Cost of Medical Care for Chronic Kidney Disease and Comorbidity among Enrollees in a Large HMO Population

DAVID H. SMITH,*† CHRISTINA M. GULLION,* GREGORY NICHOLS,* DOUGLAS SCOTT KEITH,‡ and JONATHAN BETZ BROWN*

**Kaiser Permanente Center for Health Research, Portland, Oregon; †University of Washington School of Pharmacy, Portland Oregon; ‡Kaiser Permanente Northwest Region, Department of Nephrology, Portland Oregon.*

Abstrct. Chronic kidney disease (CKD) afflicts up to 20 million people in the United States, but little is known about their health care costs. The authors analyzed costs and resource use associated with CKD by using National Kidney Foundation staging definitions. Patients insured through a large health maintenance organization with a laboratory finding of CKD (defined as estimated GFR between 15 and 90 ml/min per 1.73 m^2 in 1996 followed by a second GFR below 90 at the next creatinine measurement occurring at least 90 d later) were followed from 1996 for up to 66 mo. The final cohort included 13,796 persons with CKD and their age- and gender-matched controls; 1741 in stage 2; 11,278 in stage 3; and 777 in stage 4. Depending on stage, cases had 1.9 to 2.5 times more prescriptions, 1.3 to 1.9 times more outpatient visits, were 1.6 to 2.2 times more likely to have had an inpatient stay, and had 1.8 to 3.1 more stays than did controls. Total per patient follow-up costs were [$total, (95% CI) cases and controls, respectively] $38,764 (95% CI, 37,033 to $40,496) and $16,212 (95% CI, $15,644 to $16,780) in stage 2; $33,144 (95% CI, $32,578 to $33,709) and $18,964 (95% CI, $18,730 to $19,197) in stage 3; and $41,928 (95% CI, $39,354 to $44,501) and $19,106 (95% CI, $18,212 to $20,000) in stage 4. Cases with no CKD-related comorbidities had costs double that of controls with no CKD-related comorbidities, and comorbidities related to CKD were more costly to manage than CKD alone. Future research in this area could be usefully directed toward analyzing the clinical and economic consequences of better managing or preventing comorbidities in patients with CKD.

Between 4 million (1) and 20 million (2) Americans are affected with chronic kidney disease (CKD), and nearly 350,000 people in the United States were treated for end-stage renal disease (ESRD) in 1999 (3). The age-, gender-, and race-adjusted incidence rate of ESRD increased by 65% from 1990 to 2001 (3). Although ESRD represents a population with severe disease, these data suggest that those with CKD make up the vast majority among patients with kidney disease. The recent NKF K/DOQI guidelines (National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification) highlight a growing recognition of the public health concern around the rising incidence and prevalence of kidney failure (2). Focusing appropriate attention on those with CKD may prove to be an effective method of reducing the health and economic burden of both ESRD and CKD.

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Dr. Keith's current affiliation: Department of Nephrology, McGill University Medical School, Montreal, Quebec, Canada.

Correspondence to Dr. David H. Smith, Investigator, Kaiser Permanente Center for Health Research, 3800 N Interstate Ave, Portland, OR 97211. Phone: 503-335-6302; Fax: 503-335-2428; E-mail david.h.smith@kpchr.org

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The economic burden of CKD has not been well described. Some authors have examined the contribution of kidney disease to related diseases such as diabetes (4,5). Other researchers have analyzed the cost and utilization patterns associated with the time period immediately before dialysis (6) and for the broader population of those with CKD (7). But no researchers of which we are aware have compared the economic burden of CKD to a group without CKD, nor have any used the recent standard introduced by the NKF K/DOQI staging guideline. The economic implications of renal dysfunction extend beyond health care resource use. There are, for example, profound implications for quality of life and productivity losses. Data on direct health care resource use and indirect implications are necessary to perform economic evaluations of both new and currently used interventions in the treatment of renal disease.

In this analysis, we used the new staging standard, the NKF K/DOQI guidelines (2), and we compared, from the perspective of the health care system, direct health care costs and resource use of patients with CKD to a group without CKD.

Materials and Methods

Research Setting And Study Population

Participants were adult (>17 yr of age) members of Kaiser Permanente Northwest region (KPNW), a large, not-for-profit, group-model HMO. Kaiser Permanente provides comprehensive, prepaid coverage to 450,000 individuals (about 20% of the greater Portland, OR population). Subscribers' demographics are similar to the area population as a whole, with non-Hispanic whites representing about

78% of the population. The remainder are African Americans, Asians/Pacific Islanders, Native Americans, and persons of Hispanic descent.

