving any loss of effectiveness. Following this approach, the acceptance probability of timely dialysis referral increased

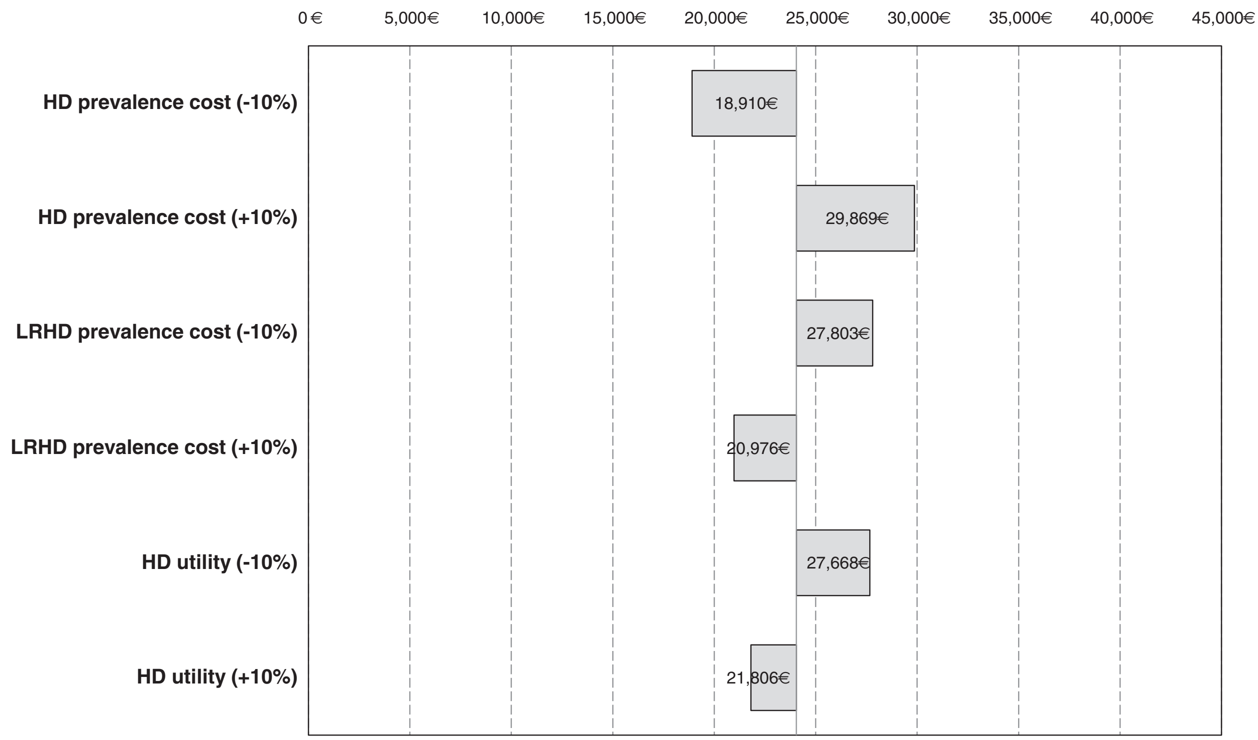

Figure 2 Incremental cost-effectiveness ratio for univariate parameter changes (Tornado). HD: hemodialysis. LRHD: late referral hemodialysis.

