Chronic kidney disease in Spain: analysis of patient characteristics, incidence and direct medical costs (2011-2017)

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Abstract

Objectives: To review the characteristics of patients with chronic kidney disease (CKD) attended in primary and specialised care centres in Spain, analyse patients' use of medical resources and direct medical costs of specialised care.

Methods: Records of patients with CKD admitted in primary and specialised healthcare centres in Spain between 2011 and 2017 from two national discharge databases were analysed in a retrospective multicentre observational study. Records were classified into 1 to 5 CKD stages plus a 5b stage indicating end-stage renal disease.

Results: Most of the patients registered in hospital settings were in stage 5. Registered secondary conditions included hypertensive chronic kidney, diabetes, anaemia, hypercholesterolaemia and hypertension. The number of cases registered in primary care settings increased over time, whereas in specialised care centres incidence decreased; hospital incidence of CKD in 2017 was 10.72 per 10,000 persons. Mean in-hospital mortality was 5.90%, and remained stable during the study period. Mortality was associated to respiratory and heart failure. Mean length of hospital stay was 8.19 days, decreasing over the study period, whilst increasing with CKD progression. Mean annual direct medical cost of specialised care was €10,436 per patient. Complications of a transplant and bacterial infections were responsible for major increases in medical costs, that otherwise decreased over the study period.

Conclusions: The costs of specialised care decreased with the length of hospital stay reduction. Cardiovascular risk factors were crucial in in-hospital mortality. This study

provides population-based data to assist decision-makers at the national level and to contribute to worldwide evaluations and disease surveillance.

Keywords: Chronic kidney disease; incidence; mortality; comorbidity; direct medical costs.

Short title: Chronic kidney disease in Spain

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Introduction

Chronic kidney disease (CKD) is a major social and economic burden across the socioeconomic spectrum, with risk factors that are influenced by sex, ethnicity and lifestyle. Its estimated global prevalence is between 11 and 13%, increasing worldwide, with the fastest growth taking place in low and middle-income regions [1-3]. CKD is associated with a reduced quality of life and over 35 million global all-age disability-adjusted life-years (DALYs) estimated in 2016 [4]. In terms of mortality, kidney diseases were the 12th cause of death worldwide in 2016, and the percentage of all deaths attributable to CKD globally was estimated to increase a 33.7% between 2007 and 2017, when it caused over 1.2 million deaths [5,6]. In Spain, the prevalence of CKD remains around the 15%, although in males it is estimated to reach the 23%, and mortality rates are similar to global estimations [7,8].

The Kidney Disease: Improving Global Outcomes (KDIGO) guideline statements defined CKD as abnormalities of kidney structure or function, present for more than 3 months, with implications for health and classified it based on cause, the glomerular filtration rate (GFR) category, and albuminuria category (CGA) [9]. CKD has been associated to conditions such as vascular disease and diabetes that affect health outcomes [9].

Overall, this growing social burden is accompanied by great direct and indirect economic costs. In addition, evidence suggests a relation between costs and disease progression and with the presence of comorbid conditions that requires further evaluation [10].

Obtaining and evaluating real-world data is crucial to tackle the challenge that is CKD, providing evidence that reflects current practice, patients' characteristics and needs, in order to improve understanding and treatment of chronic kidney disease [11].

This study aimed to provide an updated description of the characteristics of patients with CKD attended in primary and specialised care centres in Spain, to review CKD epidemiology within these settings and to analyse patients' use of healthcare resources and the associated direct medical costs.

Methods

Study design

A retrospective multicentre observational study was set to investigate the characteristics and use of healthcare resources of patients with CKD attended in primary and specialised healthcare centres in Spain between 2011 and 2017. Admission records were obtained from two national discharge databases managed by the Spanish Ministry of Health that gather medical information from 90% of public and private hospitals in Spain, and around 10% of primary care admissions, respectively [12,13]. Any healthcare visit was considered an admission (inpatient and outpatient) in each dataset. Primary care admissions are inherently outpatient and specialised care inpatient and outpatient admissions are discernible by the length of stay parameter, including both inpatient and outpatient care.