KPNW maintains electronic administrative and clinical databases that include information on inpatient admissions, ambulatory contacts, pharmacy dispensations, laboratory tests, and outside claims and referrals. All of these databases are linked through unique health record numbers that are given to each member at the time of his or her first enrollment in the health plan. We used these databases to extract data on clinical, utilization, and cost of care variables.

Sample Selection

Kidney disease in subjects meeting inclusion criteria was staged according to recent criteria from the NKF (2). A patient's data were included if they had a GFR between 15 and 90 ml/min per 1.73 m^2 in 1996 (the index GFR), followed by a second GFR below 90 ml/min per 1.73 m^2 at the first creatinine measurement that occurred at least 90 d later. We estimated GFR from serum creatinine values captured in KPNW's laboratory information system. All KPNW laboratory tests are performed by a single regional laboratory using standardized methods that are frequently recalibrated against reference samples. We used the Modification Diet in Renal Disease Study (MDRD) formula (8) as shown below:

Estimated GFR (ml/min per 1.73 m^2) = $186.3 \cdot (sCr)^{-1.154} \cdot Age^{-0.203} \cdot (0.742 \text{ if female}) \cdot (1.21 \text{ if African-American})$

Information regarding the race of KPNW members is not available to us; therefore, it was not included in the estimation of GFR. This missing variable has the effect of underestimating GFR by 21% for African Americans. While the resulting inaccuracy of estimation and potential misclassification are a concern, African American patients make up less than 5% of our source population, suggesting that the problem is small from a population perspective.

Stage 4 disease was defined as an estimated index GFR of 15 to 29 ml/min per 1.73 m^2, and stage 3 disease was defined as an estimated index GFR of 30 to 59 ml/min per 1.73 m^2. Consistent with the NKF guidelines, individuals with stage 2 disease are those with an estimated index GFR between 60 and 89 ml/min per 1.73 m^2 who also had proteinuria. We defined proteinuria as 1+ or greater protein on urinalysis within 6 mo of the index GFR. To minimize inclusion of individuals with decreased GFR secondary to infection, we further required a leukocyte esterase of less than 10/μl within 6 mo of the index GFR on the same urinalysis.

A comparison group was selected by utilizing a 1:1 age (year of birth) and gender match from enrollees who did not meet the criteria for inclusion as a case and were eligible for at least 90 d from the index GFR of their matched case.

This study was approved by Human Subjects committee at Kaiser Permanente Northwest.

Follow-Up and End Points

Subjects were followed for up to 66 mo from the date of the index GFR through June 30, 2001, or until death, disenrollment from the health plan, or advancement to ESRD as defined by dialysis, transplant, or GFR less than 15 ml/min per 1.73 m^2. Death and disenrollment were identified from membership records. Transplant and dialysis were captured in the medical records.

Variables

Categories of cost and utilization included prescriptions, outpatient visits, and inpatient stays. Prescription drug use was examined for three broad classes of medications—cardiac, erythropoietin, and diabetes. Age (at index date) and gender were extracted from membership records. From the electronic medical record and laboratory data, we identified five CKD-related comorbidities (coronary artery disease, congestive heart failure, diabetes mellitus, hypertension, and anemia) Using ICD-9-CM codes, we identified diagnoses for coronary artery disease, congestive heart failure, diabetes mellitus, and hypertension. We included diagnoses that were ever present in the outpatient medical record during the time of follow-up (see Appendix for a list of ICD-9-CM codes). Anemia was defined as a hemoglobin less than 12 g/dl. To minimize inclusion of anemia from nonrenal causes, those with anemia were required to have a normal mean corpuscular volume (MCV). These five diseases were chosen because they have been shown to be associated with kidney disease (9–12). We report costs of care with and without CKD-related comorbidities.