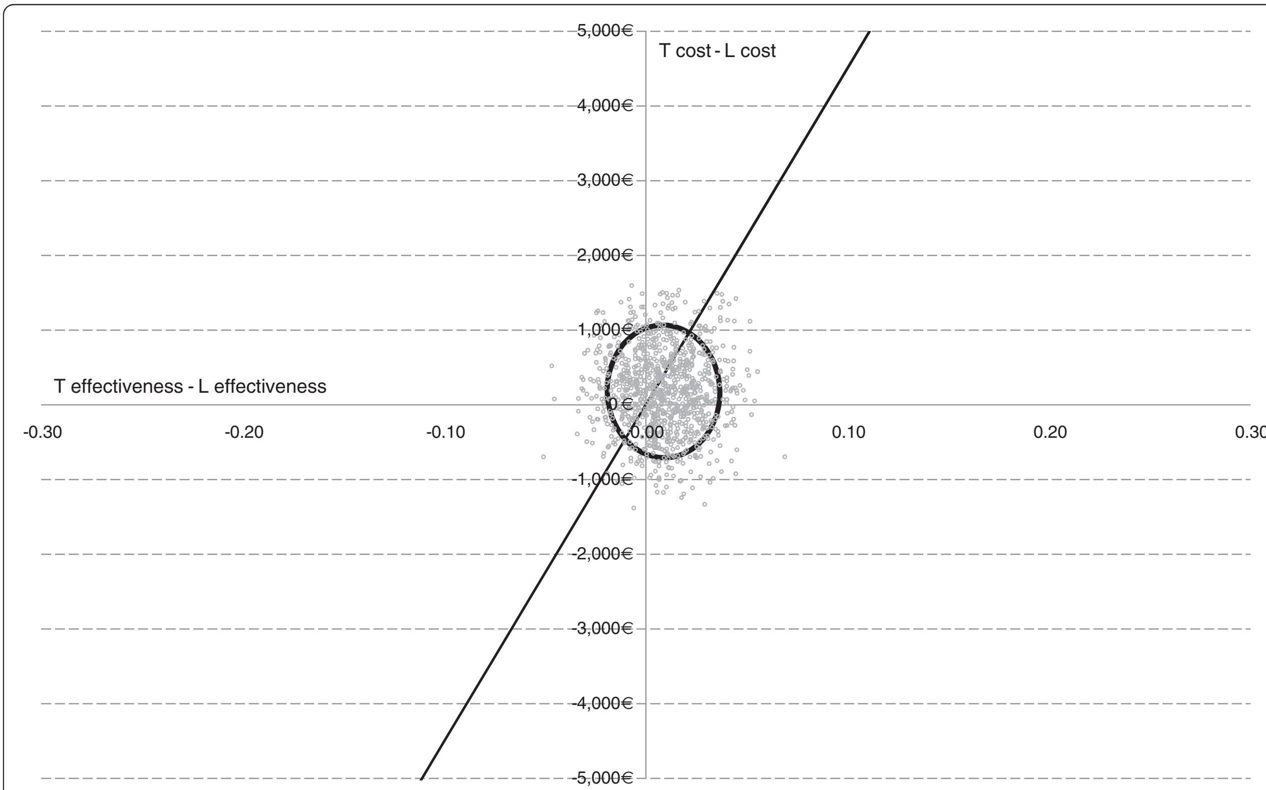

Figure 3 Cost-effectiveness plane and 95 % confidence ellipse. T: Scenario T. L: Scenario L.

