Kidney International, Vol. 62 (2002), pp. 229–236

Health care utilization among patients with chronic kidney disease

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Background. Higher hospitalization rates among end-stage renal disease (ESRD) patients impose a substantial burden on the U.S. health care system. Early identification of patients with chronic kidney disease (CKD) and determination of factors associated with increased morbidity may lead to appropriate interventions to attenuate the complications of CKD and possibly reduce future resource utilization.

Methods. This retrospective cohort study of CKD patients in an outpatient nephrology clinic was performed to identify risk factors for hospitalization. The study population consisted of adults with elevated serum creatinine (females ≥1.5 mg/dL, males ≥2.0 mg/dL). Hospitalizations, hospital days and outpatient nephrology visits were examined.

Results. Among the 259 patients, 123 (47%) were hospitalized during a median follow-up of 11.4 months. The number of hospitalizations and hospital days per patient-year at risk were 0.96 and 6.6, respectively. Cardiovascular disease/hypertension accounted for the majority of hospitalizations. In a multivariate regression analysis, older age (RR 1.01, 95% CI 1.00, 1.03) and presence of cardiac disease (RR 1.91, 95% CI 1.19, 3.07) were associated with higher risk of hospitalization while higher serum albumin (RR 0.58, 95% CI 0.35, 0.95) and higher hematocrit (RR 0.92, 95% CI 0.87, 0.97) were associated with lower risk of hospitalization. Higher serum albumin (RR 0.34, 95% CI 0.21, 0.55), higher hematocrit (RR 0.87, 95% CI 0.81, 0.93) and use of ACE-inhibitors (RR 0.63, 95% CI 0.47, 0.84) were associated with lower risk of subsequent hospital days. Erythropoietin (RR 1.47, 95% CI 1.11, 1.82) use was associated with higher risk of outpatient nephrology visits.

Conclusion. Certain potentially modifiable factors appear to be associated with increased resource utilization. It is hypothesized that attention to these factors may lead to improved outcomes in this patient population, which could result in reduced utilization.

Key words: renal disease, hospitalization, outpatient visit, end-stage renal disease, risk for hospitalization, generalized estimating equation.

Received for publication June 12, 2001
and in revised form February 25, 2002
Accepted for publication February 27, 2002

The growing incidence and prevalence of end-stage renal disease (ESRD), and the rising resource expenditures related to the care of ESRD patients are a cause for concern [1]. In the United States, the prevalence of ESRD doubled in the last decade [2] and is expected to rise further as the U.S. population ages and medical advances result in prolonged survival of individuals with chronic illnesses. The total annual cost of care of the ESRD population in the U.S. was estimated to be $17.9 billion in 1999 [3], and is expected to exceed $20 billion in the year 2000 [2, 4]. Hospitalizations account for a large fraction of the cost of care in this population, followed by dialysis and non-dialysis physician and supplier costs [3]. The most recent data from the United States Renal Data System (USRDS) reveal that between 1996 and 1998, the average ESRD patient had 1.9 hospitalizations and spent 14 days in hospital each year [5].

Analyses of large national databases and single-center experiences have improved our understanding of the factors associated with a higher risk of hospitalization among ESRD patients [6–8]. The majority of hospitalizations among ESRD patients appear to be for the management of complications and comorbid conditions that may begin to arise early during the course of chronic kidney disease (CKD). These conditions progressively worsen with advancing kidney failure and result in a substantial proportion of patients having severe complications by the time they begin renal replacement therapy. Thus, patients with CKD are an ideal target for interventions aimed at reduction of morbidity and mortality among ESRD patients. Resource utilization in this group is likely to have a substantial economic impact, since estimates from the Third National Health and Nutritional Examination Survey (NHANES III) suggest that 6.2 million U.S. residents have serum creatinine levels ≥1.5 mg/dL [9], a conservative estimate of the prevalence of CKD. A better understanding of the rates, causes and risk factors for hospitalization among CKD patients would allow estimates of the economic burden of CKD,

identification of patients at risk for increased resource utilization, and selection of interventions that could reduce morbidity, mortality and costs in these populations.