Ascertainment Of Costs Of Care

We based our costing method on procedures developed and validated by the Kaiser Permanente Center for Health Research (13). This method creates standard costs for units of medical care (defined in the outpatient setting as office visits and in the inpatient setting as direct hospital service components). Costs are identified from aggregate departmental expenditures rather than from procedure-specific charges or prices. Administrative costs and other indirect and joint costs are allocated to units of direct costs. We then multiply standard unit costs by utilization volume to obtain total costs over an interval of time. The pharmaceutical costs reported approximate retail costs in the local market. To ascertain the costs of care provided in non-KPNW facilities, we used as costs the amounts that KPNW actually paid to vendors for procedures, hospitalizations, and professional and related services. We adjusted all costs to reflect 2001 prices. KPNW's expenditures include essentially all the costs of acute inpatient care received by its members, nearly 100% of outpatient costs (fewer than 10% of members use an out-of-plan service in any given year), and nearly all pharmacy costs (fewer than 5% of prescriptions are filled outside the plan).

Because patients with CKD were required to have a serum creatinine measurement (and for stage 2, a urinalysis), this introduced a possible bias in that cases seemed more likely to have had a resource utilization event (*i.e.*, outpatient or inpatient visit), which led to the laboratory measurement, potentially creating an artificially high starting point for costs. To reduce this potential bias, we began counting costs 60 d after the index event.

Statistical Analyses

Cumulative costs and variance estimates were calculated using monthly time intervals following methods from Lin *et al.* (14). These methods appropriately adjust for censoring in estimating total costs over a follow-up period. Utilization analyses were carried out by performing generalized linear regression with weighting for individual patient-months of follow-up, and 95% confidence intervals were calculated using methods appropriate for these data (SAS version 6.12 and 8.2, Cary NC). Except for the comorbidity comparison, contrasts between cases and controls were made using controls specific to the given stage of disease; these comparisons within a stage are implicitly age and gender adjusted.

Results

There were 43,178 persons who met the initial inclusion criteria of two GFR measurements between 15 and 90 ml/min per 1.73 m^2 separated by at least 90 d. A total of 30,890 of these had an index GFR of 60 to 89 ml/min per 1.73 m^2, and were thus potential stage 2 candidates, but 14,295 of them

Table 1. Baseline characteristics

	Stage 2		Stage 3		Stage 4	
	GFR 60 to 89 + Proteinuria (n = 1741)	Controls (n = 1741)	GFR 30 to 59 (n = 11,278)	Controls (n = 11,278)	GFR 15 to 29 (n = 777)	Controls (n = 777)
Mean age at index (SD)	60.8 (14.9)	60.4 (14.9)	71.6 (11.9)	71.3 (11.9)	73.6 (13.6)	73.6 (13.6)
Percent male	56.5%	56.5%	37.8%	37.8%	35.9%	35.9%
Mean mo of observation, total (SD)	49.8 (17.9)	52.3 (21.1)	51.1 (16.5)	53.1 (20.2)	37.6 (20.6)	52.9 (20.1)

could not be staged due to lack of data on urinary protein status. Our final cohort included 13,796 persons with CKD (based on the NKF K/DOQI staging criteria) and their age- and gender-matched controls (27,998 total): 1741 cases in stage 2; 11,278 in stage 3; and 777 in stage 4 (Table 1). The average age (70.3 yr) and proportion who were female (40.0%) increased with stage of disease. Average follow-up time ranged from 38 to 51 mo. During follow-up, 24.9% of cases and 18.0% of controls died, 2.3% of cases and <1% of controls went on to dialysis or transplant, and 10.8% of cases and 18.5% of controls disenrolled During every year of observation, people in stage 4 died at a higher rate *versus* their age- and gender-matched controls than did those stages 2 or 3 *versus* their age- and gender-matched controls.

Patients with CKD used 1.9 to 2.5 times more prescriptions (depending on stage) than controls. Increases in likelihood of treatment were highest for erythropoietin (6.7, 5.1, and 44 times more than controls for stages 2, 3, and 4, respectively) and diabetes medication (3.6, 2.5, and 4.1 times more than controls for stages 2, 3, and 4, respectively). Virtually all patients (100% of those with CKD and 96% of controls) had an outpatient visit during the follow-up period, but those with CKD had more outpatient visits (1.3 to 1.9 times more than controls, across stages). There were no significant differences