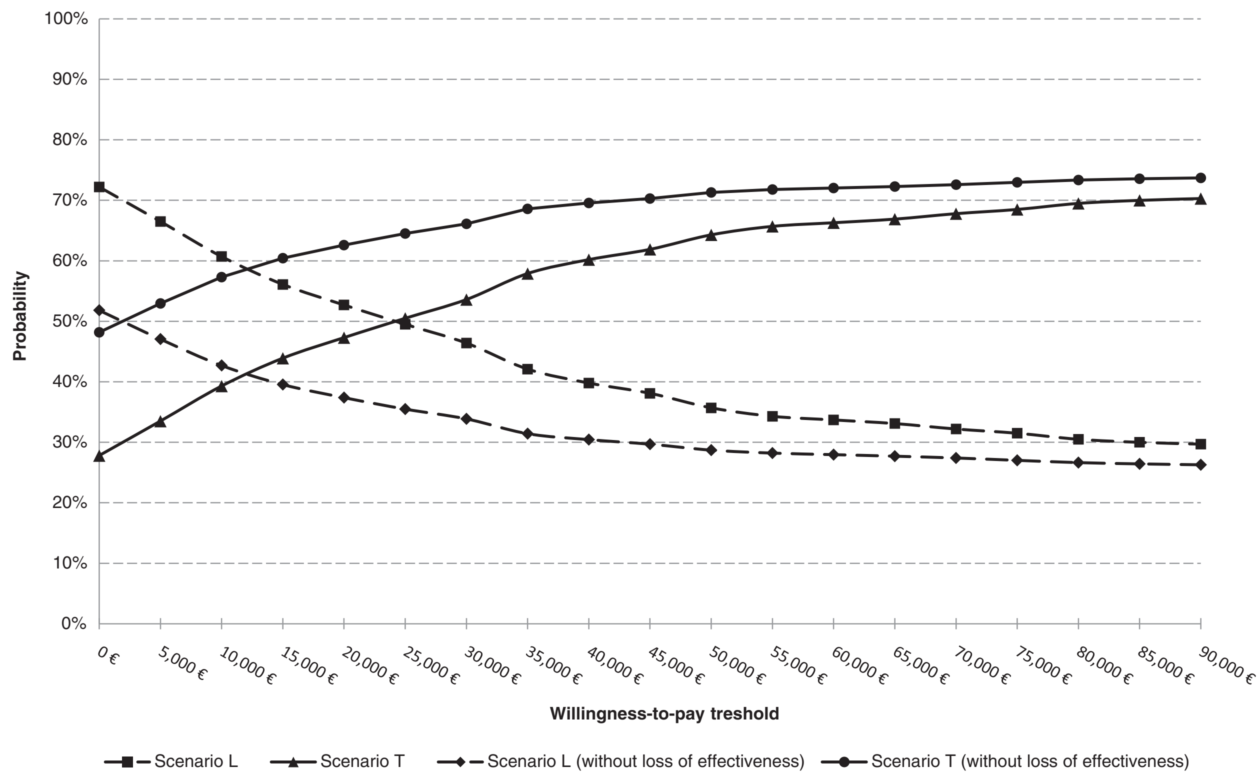

Figure 4 Acceptability curves.

twofold that one of the current Spanish scenario. Based on these results, nephrologists might inform patients on the increased morbidity and mortality risks associated with late dialysis referral.

A limitation of this study is that costs and outcomes in our model are mainly based on single punctual estimates gathered from the existing literature, due to unavailability of micro-data in our country. We were therefore unable to attach confidence intervals to the vast majority of model parameters and had to assume a dispersion of 10% of the central value for all the model parameters. We suspect that the ICER dispersion might be overestimated in our model and therefore the results of the probabilistic sensitivity analysis should be taken with caution.

It is worth noting that late referral patients are also expected to incur higher loss of labor productivity costs due to morbidity and mortality than timely referral patients do. A second limitation of this study is that a Public Administration perspective was adopted rather than including indirect costs (societal perspective), since reliable estimates of the unemployment and retirement rates for late referral patients are not available in Spain and further research would be required. In an exploratory analysis, we quantified loss of labor productivity costs due to mortality in 29,345 € per death and year for RRT patients under 67 years old [12,33], resulting in an ICER of −146 €/QALY when included in the model. The inclusion of loss of labor productivity costs due to morbidity is expected to reduce the ICER obtained, further validating the timely referral approach proposed.

Conclusions

Timely dialysis referral after graft function loss might be an efficient alternative in Spain, improving both patients' survival rates and health-related quality of life at an affordable cost. Spanish Public Health authorities might promote the inclusion of specific recommendations for this group of patients within the existing clinical guidelines, also monitoring their proper implementation and outcomes.

Abbreviations

CKD: Chronic kidney disease; D: Death; GFR: Glomerular filtration rate; HD: Hemodialysis; ICER: Incremental cost-effectiveness ratio; IV: Intravenous iron; LRHD: Late referral hemodialysis; LRPD: Late referral peritoneal dialysis; PD: Peritoneal dialysis; QALY: Quality-adjusted life year; rHuEPO: recombinant human erythropoietin; RRT: Renal replacement therapy; SEN (Spanish acronym): Sociedad Española de Nefrología; Tx: Kidney transplantation; WTPT: Willingness-to-pay threshold.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

GV has contributed to the conception and design of the study. He has managed the acquisition, analysis and interpretation of data, and has been also involved in drafting the manuscript. JC and LFO have participated in the design of the study and in the acquisition and interpretation of data. They have been also involved in critically revising the manuscript. ESA, PR, FO have contributed to the conception of the study and have participated in the interpretation of data. They have been also involved in critically revising the manuscript. Finally, all the authors have given final approval of the version to be published.