METHODS

Patient population

This is a retrospective cohort study of adult (age 18 years or older) patients with CKD followed in the outpatient Nephrology clinic at New England Medical Center (NEMC) in Boston, Massachusetts, between October 1994 and September 1998. CKD was defined for purposes of this study as serum creatinine ≥1.5 mg/dL for women and ≥2.0 mg/dL for men on at least two consecutive occasions. The study patients were selected by reviewing the serum creatinine levels and diagnoses of all patients identified as having a nephrology clinic visit during the study period in the computerized utilization database of NEMC. Patient data were collected from the first date of service during the study period that criteria for CKD were met until the start of dialysis, transplant, transfer to another facility, loss to follow-up, end of study (September 31, 1998), or death, whichever occurred earlier.

Data collection and categorization

Clinical and laboratory data were extracted from the conventional and electronic medical records of NEMC using a computerized data collection form designed for the study. Collected data included demographic characteristics, insurance status, clinical parameters, use of medications, and laboratory values at baseline. Longitudinal data were collected on clinical parameters, use of medications, and laboratory values at each nephrology visit. When laboratory values were not available for a given visit, laboratory values nearest to the date of the visit within 45 days before or after the visit were entered. All hospitalizations at NEMC from within 90 days prior to the first study visit until September 31, 1998 were recorded, with the intent to capture all hospitalizations at NEMC within the four fiscal years of the study among patients followed for CKD. Race was categorized as Caucasian, African American, Asian or other. Insurance was categorized as private, health maintenance organization (HMO), Medicare, Medicaid and none. Cause of CKD was classified as diabetes, hypertension, glomerulonephritis/interstitial nephritis/polycystic kidney disease (GN/IN/PKD) and others. Medications recorded in the clinic chart were assumed to be used by the patients, and actual medication adherence could not be determined given the retrospective nature of the study. The primary cause of hospitalization was considered to be the diagnosis listed as primary on the discharge summary. Among the multiple secondary causes listed, the most fitting diagnosis accounting for the hospitalization was determined after careful review of the discharge summary. The causes of hospitalization were categorized as: cardiac/hypertension, congestive heart failure/volume overload, hemodialysis access related, peritoneal dialysis access related, infection, metabolic (includes electrolyte abnormalities and diabetic ketoacidosis), peripheral vascular disease, acute kidney failure or progression of chronic kidney failure, psychiatric/central nervous system/cerebrovascular, gastrointestinal, kidney/genitourinary, malignancy, and others.

Definitions and equations

The presence and severity of comorbid conditions was determined using the index of disease severity (IDS) score developed by Greenfield and Nelson [10] and later modified by Athienites et al for use in ESRD patients [11]. The modified IDS score stages the severity of twenty major medical conditions. Five common comorbid conditions were separately determined: cardiac diseases, peripheral vascular disease, cerebrovascular disease, hypertension and diabetes. Hypercholestrolemia was defined as serum cholesterol >200 mg/dL and/or use of lipid-lowering agents. Abnormal calcium-phosphorus metabolism was defined as a parathyroid hormone (PTH) level >100 pg/dL and/or serum phosphorus level >4.5 mg/dL and/or use of calcitriol and/or phosphate binders. Acidosis was defined as a serum bicarbonate level <20 mmol/L. Glomerular filtration rate (GFR) was estimated using a prediction equation derived from the results of the Modification of Diet in Renal Disease (MDRD) Study, which is based on age, gender, race, and serum creatinine (abstract; Levey et al, *J Am Soc Nephrol* 11:155A, 2000).

Statistical analysis

Summary descriptive statistics of baseline characteristics were performed for the entire population and for subsets of patients with and without hospitalizations. Results of continuous variables are presented as mean ± standard deviation (SD), and discrete variables as proportions. Baseline characteristics of patients with and without hospitalizations after the first study visit were compared using Student *t* test or Pearson chi-square test, as appropriate.

All hospitalizations within 90 days prior to the first study visit until the end of study were used to calculate the hospitalizations and hospital days per patient-year at risk. Time at risk was calculated from the first study visit or hospitalization (if within 90 days prior to the first study visit), whichever came first, to the start of dialysis, transplant, transfer to another facility, loss to follow-up, end of study, or death. The total number of hospital days was subtracted from time at risk for analyses of hospitalization and outpatient nephrology visits. The number of hospitalizations and number of hospital days per patient-year at risk were obtained by dividing the total number of hospitalizations and hospital days observed by the

total calculated patient-years at risk of the entire cohort. The relationship between number of hospitalizations and hospital days was determined by obtaining the Pearson correlation coefficient.