Table 2. Per person annual adjusted utilization counts and ratios by stage

	Stage 2		Stage 3		Stage 4	
	Case	Control	Case	Control	Case	Control
Prescriptions (count)	35.7	14.4	33.0	17.5	44.1	17.4
Treated with						
cardiac medication	86.4%	54.2%	92.2%	66.4%	97.9%	68.2%
erythropoietin	2.3%	0.3%	2.8%	0.5%	16.9%	0.4%
diabetes medication	38.1%	10.6%	22.6%	9.0%	32.8%	8.1%
Percent with any outpatient visits (count)	17.5	10.0	15.3	11.8	22.1	11.9
Outpatient visit	100.0%	96.6%	100.0%	96.1%	100.0%	96.1%
Percent with any inpatient stays (count)	0.43	0.14	0.38	0.21	0.92	0.22
Inpatient stay	61.5%	28.0%	59.8%	37.7%	81.0%	40.8%
Average days per stay	4.14	3.87	4.09	4.05	4.50	4.18
Serum creatinine[a]	89.3%	72.0%	91.7%	80.6%	93.8%	79.2%
Case/control ratios for counts (95% CI)						
prescriptions (ratio of count)	2.48 (2.37 to 2.60)		1.89 (1.85 to 1.92)		2.53 (2.40 to 2.67)	
ratio of % ever treated with						
cardiac medication	1.60 (1.52 to 1.67)		1.39 (1.37 to 1.41)		1.44 (1.37 to 1.51)	
erythropoietin	6.67 (2.83 to 15.68)		5.08 (3.87 to 6.68)		44 (14 to 137)	
diabetes medication	3.56 (3.09 to 4.17)		2.50 (2.34 to 2.68)		4.05 (3.13 to 5.24)	
outpatient visits (ratio of count)	1.75 (1.66 to 1.83)		1.30 (1.27 to 1.32)		1.86 (1.71 to 2.00)	
ratio of % with any outpatient visit	1.04 (1.03 to 1.05)		1.04 (1.03 to 1.04)		1.04 (1.03 to 1.06)	
inpatient stays (ratio of count)	3.07 (2.79 to 3.36)		1.81 (1.71 to 1.86)		4.18 (3.68 to 4.68)	
ratio of % with any inpatient stay	2.20 (2.02 to 2.39)		1.59 (1.54 to 1.63)		1.98 (1.81 to 2.17)	
ratio of average days per stay	1.07 (0.99 to 1.15)		1.01 (0.98 to 1.03)		1.08 (0.99 to 1.17)	
ratio of serum creatinine measurement[a]	1.24 (1.20 to 1.28)		1.14 (1.13 to 1.15)		1.19 (1.14 to 1.23)	

[a] Percent tested post study enrollment.

in the average days per inpatient stay, but those with CKD were 1.6 to 2.2 times more likely than controls to have had an inpatient stay and had 1.8 to 3.1 more stays than did controls. A range of 72% to 81% of controls had at least one serum creatinine test performed after study enrollment *versus* a range of 79% to 89% of those with CKD. For overall and diabetic medication use and outpatient and inpatient visits, those with stage 2 disease had higher utilization than did patients in stage 3.

Table 3 shows that patients with CKD had costs significantly (as evidenced by nonoverlapping confidence intervals) higher than their controls for all categories of care. For total costs: stage 2 costs were $38,764 (95% CI, 37,033 to $40,496) and $16,212 (95% CI, $15,644 to $16,780) for cases and controls, respectively; stage 3 costs were $33,144 (95% CI, $32,578 to $33,709) and $18,964 (95% CI, $18,730 to $19,197) for cases and controls, respectively; and stage 4 costs were $41,928 (95% CI, $39,354 to $44,501) and $19,106 (95% CI, $18,212 to $20,000) for cases and controls, respectively. Dividing these numbers by 5.5 yields approximate annual costs; for the cases and controls, respectively, this is $7050 and $3473 for stage 2, $6026 and $3448 for stage 3, and $7623 and $2947 for stage 4 patients.

Inspection of Figure 1 reveals that costs accumulated at a nearly constant rate across time for stages 2 and 3. Those in stage 4 accumulated costs as a higher rate up to about 20 mo, after which the rate declined slightly over time. This suggests that for future economic evaluations it may be important to consider, as we did, appropriate methods for follow-up costs in patients with CKD, since naïve estimates of cost accumulation will conceal this dynamic relationship and overestimate or underestimate costs.

Cumulative costs are shown in Table 4 for those with and without CKD-related comorbidities by the end of follow-up. CKD-related comorbidities almost double the total cost of care for both cases and controls, and cases with no CKD-related comorbidities are about twice as expensive to manage as controls with no CKD-related comorbidities.