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VI. Resultados

Se estimó que, en 2010, existían en España 49.763 pacientes en TSR: 22.582 en HD (45%), 2.420 en DP (5%) y 24.761 en Tx (50%); lo que significaría una prevalencia de 1.058 casos pmp. De la misma manera, se estimó que, durante ese mismo año, iniciaron diálisis en nuestro país 6.251 pacientes: 5.409 en HD (87%) y 822 en DP (13%); lo que supondría una incidencia de 133 casos pmp. Finalmente, se estimó que, a lo largo de 2010, se realizaron 2.317 trasplantes renales en España [104].

Se obtuvo un coste directo[1] para la HD de 40.619€ durante el primer año y de 37.968€ en años sucesivos. El coste medio del acceso vascular fue de 2.651€. El coste directo de la DP fue de 27.634€ durante el primer año y de 25.826€ en años posteriores. El coste del acceso peritoneal, incluido el coste del entrenamiento, fue de 1.808€. El coste del trasplante renal fue de 38.313€ el primer año y de 6.283€ a partir del segundo año. Los costes indirectos[2] por pérdida de productividad laboral por morbilidad fueron de 8.025€ en HD, 6.911€ en DP y 5.359€ en Tx. Los costes indirectos por pérdida de productividad laboral por mortalidad fueron de 904€, 518€ y 124€, respectivamente [104].

A partir de las cifras anteriores, se estimaron los costes agregados del TSR para el SNS y la carga de la IRCT para la sociedad española. El coste anual del TSR para el SNS se estimó en aproximadamente 1.400€ millones. Si además se consideran los costes indirectos, la carga anual de la IRCT para la sociedad española rondaría los 1.800€ millones. El 73% de esta carga correspondería a la HD, mientras que un 21% correspondería al Tx y tan sólo un 6% a la DP [104].

Se estimó que la proporción de pacientes incidentes programados en TSR era del 57% en nuestro país. La proporción de pacientes incidentes programados era del 53% en HD y del 83% en DP, lo que supuso un 45% y un 10%, respectivamente, del

[1] Costes expresados en € de 2010. Costes por paciente y año.
[2] Costes expresados en € de 2010. Costes por paciente prevalente y año.

total de pacientes incidentes en TSR. El 2% restante correspondería a los pacientes trasplantados. Los pacientes incidentes programados en HD presentaron un coste del acceso vascular de 928€, frente a los 4.595€ de los pacientes no programados. Además, estos pacientes presentaron una menor mortalidad [104,105].

En un horizonte temporal de 15 años, un aumento en la proporción de pacientes incidentes programados (del 57% al 75%) supuso una disminución en el coste[3] (24.337€ frente a 24.448 €) y un aumento modesto en los AVAC (0,5330 frente a 0,5317), dando lugar a un RCUI de -83.150 €/AVAC (intervención dominante). Sin embargo, la carga anual la IRCT para la sociedad española aumentó (1.666€ millones frente a 1.657€ millones), debido a la mayor supervivencia de los pacientes en HD, que presentan un mayor coste [105].

De la misma manera, un aumento en la proporción de pacientes incidentes programados en DP (del 10% al 30% del total de pacientes incidentes, manteniendo constante la proporción de pacientes programados en el 57%) supuso una reducción en el coste (23.774€ frente a 24.448 €) y una aumento en los AVAC (0,5336 frente a 0,5317), dando lugar a un RCUI de -354.977 €/AVAC (intervención dominante). En este caso, la carga anual de la IRCT para la sociedad española disminuyó (1.625€ millones frente a 1.657€ millones), debido a que los pacientes incidentes en DP presentan menores costes que los pacientes incidentes en HD [105].