The end points assessed in regression analyses were time to first hospitalization, number of hospitalizations, hospital days, and number of outpatient nephrology visits. Three different types of analyses were explored to describe the relationship between patient characteristics and risk for utilization. A traditional Cox proportional hazards regression was used to examine the association between baseline demographic, clinical and laboratory variables and time to first hospitalization after the initial study visit. A Poisson regression multiple event model was developed to examine the association between baseline demographic, clinical and laboratory variables and each of the following resource utilization outcomes: (*1*) number of hospitalizations, (*2*) number of hospital days, and (*3*) number of outpatient nephrology visits. The overdispersion parameter was estimated by dividing the Pearson statistic by the degrees of freedom (df). The logarithm of the follow-up period was used as the offset parameter in the fitted Poisson model to adjust for varying time spans among patients. Lastly, generalized estimating equation (GEE) methodology with an exchangeable correlation matrix was used to analyze the different utilization outcomes. Robust standard error estimates of the coefficient were used. These estimates have the property of being consistent estimators of the standard errors even if the working correlation matrix is specified incorrectly. The GEE technique incorporates multiple observations of the patient characteristics being evaluated. Thus, in addition to evaluating the relative risk of multiple events, changes over time in independent variables are captured. The probability of having a hospitalization, hospital day or an outpatient nephrology visit at any given day during the follow-up period was estimated. For these longitudinal analyses, missing variables were handled as follows: categorical variables, such as medication use, were carried over from the previous visit, whereas for continuous variables, such as hematocrit or albumin, the average of the values before and after the visit with the missing covariate was calculated. The results of the Poisson and GEE regression express the relative risk (RR) of having the first or future events of any of the repeated outcomes; for example, with hospital days, the result expresses the relative risk of a future hospital day, that is, a more prolonged hospitalization. All multivariate models were constructed using stepwise selection of independent variables with probability values of <0.10, except age, gender, race and diabetes, which were forced into the model. The results of the traditional Cox proportional hazards analysis and the GEE analysis are presented for the following reasons: (*1*) the results of the Cox model are more easily compared to other studies of such outcomes and the interpretation is more familiar, and (*2*) the GEE method theoretically captures more precisely factors which change over time that may have a potential impact on hospital utilization, such as hematocrit, serum albumin and level of kidney function. Statistical analyses were performed using SAS System for Windows, version 8.00 (SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 272 patients satisfied study criteria for CKD during the study period. Thirteen patients were excluded because no information was available after the initial study visit, thus the final study cohort was composed of 259 patients. Median follow-up was 11.4 months (range 0 to 47.7 months). Eight percent of the patients progressed to ESRD during the time frame of the study, 10% were transferred to other facilities, 2% died, 30% were lost to follow-up, and 50% were followed in clinic until the study end date.

Patient characteristics

The mean age of the patients was 62 ± 16 years, 54% were male and 75% were Caucasian. The cause of CKD was diabetes in 26%, hypertension in 22%, GN/IN/PKD in 27% and a variety of other causes in 26%. The majority of patients had substantial comorbidity. Hypertension was present in 87%, diabetes in 35%, cardiovascular disease in 40%, and peripheral vascular disease in 14%.

Among 259 patients, 123 (47%) were hospitalized during the study period. The baseline demographic and clinical characteristics of patients with and without hospitalizations are provided in Table 1. Hospitalized patients were older ($P < 0.001$), had a lower prevalence of GN/IN/PKD as cause of CKD ($P < 0.001$), and had a higher prevalence of cardiac disease ($P < 0.001$), diabetes ($P = 0.006$), cerebrovascular disease ($P < 0.001$), and peripheral vascular disease ($P = 0.002$) compared to patients without hospitalizations. Other factors were not significantly different between the two groups.

The laboratory characteristics and medication use among patients with and without hospitalizations are provided in Table 2. Patients who were hospitalized had a lower serum albumin ($P < 0.001$) and hematocrit ($P = 0.006$) and less frequent angiotensin converting enzyme (ACE) inhibitor use ($P = 0.045$) compared to patients without hospitalizations.