Discussion

In this analysis, we used the new NKF K/DOQI staging guidelines to categorize patients with CKD and followed them and their age- and gender-matched controls for up to 5.5 yr. During the follow-up period, patients with CKD exhibited significantly higher cost and utilization patterns than their age- and gender-matched controls. This finding was consistent for all categories of care (medications, outpatient visits, and inpatient admissions). While average of days per inpatient stay was

Table 3. Per person cumulative cost (95% CI) by stage

	n	Cost	SE	Lower 95% CI	Total Cost	Upper 95% CI
Stage 2						
control	1741	Outpatient	$ 60.18	$ 6539.78	$ 6657.72	$ 6775.67
		Prescriptions	$ 60.19	$ 3287.10	$ 3405.07	$ 3523.03
		Inpatient	$ 246.97	$ 5665.10	$ 6149.16	$ 6633.21
		Total	$ 289.62	$15,644.30	$16,211.94	$16,779.59
case	1741	Outpatient	$ 181.32	$10,978.73	$11,334.11	$11,689.49
		Prescriptions	$ 319.74	$ 8917.83	$ 9544.51	$10,171.19
		Inpatient	$ 659.19	$16,593.56	$17,885.56	$19,177.55
		Total	$ 883.41	$37,032.72	$38,764.17	$40,495.63
Stage 3						
control	11278	Outpatient	$ 28.68	$ 7242.21	$ 7298.42	$ 7354.63
		Prescriptions	$ 23.33	$ 3584.12	$ 3629.84	$ 3675.57
		Inpatient	$ 98.22	$ 7842.96	$ 8035.47	$ 8227.97
		Total	$ 119.18	$18,730.14	$18,963.73	$19,197.32
case	11278	Outpatient	$ 65.28	$10,365.12	$10,493.07	$10,621.03
		Prescriptions	$ 70.70	$ 7111.68	$ 7250.24	$ 7388.80
		Inpatient	$ 232.22	$14,945.11	$15,400.25	$15,855.40
		Total	$ 288.36	$32,578.39	$33,143.56	$33,708.74
Stage 4						
control	777	Outpatient	$ 109.43	$ 6811.19	$ 7025.66	$ 7240.13
		Prescriptions	$ 69.53	$ 3148.92	$ 3285.20	$ 3421.48
		Inpatient	$ 386.56	$ 8037.44	$ 8795.09	$ 9552.75
		Total	$ 456.15	$18,211.92	$19,105.96	$19,999.99
case	777	Outpatient	$ 314.64	$ 9958.83	$10,575.51	$11,192.18
		Prescriptions	$ 263.09	$ 7133.95	$ 7649.59	$ 8165.24
		Inpatient	$1,088.94	$21,568.26	$23,702.53	$25,836.80
		Total	$1,312.96	$39,354.27	$41,927.63	$44,500.99