Finalmente, la combinación de los dos escenarios anteriores (un 75% de pacientes incidentes programados, con un 30% del total de pacientes incidentes que inician DP de manera programada) produjo una reducción en el coste (23.780€ frente a 24.448€) y un aumento en los AVAC (0,5345 frente a 0,5317), dando lugar a un RCUI de -235.886 €/AVAC (intervención dominante). Nuevamente, la carga anual de la IRCT para la sociedad española disminuyó (1.639€ millones frente a 1.657€ millones) [105].

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[3] Costes expresados en € de 2010. Se incluyeron costes directos e indirectos. Costes y AVAC por paciente y año. Se consideró una tasa de descuento del 3,5% para costes y AVAC.

Se estimó que, cada año, un 4% de los pacientes españoles trasplantados sufrirían fallo del injerto renal y volverían a diálisis de manera tardía. Además de una mayor morbilidad y mortalidad, los pacientes con pérdida del injerto renal presentan una mayor necesidad de fármacos y una mayor frecuencia de hospitalizaciones por complicaciones. Se estimó un coste directo médico[4] de incidencia de 6.627€ para los pacientes que vuelven tardíamente a HD, frente a 2.545€ para los pacientes que lo hacen de manera oportuna. En el caso de la DP, el coste del paciente que vuelve tardíamente a diálisis fue de 3.748€, frente a los 1.819€ del paciente que lo hace oportunamente [106].

En un horizonte temporal de 45 años, al comparar el escenario actual con un escenario ideal en el que todos los pacientes vuelven de manera oportuna a diálisis, se obtuvo un incremento en el coste directo médico[5] de 211€. Este incremento en el coste es consecuencia, sin embargo, de la mayor supervivencia observada en el nuevo escenario, ya que los enfermos renales deben recibir TSR durante toda su vida. El incremento en AVAC fue de 0,0087, dando lugar a un RCUI de 24.390 €/AVAC (intervención eficiente [101,102]). Se cuantificaron los costes indirectos[6] por pérdida de productividad laboral por mortalidad en 29.345€. Al incluir estos costes en el análisis, se obtuvo un RCUI de -146 €/AVAC (intervención dominante) [106].

En las simulaciones realizadas, la probabilidad de aceptar el escenario ideal fue del 62%, pero aumentó hasta el 70% si no se consideraban aquellas situaciones en las que la eficiencia se alcanzaba mediante una disminución en los costes, pero a costa de unos resultados en salud más pobres. Por otro lado, la eficiencia del escenario ideal aumentó a medida que lo hacía la proporción de pacientes que volvían tardíamente a diálisis en el escenario actual (24.428 €/AVAC para una proporción del 1% y 24.390 €/AVAC para una proporción del 100%) [106].

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[4] Costes expresados en € de 2012. Costes por paciente y año.
[5] Costes expresados en € de 2012. Costes y AVAC por paciente y año. Se consideró una tasa de descuento del 3% para costes y AVAC.
[6] Costes expresados en € de 2012. Costes por muerte y año no trabajado.

VII. Discusión

Desde 1996 y anualmente, el Registro de Diálisis y Trasplante de la SEN [2] proporciona datos de incidencia, prevalencia y mortalidad de los pacientes españoles en TSR, así como de la distribución de las distintas modalidades de TSR. Estos datos, aún siendo de gran utilidad, presentan dos principales limitaciones. En primer lugar, los datos registrados por la SEN se hacen públicos varios meses después de que termine el año. En segundo lugar, cada año, la inclusión o exclusión de algunos registros autonómicos provoca que las series publicadas por la SEN presenten una alta volatilidad. En esta investigación, se ha estimado un modelo de regresión no paramétrico que solventa las dos limitaciones anteriores. Por un lado, el modelo permite estimar la tendencia futura de las distintas modalidades de TSR, proporcionando información que no estaba disponible en nuestro país hasta la fecha. Por otro lado, el método de estimación elegido minimiza los posibles sesgos causados por la inclusión de observaciones influyentes en el análisis.