Data extraction

All records in which CKD was the principal diagnosis or admission motive were extracted from each database by means of the corresponding code. Primary care files are codified with the International Classification of Primary Care, Second edition (ICPC-2), thus, the

code U99.01 corresponding to CKD was used to claim patient records in this setting. Specialised care diagnoses are codified with the International Classification of Diseases, ninth and tenth Revision, Clinical Modification codes (ICD-9-CM and ICD-10-CM). These categorise patients with CKD according to their GFR category into stages 1 to 5, with an additional code strictly indicating end-stage renal disease (ESRD) (Table 1) [14,15]. Patients in an unspecified CKD stage were codified separately. CKD stage was determined upon admission and could vary during the admission process after re-evaluation.

The selected patient files were obtained from the Spanish Ministry of Health previously recoded and anonymised in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Primary care and hospital files were recoded independently, with no correlation of patient codes. This research did not involve human participants and there was no access to identifying information; in this context the Spanish legislation does not require patient consent and ethics committee approval [16].

Study variables

Records of admissions from primary and specialised care contained raw information registered on admission, detailing the patient profile and admission details. Data gathered form primary care records included patients' sex, age, date of admission and admission motive; whereas the specialised care database registers additional information including type of admission (inpatient/outpatient, scheduled/urgent), type of discharge (including death), service that discharged the patient, length of hospital stay (LOHS), up to 20 secondary diagnoses registered during the admission, medical procedures and cost of the admission.

130 ***Data analysis***

131 Single-patient data obtained from the first admission registered per patient due to CKD
132 was used to characterise the patient population in both primary and specialised care.
133 Direct medical costs of specialised care were calculated using the cost per admission
134 originally indicated in each admission file; such cost is estimated by using the standardised
135 average expenses of admissions and medical procedures determined by the Spanish
136 Ministry of Health [17]. This calculation included all expenses related to specialised care
137 admissions: treatment (examination, medication and surgery), nutrition, costs associated
138 to personnel, medical equipment and resources per groups of patients.

139 Frequencies and percentages are presented for dichotomous variables and mean and
140 standard deviation were calculated for continuous variables. Hospital incidence was
141 calculated as the proportion of patients admitted with CKD as the admission motive within
142 the database. To assess the association of secondary conditions with in-hospital mortality,
143 odd ratios (OR) with 95% confidence interval (CI) were used, calculated from frequency of
144 diagnoses, using the group of patients non-deceased during the hospitalisation as the
145 reference group. Readmission was defined as a second admission within a 30-day period
146 following discharge. Patients with an unspecified CKD stage were excluded from
147 comparative analysis.

148 Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0.
149 Released 2011 (IBM Corporation, Armonk, NY, USA) and Microsoft Excel© Professional
150 Plus 2010 (Microsoft Corporation, Redmond, WA, USA).

151 # Results

Patient characteristics

Records from 125,674 patients registered with CKD were obtained from the primary care database, 48.24% of the patients were males with a mean age of 77.27 years (SD=12.64). Specialised care records were obtained from 24,389 patients, with a 62.05% of male patients. Mean age of the total patient population in this setting was 60.79 years (SD=19.69) (Table 2). Overall, renal dialysis was registered in 23.47% of patients and renal transplants in 28.58%; 75.54% of those transplants were from a cadaver, 12.13% from a live related donor and 6.40% from a live non-related donor.

The secondary conditions that were registered in patients admitted with CKD are listed in Table 3. Hypertensive chronic kidney disease was the most commonly diagnosed condition, followed by diabetes, anaemia, hypercholesterolaemia and hypertension. Patients in stage 5b (ESRD) displayed higher rates of secondary hyperparathyroidism of renal origin, bacterial infection and complications derived from a transplanted kidney.