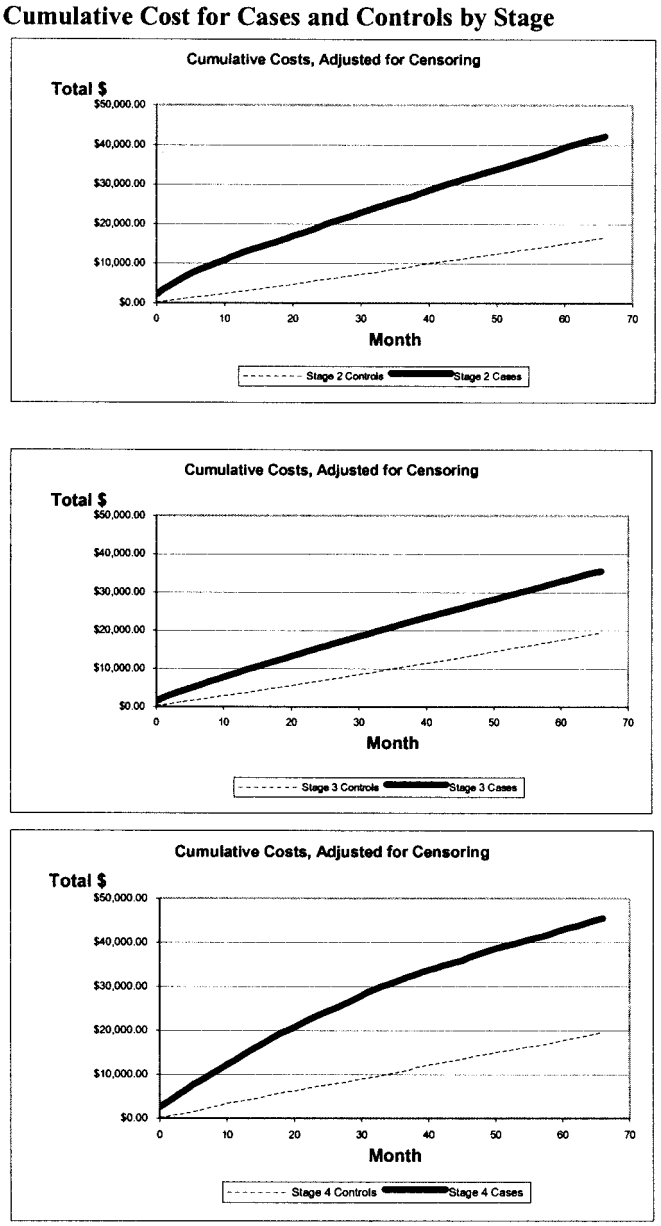

Figure 1. Cumulative cost for cases and controls by stage.

similar for cases and controls, those with CKD were more likely to have an inpatient hospitalization.

The analysis of the contribution of CKD-related comorbidities presents some interesting findings. As shown in Table 4, the total cost of care for those without disease or CKD-related comorbidities is $10,000 per patient; this can be taken as an estimation of the average health care cost for patients without CKD or CKD-related comorbidities. Subtracting this figure from the remaining total cost estimates suggests that the cost of CKD-related comorbidities alone is $14,000 ($24,000 minus $10,000); that the cost of CKD alone is $8,000 ($18,000 minus $10,000); and that the overall burden to the health plan of CKD + CKD-related comorbidities is $26,000 ($36,000 minus $10,000). This $26,000 burden estimate is 18% ($4000) higher than one would expect from simply adding the cost of CKD and CKD-related comorbidities.

That the joint contribution of CKD and CKD-related comorbidities to total cost of care was greater than the expected additive cost suggests there is an interaction between CKD and certain comorbidities. This is consistent with findings in diabetes, where it has been shown that there is an interaction with the cost of care for people with diabetes and renal disease (4). Furthermore, the estimated burden of CKD-related comorbidities was found to be greater than the estimated burden of the kidney component of CKD. Focused attention on managing these diseases for patients with CKD may prove to be a useful strategy for improving outcomes and controlling expenditures.

Within every resource use comparison made, those in stage 2 were more likely than those in stage 3 to utilize services *versus* their age- and gender-matched controls. Costs for those in stage 2 were higher not only for stage 2 controls, but were also higher than patients in stage 3. This was true despite stage 3 patients being, on average, 11 yr older than stage 2 patients. This surprising finding may be in part due to the NKF K/DOQI requirement that patients must have evidence of urinary protein to qualify for stage 2. We undertook further analyses to help explain these findings (data not shown). Since proteinuria is a marker for other diseases, namely diabetes, we examined the baseline prevalence of diabetes and found that it was 30%, 18%, and 28% in stages 2, 3, and 4, respectively, indicating that patients in stage 2 carry at least some higher disease burden. We also examined cost for those with and without baseline proteinuria and found that the presence of baseline proteinuria was associated with an average per person increase of $4500 in annual costs across all levels of GFR. The prevalence of baseline proteinuria was 10% and 27% in stages 3 and 4, respectively, implying that baseline proteinuria had a much greater differential impact on stage 2. These findings of increased disease burden and cost help explain the unexpected lack of difference in the cumulative costs between stage 2 and 3.

The higher burden of disease exhibited by stage 2 patients may also be due to a possible selection bias. To qualify for inclusion, a patient had to have not only a serum creatinine drawn, but also a urinary protein measurement. To the extent that the reason a clinician elects to check urinary protein is related to presence of disease (testing bias), the results presented may overstate the burden associated with stage 2 CKD in the general population. However, urinary protein is often measured as part of routine laboratory panels, rather than as a sole diagnostic request. Additionally, it should be noted that over half of those with GFR 60 to 89 ml/min per 1.73 m^2 did have a urinary protein measurement; of these, more than 95% were normal. Even among patients with a plausibly greater likelihood of having proteinuria (due to testing bias, as above), the prevalence is very low. This suggests that those in stage 2 in our analysis may not be too different than would be found with a general population screening method.