En términos generales, las cifras estimadas por el modelo van en consonancia con las estimaciones para 2010 realizadas con posterioridad por el Registro de Diálisis y Trasplante de la SEN. Sin embargo, según los datos registrados, se lleva más de una década con estabilidad y, por primera vez desde 1996, se observa un ligero descenso en la incidencia de TSR en España, como ocurre en la mayoría de los países desarrollados. Este hecho, por tanto, no ha podido ser capturado por el modelo. Se ha estimado que, en 2010, un 0,1% de la población española estaba en TSR [104].

De acuerdo con los resultados presentados y tal y como han evidenciado estudios previos [50-54], el trasplante es la modalidad de TSR menos costosa a partir del segundo año. También en línea con la literatura existente [19-23], la DP presenta menores costes que la HD. Estos resultados no varían si además se consideraran los costes indirectos por pérdida de productividad laboral, que no habían sido cuantificados en nuestro país hasta la fecha. El trasplante sigue siendo la modalidad de TSR menos costosa, dado que los pacientes trasplantados presentan una mayor supervivencia y una mejor CVRS [48,49], lo que se refleja en mayores tasas de actividad [104]. Por su parte, la DP presenta unos costes indirectos inferiores a los de la HD, dado que los pacientes en DP muestran una mayor supervivencia [2,26,27] y mayores tasas de ocupación [104].

Según las estimaciones realizadas, el TSR supone un coste para el SNS equivalente al 2,2% del gasto sanitario público en España, que fue de 64.000€ millones en 2010 [107]. Un paciente en TSR supondría, por tanto, un gasto anual 22 veces superior al gasto sanitario público per cápita en España. Sin embargo, la única alternativa al TSR para el paciente terminal es la muerte, situación que no sería aceptable en una sociedad avanzada.

La mayor parte del coste del TSR corresponde a la HD, como consecuencia del elevado número de pacientes tratados bajo esta modalidad y de unos costes directos e indirectos por paciente más elevados. Dado que el número de trasplantes que se pueden realizar viene limitado por la disponibilidad de órganos, tanto desde el punto de vista del derecho del paciente a elegir la modalidad de diálisis que mejor se adapta a sus necesidades [14-18,108], como desde el punto de vista económico (minimización de costes) [104], las autoridades sanitarias deberían promover el inicio programado en diálisis y, particularmente, el inicio programado en DP.

Casi la mitad de los pacientes españoles incidentes en diálisis son pacientes no programados. De acuerdo con otros trabajos previos [39,42-46], los pacientes incidentes programados en HD presentan menores costes que los pacientes no programados, como consecuencia del menor coste del acceso vascular [104], además de una mayor supervivencia [39]. Un incremento en la proporción de pacientes incidentes programados en diálisis proporcionaría mejores resultados en salud y un menor coste por paciente que la actual situación en España. Por su parte, un aumento en la proporción de pacientes incidentes programados en DP no sólo resultaría una intervención dominante, sino que sería un factor clave para lograr una reducción en la carga de la IRCT para la sociedad española [105].

Las estructuras de atención al paciente pre-terminal ya existen en nuestro país, particularmente las llamadas consultas de enfermedad renal crónica avanzada (ERCA). Además, las principales sociedades de Atención Primaria y Atención Especializada, semFYC y SEN, han elaborado un documento de consenso sobre el diagnóstico, los objetivos terapéuticos y los criterios de derivación al nefrólogo del paciente renal [1]. La formación del personal en todos los hospitales públicos donde existan unidades de HD, las consultas de ERCA y la corresponsabilización o cesión de parte de las consultas de HD a nefrólogos especializados en DP serían factores clave para garantizar el derecho del paciente a elegir el tratamiento que mejor se adapte a sus necesidades y para alcanzar una mayor eficiencia global del sistema.

Los expertos consideran que, en la actualidad, la práctica totalidad de los pacientes españoles que sufren fallo del injerto renal vuelven a diálisis de manera tardía. Esta situación afectaría a unos 1.000 pacientes españoles trasplantados cada año [106]. Además de una mayor morbilidad y mortalidad [65,67-72], los pacientes con pérdida del injerto renal presentan una mayor necesidad de fármacos [73,74] y una mayor frecuencia de hospitalizaciones como consecuencia de complicaciones [64].