Hospital incidence and in-hospital mortality

Hospital incidence of CKD was 10.72 per 10,000 patients in 2017, 11.04 for males and 7.18 for females, with a decreasing tendency over the study period (Figure 1A). Contrarily, the number of admissions due to CKD increased significantly over time in primary care centres (Figure 1B).

Mean in-hospital mortality was 5.90% during the study period. No significant differences in this rate were observed between 2011 and 2017. Mean in-hospital mortality was 6.30%, 4.54% and 5.91% in patients in CKD stage 4, 5a and 5b, respectively. Overall mortality was greater in females than in males (4.40% vs. 5.70%; $p<0.001$).

The diagnosis of secondary conditions was evaluated as well in deceased patients. In-hospital mortality was predominantly associated with respiratory failure (18.20%, OR=5.72; 95%CI 4.78-6.85) and heart failure (18.10%, OR=3.77; 95%CI 3.16-4.49), followed by atrial fibrillation (23.54%, OR=2.97; 95%CI 2.55-3.46), disorders of fluid electrolyte and acid-base balance (23.54%, OR=2.62; 95%CI 2.25-3.06), chronic ischemic heart disease (12.34%, OR=2.31; 95%CI 1.89-2.83), chronic airway obstruction (11.61%, OR=2.02; 95%CI 1.64-2.48) and acute kidney failure (10.88%, OR=1.56; 95%CI 1.26-1.92).

Use of medical resources and costs

Referral for specialist treatment was only registered in 15.41% of primary care admissions, and only in 12.23% of those admissions patients were referred to nephrology and urology services. Nonetheless, 62.39% of the analysed hospital admissions were into nephrology services and 11.31% into internal medicine services. Only 3.15% of specialised care admissions were outpatient admissions.

In early CKD stages, most hospital admissions were scheduled, with a higher percentage of urgent admissions found in advanced CKD stages (stage 1, 73.33%; stage 2, 65.92%; stage 3, 56.58%; stage 4, 46.18%; stage 5a, 56.98%; stage 5b, 53.82%) (Figure 2A). Mean length of hospital stay (LOHS) was 8.19 days (0-334), increasing with CKD progression, especially in patients under 61 years of age ($p<0.001$, Stage 1 vs. Stage 5b) (Figure 2B). Additionally, LOHS decreased significantly over time, from 8.85 days in 2011 to 7.20 days in 2017 ($p<0.001$). Patients' readmission rate was 13.07% over the study period.

Kidney transplants and haemodialysis were the most common medical procedures registered for these patients, listed in 24.18% and 19.85% of all admissions, respectively,

followed by various diagnosis techniques that were more common in early disease stages (Table 4)

Over the study period, 6,706 kidney transplants were registered, performed in 6,610 patients, mainly in stage 5. Mean age of these patients was 51.70 years and mean length of hospital stay was 16.52 days.

Mean annual direct medical cost of specialised care was €10,436 per patient, decreasing significantly over the study period from €11,739 in 2011 to €8,227 in 2017 ($p<0.001$) due to the decrease in the costs incurred by patients in Stage 5 (Figure 3). In addition, cost per patient increased significantly with CKD stage ($p<0.001$, Stage 1 vs. Stage 5b). Mean costs per patient over the study period were: €4,984 in stage 1, €4,535 in stage 2, €4,770 in stage 3, €5,887 in stage 4, €9,394 in stage 5a and €14,329 in stage 5b, with a 1.23 fold increase between stages 3 and 4, a 1.57 fold increase between stages 4 and 5a and a 1.44 fold increase between stages 5a and 5b.

On the other hand, the average cost per admission was €8,660, increasing to €10,213 in admissions to receive haemodialysis and to €23,049 in admissions in which a renal transplant was registered. Several secondary conditions were associated with raises in admission costs, with the highest costs associated to complications of a renal transplant (Table 5).

Finally, the patient sample included in this study represented a total annual cost of €36.4 million in specialised care for the Spanish healthcare system, €28.6 million for dialysis and transplants alone.