We found that stage 4 patient care costs declined slightly with follow-up, possibly due to a survivor effect. People with stage 4 disease died at a higher rate during every year of

Table 4. Cumulative cost for cases and controls, by presence of kidney disease-related comorbidity

	n	Cost	SE	Lower 95% CI	Total Cost	Upper 95% CI
Controls						
no related comorbidities	5665	Outpatient	$ 28.54	$ 4693.11	$ 4749.04	$ 4804.97
		Prescriptions	$ 19.26	$ 1751.49	$ 1789.24	$ 1826.99
		Inpatient	$ 90.52	$ 3125.81	$ 3303.22	$ 3480.64
		Total	$103.77	$ 9638.11	$ 9841.50	$10,044.89
with related comorbidities	8131	Outpatient	$ 35.25	$ 8627.34	$ 8696.43	$ 8765.52
		Prescriptions	$ 30.66	$ 4596.52	$ 4656.61	$ 4716.69
		Inpatient	$127.26	$10,337.11	$10,586.54	$10,835.97
		Total	$151.14	$23,643.36	$23,939.58	$24,235.80
Cases						
no related comorbidities	1337	Outpatient	$154.44	$ 7349.23	$ 7651.93	$ 7954.63
		Prescriptions	$245.80	$ 3966.97	$ 4448.74	$ 4930.50
		Inpatient	$347.21	$ 5332.04	$ 6012.57	$ 6693.10
		Total	$534.21	$17,066.20	$18,113.23	$19,160.26
with related comorbidities	12459	Outpatient	$ 64.45	$10,770.79	$10,897.11	$11,023.44
		Prescriptions	$ 74.79	$ 7713.88	$ 7860.46	$ 8007.05
		Inpatient	$233.29	$16,698.46	$17,155.69	$17,612.93
		Total	$289.93	$35,345.02	$35,913.27	$36,481.53

follow-up, possibly leaving behind a relatively healthier cohort. Additionally, the gender mix in this CKD cohort is not consistent with findings in the ESRD population. USRDS data suggest about 59% of those with ESRD are male, consistent with our stage 2 findings; however, we found 38% and 36% males in stage 3 and 4, respectively. This may be a reflection of the MDRD equation identifying more females as having low GFR, or perhaps it is indicative of a true gender-based differential in disease burden. We also found that age increased with stage. This may be due to declining renal function with age, or may be an artifact of the MDRD equation inclusion of age as a predictor of renal function.

Our findings are similar to the few other reports of utilization for those with CKD. Pereira *et al.* (6) reported that about 95% of patients with CKD not on dialysis have multiple comorbidities (such as cardiovascular disease) and annually experience about one hospitalization of about 6.5 d, similar estimates to what Khan *et al.* (15) recently reported. This matches most closely with patients in stage 4; we found considerably less use of resources for those with less-severe CKD. Other research has found that inpatient stays, visits to a nephrologist, erythropoetin use, and per-month charges increase with worsening kidney disease (7). To further put our estimates in context, data from the Centers for Medicare and Medicaid show that per person calendar year expenditures for 1999 in Oregon were $4245 (16). Our comparison group annual costs are slightly lower than this amount, but the cost of treating cases was more than 50% higher.

There are several limitations to this research. First, while the results of this analysis are valid for making inferences regarding per person clinical resource use and disease patterns in identified cases, this analysis should not be used to estimate prevalence of kidney disease. Those eligible for inclusion in the study were only patients who had a creatinine measurement during the baseline year. Prevalence estimation would require laboratory measures on a random sample. Second, it is important to note that no inferences should be made regarding relative population sizes between stages of disease, especially with regard to stage 2. For stage 2, to follow the proposed KDOQI guidelines, we required 1+ proteinuria for inclusion. About 50% of those with a GFR of 60 to 89 ml/min per 1.73 m^2 did not have a proteinuria measurement, so they were not even considered for inclusion in the stage 2 sample. Thus we can make no statements about the actual size of the CKD population from these data. Third, patients with both incident and prevalent disease were included in this analysis. This means that at the initial observation point in our analysis, the patients within a disease stage were mixed with respect to the natural history of their disease. Our findings are a proper reflection of a steady state that one would expect to find within the given population, but are less useful for estimating lifetime disease burden. Fourth, the control group may not have been disease free, but rather, not tested, making the estimates of burden more conservative. Also, the cases may have more health care use than controls simply because of opportunities for contact with the system. This is probably of minimal concern, because >95% of controls had at least one outpatient visit.