Hospitalizations

There were 0.96 hospitalizations and 6.6 hospital days per patient-year at risk. The causes of hospitalization are shown in Figure 1. Cardiac disease and hypertension (cardiac/HTN), which includes all cardiovascular causes except congestive heart failure, was the most common primary diagnosis of the hospitalizations, accounting for

Table 1. Demographic and clinical characteristics of patients with chronic kidney disease

	Hospitalized (N = 123)	Non-hospitalized (N = 136)	P[a]
Age	65 ± 14	58 ± 16	<0.001
Male	53%	56%	0.62
Race			0.15
Caucasian	71%	78%	
African American	12%	6%	
Asian	16%	13%	
Other	1%	3%	
Insurance			0.92
Private	18%	16%	
HMO	66%	68%	
Medicare	11%	10%	
Medicaid	2%	3%	
None	3%	3%	
Cause of chronic kidney disease			<0.001
Diabetes	33%	19%	
Hypertension	28%	17%	
GN/IN/PKD	14%	39%	
Other	26%	25%	
Comorbid conditions			
Cardiac diseases	54%	28%	<0.001
Hypertension	88%	86%	0.66
Diabetes	44%	27%	0.006
Cerebrovascular disease	18%	5%	<0.001
Peripheral vascular disease	20%	7%	0.002

Abbreviations are: HMO, health maintenance organization; GN, glomerulonephritis; PKD, polycystic kidney disease; IN, interstitial nephritis. Percentages may not add up to 100 due to rounding.

[a] Probability value for comparison between hospitalized and non-hospitalized patients

Table 2. Laboratory characteristics and medication use among patients with chronic kidney disease

	Hospitalized (N = 123)	Non-hospitalized (N = 136)	P[a]
Creatinine *mg/dL*	2.7 ± 1.0	2.8 ± 1.2	0.50
GFR *mL/min/1.73 m²*	26.8 ± 10.4	26.3 ± 9.0	0.70
Albumin *mg/dL*	3.6 ± 0.7	3.8 ± 0.4	<0.001
Hematocrit %	34.2 ± 5.0	36.1 ± 5.6	0.006
Proteinuria *g/day*	2.0 ± 2.4	1.5 ± 2.0	0.12
Hyperlipidemia[b]	28%	29%	0.83
Abnormal Ca-PO_4 metabolism[c]	18%	15%	0.55
Acidosis[d]	3%	7%	0.22
Medications			
ACE inhibitor	39%	52%	0.05
Erythropoietin	4%	2%	0.39
Oral iron	8%	9%	0.66
Vitamin D	2%	3%	0.49
Lipid lowering agents	20%	16%	0.37

Abbreviations are: GFR, glomerular filtration rate; ACE, angiotensin converting enzyme; Ca, calcium; PO_4, phosphorus.

[a] Probability value for comparison between hospitalized and non-hospitalized patients

[b] Total serum cholesterol >200 mg/dL and/or use of anti-lipemics

[c] Parathyroid hormone level >100 pg/dL and/or serum phosphorus level >4.5 mg/dL or use of calcitriol and/or phosphate binders

[d] Serum bicarbonate level <20 mmol/L

24.5% of hospitalizations. Progression of CKD/acute kidney failure was the most common secondary cause of hospitalization.

Time to first hospitalization. Univariate analyses using Cox proportional hazards methodology revealed a higher risk of hospitalization associated with increasing age (RR 1.02, 95% CI 1.01, 1.03), and among patients with cardiac disease (RR 1.69, 95% CI 1.15, 2.47), diabetes (RR 1.67, 95% CI 1.12, 2.47), peripheral vascular disease (RR 1.84, 95% CI 1.14, 2.97), and cerebrovascular disease (RR 1.76, 95% CI 1.07, 2.89). There was a lower risk of hospitalization among patients with GN/IN/PKD compared to hypertension as cause of CKD (RR 0.43, 95% CI 0.24, 0.78), among patients on ACE-inhibitors at baseline (RR 0.62, 95% CI 0.42, 0.91), and patients with higher baseline serum albumin (RR 0.53, 95% CI 0.38, 0.73). A multivariate analysis with age, gender, race and diabetes forced into the model revealed a higher risk of hospitalization associated with increasing age (RR 1.02, 95% CI 1.00, 1.04), and a lower risk of hospitalization among patients on angiotensin-converting enzyme (ACE) inhibitors at baseline (RR 0.63, 95% CI 0.41, 0.96) and with higher baseline serum albumin (RR 0.49, 95% CI 0.33, 0.72).