Discussion

CKD is a major public health and social burden worldwide, with risk factors that include diabetes, systemic infections, autoimmune disorders, vascular disease and environmental toxicity, although aetiology is in many cases unknown [9,18]. The access to real-world hospitalisation data allows the evaluation of current practice and contributes with crucial information to tackle major risk factors for CKD and to improve management and health outcomes.

Previous studies indicate a prevalence of CKD in Spain of around 15%, and a mortality rate that could be increasing, as measured in the global burden of disease studies [7,8]. In the present study however, in-hospital mortality remained stable over the study period, which could be indicative of shifts in clinical practice rather than variations in disease mortality. The number of admissions linked to CKD in primary care settings increased over the study period, whereas hospital incidence, in specialised healthcare centres, decreased. An increasing tendency to treat milder symptoms of the disease in primary care must be considered when interpreting these data. Global meta-analyses indicate a higher prevalence of CKD stage 3, whilst most of the patients attended in hospital care were in stage 5 [1]. Indeed, the KDIGO guidelines recommend referral to specialist kidney care services when GFR is under 30 mL/min, namely stages 4 and 5 [9]. Another factor to be considered is the introduction of home haemodialysis as an alternative to the recurrent admissions required for in-hospital dialysis. This practice has increased progressively in many countries, yet, no records are available for Spain and its inclusion in standard practice appears distant [19]. In this study, renal dialysis and transplants in hospital settings corresponded principally to patients in CKD stage 5. A small number of patients in

early CKD stages registered renal replacement therapy, these cases corresponded to patients that changed CKD stage after an intervention or to other particular situations that could not be evaluated.

Secondary conditions corresponded to common CKD comorbidities. Hypertensive chronic kidney disease and diabetes were the most common conditions, presumably registered as the cause of CKD, followed by conditions with a renal origin, such as anaemia or secondary hyperparathyroidism [20,21]. In particular, the Spanish population with CKD had presented an important prevalence of cardiovascular risk factors as described in the EPIRCE study [22]. Indeed, mortality in this study was associated with heart failure and several cardiovascular events. For the analysis per CKD stage, patient classification process must be taken into account. CKD stage was assigned upon admission and stage often changed during the hospitalisation process as status was re-evaluated.

On the other hand, disorders of fluid electrolyte and acid-base balance appeared relevant in patients in stages 3 and 4 and were associated with in-hospital mortality. Acidosis and hyperkalaemia in CKD have been previously associated with increased morbidity and mortality, as current recommendations appeal for a rapid diagnosis and dietary and pharmacological treatment to manage the effects of these conditions [23-25]. The presence of these comorbid conditions may be distinctive in transplant and non-transplant patients, however, it could not be analysed in this study.

Previous studies suggest that LOHS is highly dependent on the time elapsed to nephrology referral; while admissions with early referral had an average LOHS of 13.5 days, late referral registered LOHS of 25.3 days [26]. Late referral has also been associated with

major hospitalisation rates, higher mortality and worsened health outcomes [27]. The mean LOHS estimated herein, of 8.19 days, could be indicative of early referrals; however, this figure must be considered within a global context of decreasing LOHS [28].

In terms of costs, the decreasing tendency measured in the direct medical cost per patient over the study period could be the result of the improvement of disease management and the effort to reduce hospitalisation times. The annual costs of specialised care, of €10,436 per patient, increased in association with complications of renal transplants and bacterial infections. Global evaluations show significant differences in cost estimations; a Italian study estimated a total medical cost of €4,508 per person on average (2016 Euros), €8,078 when summing non-medical and indirect costs, whereas costs per patient in the United States reached the €17,052 ($20,162, 2012 USD) [10,29]. In terms of CKD stage, systematic reviews have identified increases in costs of 1.1-1.7 fold between CKD stage 3 and stages 4-5 [30]. Herein, progression between CKD stages 3 and 4 was associated to an increase in medical costs of 1.23 fold, 1.57 fold between stages 4 and 5a.