La vuelta oportuna a diálisis tras el fallo del injerto renal resultaría una intervención eficiente en nuestro país, considerando los umbrales de disponibilidad a pagar comúnmente aceptados [101,102]. Sin embargo, conllevaría un ligero incremento en los costes directos médicos, como consecuencia de la mayor supervivencia que se alcanzaría y dado que los enfermos renales deben recibir TSR durante toda su vida. Si además se consideran los costes indirectos por pérdida de productividad laboral por mortalidad, la vuelta oportuna a diálisis resultaría una intervención dominante. Cabe esperar que la inclusión de costes indirectos por pérdida de productividad laboral por morbilidad propicie una reducción aún mayor del RCUI obtenido. Sin embargo, hasta la fecha, no se dispone de datos de actividad específicos para los pacientes que sufren pérdida del injerto renal.

La negativa del paciente a volver a diálisis y la reticencia del clínico a asumir el fracaso del trasplante parecen ser las causas principales de la vuelta tardía a diálisis. La información disponible para el paciente y la inclusión de recomendaciones específicas para este grupo de pacientes dentro de las guías de práctica clínica existentes resultarían factores clave para lograr unos mejores resultados en salud y para garantizar una mayor eficiencia global del sistema.

VIII. Conclusiones

En esta tesis doctoral, se ha presentado una evaluación económica del TSR en España. Se han analizado los costes del TSR para el SNS y se ha aproximado la carga de la IRCT para la sociedad española, se ha evaluado la RCUI de intervenciones de aumento en la proporción de pacientes incidentes programados en diálisis y también la eficiencia de intervenciones de disminución en la proporción de pacientes que vuelven tardíamente a diálisis tras el fallo del injerto renal.

Se podrían destacar las siguientes conclusiones de esta investigación:

1. En 2010, un 0,1% de la población española se encontraba en TSR. La mitad de estos pacientes eran portadores de un trasplante renal funcionante y un 45% de los pacientes estaba en HD, mientras que la DP tenía una prevalencia mucho menor.
2. El trasplante renal es la modalidad de TSR menos costosa a partir del segundo año. Respecto a las modalidades de diálisis, la DP presenta menores costes que la HD. Los pacientes incidentes programados en HD también muestran un coste del acceso vascular inferior al de los pacientes no programados.
3. El trasplante renal presenta menores costes indirectos por pérdida de productividad laboral (por morbilidad y mortalidad) que la diálisis. La DP resulta nuevamente menos costosa que la HD. Por su parte, los pacientes programados en HD también presentan menores costes indirectos que los pacientes no programados.
4. El TSR supone un coste anual agregado elevado para el SNS, de unos 1.400€ millones. La carga de la IRCT para la sociedad española rondaría los 1.800€ millones anuales. El mayor coste agregado de la HD respecto al resto de modalidades es consecuencia del elevado número de pacientes tratados

bajo esta modalidad y de unos costes directos e indirectos por paciente más altos.

5. Casi la mitad de los pacientes españoles incidentes en diálisis son pacientes no programados. Un incremento en la proporción de pacientes incidentes programados en diálisis proporcionaría un menor coste por paciente y mejores resultados en salud que la actual situación en España (intervención dominante). Por su parte, un aumento en la proporción de pacientes incidentes programados en DP no sólo resultaría una intervención dominante, sino que sería un factor clave para lograr una reducción en la carga de la IRCT para la sociedad española.
6. Dado que el número de trasplantes que se pueden realizar viene limitado por la disponibilidad de órganos, tanto desde el punto de vista clínico, como desde un punto de vista de económico, las autoridades sanitarias deberían promover el inicio programado en diálisis y particularmente el inicio programado en DP.
7. La práctica totalidad de los pacientes españoles que sufren fallo del injerto renal vuelven a diálisis de manera tardía. Además de una mayor morbilidad y mortalidad, estos pacientes presentan una mayor necesidad de fármacos, una mayor frecuencia de hospitalizaciones y, por tanto, un mayor coste que los pacientes que vuelven a diálisis oportunamente.
8. Si comparamos la situación actual en España con un escenario ideal en el que todos los pacientes con fallo del injerto vuelven oportunamente a diálisis, se incrementarían ligeramente los costes directos médicos, debido a la mayor supervivencia alcanzada, pero se obtendrían mejores resultados en salud. Esta intervención resultaría eficiente si se consideran los umbrales de disponibilidad a pagar frecuentemente aceptados. Si además se tuvieran en cuenta los costes indirectos, el inicio oportuno en diálisis tras el fallo del injerto resultaría una intervención dominante.