These are the first burden estimates for patients with CKD that use the standard staging guidelines, and the first to compare patients with CKD to a cohort with no CKD. We found that CKD doubles costs to the health care system, and that comorbidities related to CKD contribute more to the cost of managing these patients than does CKD alone. Future research in this area could be usefully directed toward analyzing the clinical and economic consequences of better managing patients with CKD. This information is important in helping clinicians and policy makers focus their efforts in managing this patient population. The findings presented here provide valuable information regarding the burden imposed by comorbid conditions. Managing these conditions, as suggested by existing treatment recommendations (2), may prove to be effective and efficient investments, and the potential impact should be examined in detail.

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Appendix

ICD-9 Codes

- Coronary Artery Disease: 410.xx–414.xx (excluding 414.10, 414.11, 414.19)
- Congestive Heart Failure: 428.0, 428.9, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 429.4A, 429.9B, 429.9A, 428.1
- Hypertension: 401.xx–405.xx
- Diabetes: 250.xx

References

1. Nissenson A, Pereira B, Collins A, Steinberg E: Prevalence and characteristics of individuals with chronic kidney disease in a large health maintenance organization. *Am J Kidney Dis* 37: 1177–1183, 2001
2. Chronic Kidney Disease Workgroup. Kidney disease outcomes quality initiative clinical practice guidelines. *Am J Kidney Dis* 39: S17–S31, 2002
3. US Renal Data System: USRDS 1999 Annual Data Report. Bethesda, MD, The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease, 1999
4. Brown JB, Pedula KL, Bakst AW: The progressive cost of complications in type 2 diabetes mellitus. *Arch Intern Med* 159: 1873–1880, 1999
5. Ramsey SD, Newton K, Blough D, McCulloch DK, Sandhu N, Wagner EH: Patient-level estimates of the cost of complications in diabetes in a managed-care population. *Pharmacoeconomics* 16: 285–295, 1999
6. Combating chronic kidney disease: A managed care perspective. *Am J Manag Care* 8[Suppl 4]: S109–s136, 2002
7. Nissenson, AR, Collins, AJ, Hurley, J, Petersen, H, Pereira, BJG, and Steinberg, EP. Opportunities for improving the care of patients with chronic renal insufficiency: Current practice patterns. *J Am Soc Nephrol* 12: 1713–1720, 2001
8. Manjunath M, Sarnak M, Levey A: Prediction equations to estimate glomerular filtration rate: An update. *Curr Opin Nephrol Hypertens* 10: 785–792, 2001
9. Klag M, Whelton P, Randall B, Neaton J, Frederick L, Ford C et al: Blood pressure and end-stage renal disease in men. *N Engl J Med* 334: 13–18, 1996
10. Diabetes Control and Complications Trial Research Group. The effect of intensive treamtent of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329: 977–986, 1993
11. Nelson R, Bennett P, Beck G, Tan M, Knowler W, Mitch W, et al: Development and progression of renal disease in pima indians with non-insulin-dependent diabetes mellitus. *N Engl J Med* 335: 1636–1642, 1996
12. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 352: 837–853, 1998
13. Hornbrook M, Goodman MJ. Adjusting health benefit contributions to reflect risks. In: *Risk-Based Contributions to Private Health Insurance*, edited by Hornbrook M, Greenwich, JAI Press Inc, 1991, pp 41
14. Lin D, Feuer E, Etzioni R, Wax Y: Estimating medical costs from incomplete follow-up data. *Biometrics* 53: 419–434, 1997
15. Khan S, Kazmi W, Abichandani R, Tighiouart H, Pereira B, Kausz A: Health care utilization among patients with chronic kidney disease. *Kidney Int* 62: 229–236, 2002
16. Centers for Medicare and Medicaid Services, Office of Information Services. Medicare Enrollees and Benefit Payments, by Area of Residence, Calendar Year 1999. Centers for Medicare and Medicaid Services, 2003. Available at: www.cms.hhs.gov/review/supp/2001/table73.pdf Accessed: 12-10-2003

See related editorial, “The Consequences and Costs of Chronic Kidney Disease before ESRD,” on pages 1363–1364.