Efforts to reduce medical costs are centred on the improvement of disease management, which may reduce length of hospital stays, and early referral. Moreover, nephrologist-based multidisciplinary care has been associated with cost reduction as well as improved health outcomes [31]. The effect of bacterial infections in increasing hospitalisation costs must be considered in the revision of treatment protocols.

A number of limitations may have influence in the results of this study. This study included all the patients with CKD registered in the primary care and specialised care databases. The patient sample included does not aim to reflect the situation of CKD in the general

Spanish population; a bias towards big hospitals that treat an important portion of severe cases cannot be discarded. Hospital incidence estimations are limited to the cases registered in the database, which must be taken into account when comparing with general evaluations. Similarly, data regarding renal transplants is subjected to this restriction, and transplants performed before the study period or in other healthcare centres were not included. Further studies will be required to evaluate the total burden associated to CKD, considering primary care costs, indirect costs and non-medical costs.

Conclusions

The decreasing tendency measured in specialised care costs responds to the reduction of the length of hospital stay and disease management improvement. Cardiovascular risk factors were crucial in in-hospital mortality. Overall, this study provides new data, characterising the Spanish population hospitalised due to CKD, to assist decision-makers at the national level and to contribute to worldwide evaluations with real-world population-based data.

Transparency section

Declaration of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of financial and other interest

The authors declare that they have no competing interests.

Data Availability Statement

The data that support the findings of this study is available from the Spanish Ministry of Health via the Unit of Health Care Information and Statistics (Spanish Institute of Health Information) for researchers who meet the criteria for access to confidential data at https://www.mscbs.gob.es/estadEstudios/sanidadDatos/home.htm

Author contributions

JD contributed to the investigation by analysing and interpreting the burden associated to CKD in Spain and was a major contribution in the intellectual content revision. AM analysed the current situation of CKD in Spain, interpreted the statistical data and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Patient classification criteria according to ICD-9 and ICD-10 codes

ICD-9 code	ICD-10 code	CKD Stage	Definition
585.1	N18.1	Stage 1	Kidney damage with normal or high GFR (GFR 90 to 130 mL/min)
585.2	N18.2	Stage 2	Kidney damage with mild GFR reduction (GFR 60 to 89 mL/min)
585.3	N18.3	Stage 3	Moderate dysfunction (GFR 30 to 59 mL/min); includes the KDIGO defined stages 3A and 3B [9]
585.4	N18.4	Stage 4	Severe dysfunction (GFR 15 to 29 mL/min); pre renal replacement therapy
585.5	N18.5	Stage 5a	Kidney failure or permanent renal replacement therapy (GFR < 15 mL/min); excludes CKD requiring chronic dialysis.
585.6	N18.6	Stage 5b	ESRD (GFR < 15 mL/min); CKD stage 5 requiring chronic dialysis.
585.9	N18.9	Unspecified	Includes unspecified chronic renal disease, chronic renal failure, chronic renal insufficiency and chronic uraemia.

GFR, glomerular filtration rate; ERSD, end-stage renal disease.

Table 2 Characteristics of patients registered with chronic kidney disease in specialised care centres in Spain, number of admissions and dialysis/renal transplants registered upon admission.

CKD stage	Patients (N)	Males (%)	Age (SD)	Admissions (N)	Renal dialysis (%)	Renal transplant (%)
Stage 1	119	51.26	47.01 (24.44)	135	0.00	0.00
Stage 2	294	62.24	53.12 (26.06)	311	2.25	0.45
Stage 3	1,452	64.67	61.78 (21.53)	1603	0.35	0.06
Stage 4	1,842	60.97	64.04 (22.41)	2133	6.91	3.34
Stage 5a	5,223	61.78	60.38 (20.11)	6509	28.65	21.68
Stage 5b	10,691	62.82	57.87 (17.83)	13377	32.87	47.73
Unspecified	4,768	60.51	67.82 (19.18)	5323	9.67	11.07
Total	24,389	62.05	60.79 (19.69)	29391	23.47	28.58

Table 3 Secondary conditions registered in more than 10% of admissions per chronic kidney disease stage in specialised care centres.