9. Las autoridades sanitarias deberían promover una vuelta oportuna a diálisis tras el fallo del injerto renal mediante recomendaciones específicas para este grupo de pacientes dentro de las guías existentes, proporcionando, además, una adecuada información al paciente.

IX. Abreviaturas

ACE	análisis coste-efectividad
AVAC	años de vida ajustados por calidad
CVRS	calidad de vida relacionada con la salud
CRI	chronic renal insufficiency
DP	diálisis peritoneal
ETS	evaluación de tecnologías sanitarias
ERCA	enfermedad renal crónica avanzada
FG	filtrado glomerular
HD	hemodiálisis
IRC	insuficiencia renal crónica
IRCT	insuficiencia renal crónica terminal
NHS	National Health System
pmp	por millón de población
PD	peritoneal dialysis
RCUI	relación coste-utilidad incremental
RRT	renal replacement therapy
SEN	Sociedad Española de Nefrología
semFYC	Sociedad Española de Medicina Familiar y Comunitaria
SNS	Sistema Nacional de Salud
TCRI	terminal chronic renal insufficiency
TSR	tratamiento sustitutivo renal
Tx	trasplante renal

X. Referencias

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XI. Informe del factor de impacto de las publicaciones

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☐	45	NAT REV UROL	1759-4812	489	4.415	4.415	0.344	61	1.8	0.00329	1.691
☐	46	NEFROLOGIA	0211-6995	694	1.000	0.688	0.592	76	4.4	0.00110	0.101
☐	47	NEPHROL DIAL TRANSPL	0931-0509	19988	3.396	3.375	0.834	596	6.0	0.04995	0.964
☐	48	NEPHROL THER	1769-7255	208	0.465		0.060	67	3.4	0.00062	
☐	49	NEPHROLOGY	1320-5358	1373	1.311	1.454	0.371	105	4.4	0.00478	0.406
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☐	53	NEUROUROL URODYNAM	0733-2467	3139	2.958	2.729	0.384	198	5.5	0.00802	0.750
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☐	55	PELVI-PERINEOLOGIE	1778-3712	19	0.074		0.000	30		0.00003	
☐	56	PERITON DIALYSIS INT	0896-8608	2807	2.097	1.919	0.392	97	6.9	0.00374	0.352
☐	57	PROG UROL	1166-7087	948	0.578	0.529	0.050	179	4.6	0.00107	0.056
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☐	9	BMC HEALTH SERV RES	1472-6963	3262	1.660	2.254	0.182	346	3.8	0.01776	0.778
☐	10	BMC MED RES METHODOL	1471-2288	2259	2.668		0.231	173	5.1	0.01103	
☐	11	BMJ QUAL SAF	2044-5415	119			0.667	165	0.5	0.00001	
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☐	13	DISABIL HEALTH J	1936-6574	92	0.982	0.988	0.273	33		0.00048	0.313
☐	14	DRUG INF J	0092-8615	598	0.360	0.516	0.130	69	>10.0	0.00137	0.215
☐	15	EUR J CANCER CARE	0961-5423	1174	1.171	1.437	0.453	95	5.6	0.00305	0.408
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☐	18	GEOSPATIAL HEALTH	1827-1987	330	3.000	3.038	0.467	30	3.3	0.00110	0.574