Risk of hospitalization. Results of the multiple event model regression analyses are presented in Table 3. Univariate analyses using the GEE method incorporating changes in patient characteristics over time revealed a higher risk of hospitalization with increasing age (RR 1.01, 95% CI 1.00, 1.03), and among patients with cardiac disease (RR 2.43, 95% CI 1.66, 3.58), cerebrovascular disease (RR 1.89, 95% CI 1.12, 3.19) and peripheral vascular disease (RR 1.66, 95% CI 1.02, 2.68). There was a lower risk of hospitalization among patients with higher serum albumin (RR 0.48, 95% CI 0.35, 0.65), higher hematocrit (RR 0.89, 95% CI 0.86, 0.93) and among patients on ACE inhibitors (RR 0.64, 95% CI 0.47, 0.88). Multivariate analyses revealed a higher risk of hospitalization with increasing age (RR 1.02, 95% CI 1.00, 1.03), and among patients with cardiac disease (RR 1.91, 95% CI 1.19, 3.07). There was a lower risk of hospitalization among patients with higher serum albumin (RR 0.58, 95% CI 0.35, 0.95) and higher hematocrit (RR 0.92, 95% CI 0.87, 0.97).

Risk of subsequent hospital days. Results of the multiple event model regression analyses are presented in Table 4. Univariate analyses using the GEE method revealed a higher risk of subsequent hospital days with increasing age (RR 1.01, 95% CI 1.00, 1.03), and among patients with cardiac disease (RR 3.18, 95% CI 1.78, 5.65), cerebrovascular disease (RR 2.32, 95% CI 1.17, 4.60), peripheral vascular disease (RR 2.52, 95% CI 1.32, 4.80), and among patients with abnormal calcium-phosphorus metabolism (RR 1.50, 95% CI 1.10, 2.04) and on vitamin D (RR 1.26, 95% CI 1.00, 1.59). There was a lower risk of subsequent hospital days with patients with higher serum albumin (RR 0.35, 95% CI 0.23, 0.52),

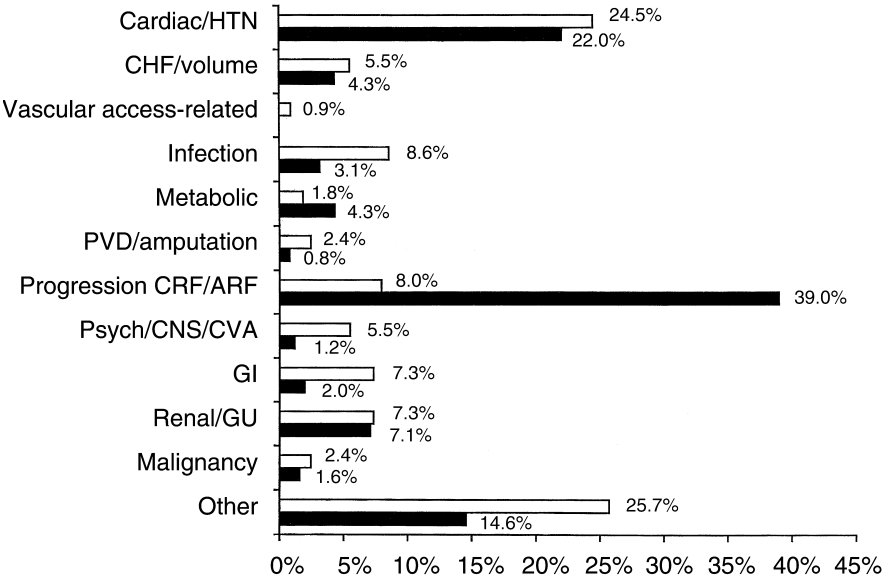

Fig. 1. Primary (□) and secondary (■) causes of hospitalization among patients with chronic kidney disease. Abbreviations are: GU, genitourinary; GI, gastrointestinal; Psych, psychiatry; CNS, central nervous system; CVA, cerebrovascular accident; CRF, chronic renal failure; ARF, acute renal failure; PVD, peripheral vascular disease; CHF, congestive heart failure; HTN, hypertension.