Condition	Stage 1 (N=135)	Stage 2 (N=311)	Stage 3 (N=1603)	Stage 4 (N=2133)	Stage 5a (N=6509)	Stage 5b (N=13377)
Hypertensive chronic kidney disease	21.48	30.87	43.42	39.43	43.48	42.92
Diabetes	17.04	18.65	33.19	43.41	33.42	26.68
Anaemia	8.89	15.43	24.95	35.68	32.26	27.79
Hypercholesterolemia and hyperlipidaemia	17.78	26.37	32.38	28.88	24.83	23.06
Unspecified essential hypertension	19.26	19.61	22.58	26.86	23.48	15.48
Disorders of fluid electrolyte and acid-base balance	5.19	12.22	16.72	21.00	11.94	6.20
Secondary hyperparathyroidism	2.96	1.61	3.31	9.38	13.70	12.14
Bacterial infection	8.15	4.50	4.68	7.08	7.70	12.66
Nephritis	11.11	4.82	8.73	9.10	8.96	8.45
Atrial fibrillation	3.70	5.14	10.04	11.11	7.07	6.49
Complications of transplanted kidney	1.48	0.32	0.44	0.70	4.69	12.21
Overweight and obesity	12.59	9.97	11.35	8.67	7.14	5.88
Acute kidney failure	4.44	4.82	10.48	8.11	3.40	5.49

475 **Table 4 Medical procedures registered in more than 10% of admissions per chronic**

476 **kidney disease stage**

Procedure	Stage 1 (N=135)	Stage 2 (N=311)	Stage 3 (N=1603)	Stage 4 (N=2133)	Stage 5a (N=6509)	Stage 5b (N=13377)
Transplant of kidney	0.00	0.43	0.55	2.88	17.73	39.28
Haemodialysis	0.00	2.15	3.12	5.96	23.43	27.05
Arteriovenostomy for renal dialysis	0.00	0.43	1.01	11.15	22.23	16.05
Venous catheterisation for renal dialysis	7.53	4.72	5.32	8.40	16.71	11.94
Percutaneous biopsy of kidney	49.46	36.48	33.67	9.42	4.16	7.54
Ureteral catheterization	0.00	1.29	0.73	0.90	5.72	11.17
Diagnostic ultrasound of urinary system	17.20	23.18	20.64	18.01	17.82	27.22
Diagnostic ultrasound of abdomen	19.35	16.31	20.28	18.85	11.83	8.82
Chest x-ray	8.60	9.44	12.57	16.92	16.73	10.04
Electrocardiogram	6.45	11.59	11.38	14.49	13.78	8.18
Microscopic examination of blood	20.43	12.45	15.69	17.18	16.83	8.74
Microscopic examination of specimen from bladder, urethra, and of urine	10.75	7.73	10.73	9.04	9.01	4.29

Renal scan and radioisotope function study	3.23	1.29	1.10	1.47	5.00	11.46
Transfusion of packed cells	5.38	4.72	6.97	9.49	13.10	15.33

Table 5 Mean cost per admission due to chronic kidney disease per comorbid conditions

Secondary conditions	Mean cost per admission
Complications of transplanted kidney	€ 20,322
Bacterial infection	€ 15,341
Acute kidney failure	€ 12,747
Secondary hyperparathyroidism of renal origin	€ 12,184
Anaemia in chronic kidney disease	€ 10,566

Figures

Figure 1 (A) Hospital incidence of chronic kidney disease (CKD) and (B) annual number of admissions linked to CKD registered in primary care settings in Spain.

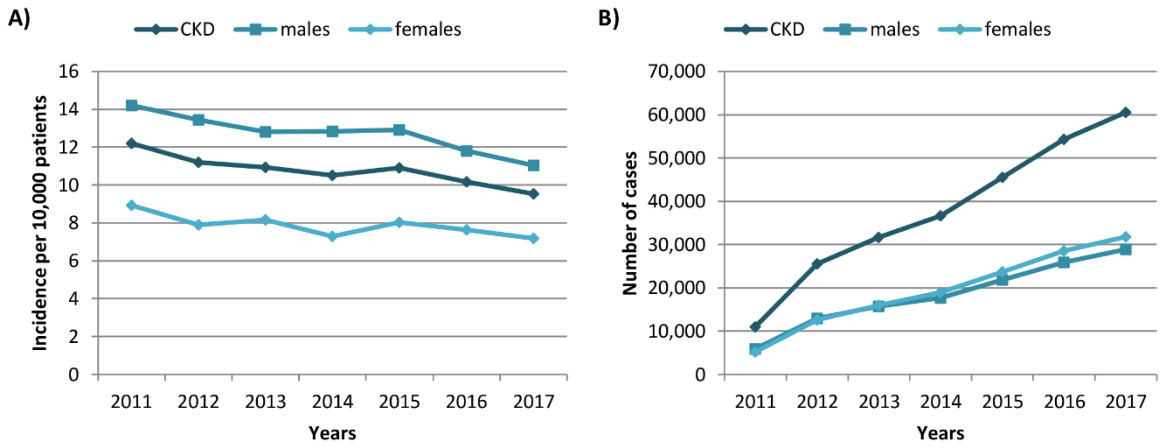

Figure 2 (A) Percentage of urgent and scheduled hospital admissions per chronic kidney disease (CKD) stage and (B) mean length of hospital stay per age groups per chronic kidney disease stage. Stage 1, GFR 90-130 mL/min; stage 2, GFR 60-89 mL/min; stage 3, GFR 30-59 mL/min; stage 4, GFR 15-29 mL/min; stage 5a, GFR <15 mL/min without chronic dialysis; stage 5b, GFR <15 mL/min with chronic dialysis.

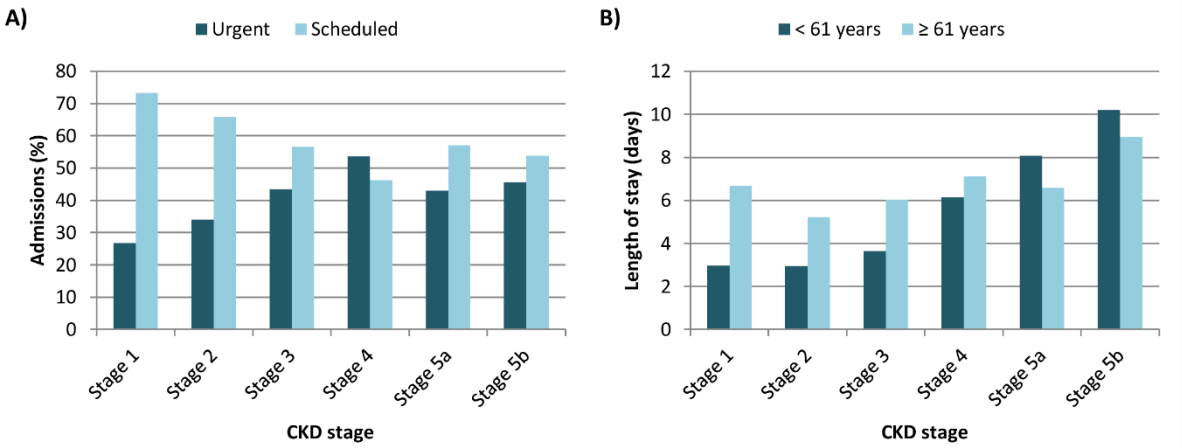

Figure 3 Annual direct medical cost per patient per chronic kidney disease stage. Stage 1, GFR 90-130 mL/min; stage 2, GFR 60-89 mL/min; stage 3, GFR 30-59 mL/min; stage 4, GFR 15-29 mL/min; stage 5a, GFR <15 mL/min without chronic dialysis; stage 5b, GFR <15 mL/min with chronic dialysis.