Table 3. Relative risk of hospitalization among patients with chronic kidney disease

	Generalized estimating equation	
Variables	Univariate RR (95% CI)	Multivariate RR (95% CI)
Age *per year increase*	1.01 (1.00, 1.03)[a]	1.02 (1.00, 1.03)[a]
Male *vs. female*	0.75 (0.51, 1.12)	1.01 (0.62, 1.63)
White *vs. non-white*	0.69 (0.44, 1.07)	0.82 (0.47, 1.44)
Comorbid conditions		
Diabetes	1.50 (0.99, 2.29)	1.15 (0.72, 1.83)
Cardiac disease	2.43 (1.66, 3.58)[a]	1.91 (1.19, 3.07)[a]
Cerebrovascular disease	1.89 (1.12, 3.19)[a]	
Peripheral vascular disease	1.66 (1.02, 2.68)[a]	
Albumin *per g/dL increase*	0.48 (0.35, 0.65)[a]	0.58 (0.35, 0.95)[a]
Hematocrit *per % increase*	0.89 (0.86, 0.93)[a]	0.92 (0.87, 0.97)[a]
ACE inhibitor use *vs. non-use*	0.64 (0.47, 0.88)[a]	

[a] Significant associations

Table 4. Relative risk of hospital days among patients with chronic kidney disease

	Generalized estimating equation	
Variables	Univariate RR (95% CI)	Multivariate RR (95% CI)
Age *per year increase*	1.01 (1.00, 1.03)[a]	1.02 (0.99, 1.05)
Male *vs. female*	0.71 (0.40, 1.26)	1.68 (0.83, 3.40)
White *vs. non-white*	0.77 (0.42, 1.44)	1.01 (0.50, 2.03)
Co-morbid conditions		
Diabetes	1.24 (0.68, 2.25)	1.10 (0.48, 2.48)
Cardiac disease	3.18 (1.78, 5.65)[a]	
Cerebrovascular disease	2.32 (1.17, 4.60)[a]	
Peripheral vascular disease	2.52 (1.32, 4.80)[a]	
Albumin *per g/dL increase*	0.35 (0.23, 0.52)[a]	0.34 (0.21, 0.55)[a]
Hematocrit *per % increase*	0.90 (0.83, 0.98)[a]	0.87 (0.81, 0.93)[a]
Abnormal Ca-PO_4 metabolism	1.50 (1.10, 2.04)[a]	
Vitamin D use *vs. non-use*	1.26 (1.00, 1.59)[a]	
ACE-inhibitor use *vs. non-use*	0.52 (0.30, 0.92)[a]	0.63 (0.47, 0.84)[a]

[a] Significant associations

higher hematocrit (RR 0.90, 95% CI 0.83, 0.98), and among patients on ACE inhibitors (RR 0.52, 95% CI 0.30, 0.92). Multivariate analyses revealed a lower risk of subsequent hospital days among patients with higher serum albumin (RR 0.34, 95% CI 0.21, 0.55), higher hematocrit (RR 0.87, 95% CI 0.81, 0.93) and among patients on ACE inhibitors (RR 0.63, 95% CI 0.47, 0.84).

Outpatient nephrology visits

There were 4.0 outpatient nephrology visits per patient-year at risk. Results of the multiple event model regression analyses are presented in Table 5. Univariate analyses using the GEE method revealed a higher risk of outpatient nephrology visits among patients with abnormal Ca-PO_4 metabolism (RR 1.40, 95% CI 1.21, 1.61), and among patients on erythropoietin (RR 1.54, 95% CI 1.23, 1.92), iron (RR 1.38, 95% CI 1.08, 1.75), and vitamin D (RR 1.34, 95% CI 1.04, 1.74). There was a lower risk of outpatient nephrology visits among patients with higher hematocrit (RR 0.98, 95% CI 0.96, 0.99). Multivariate analyses revealed a higher risk of outpatient nephrology visits among patients on erythropoietin (RR 1.47, 95% CI 1.11, 1.82), while none of the other factors remained significant.

DISCUSSION

The current study reveals significant resource utilization among patients with CKD. During a median follow-up of 11.4 months, 47% of patients had at least one hospitalization, and there were on average 0.96 hospitalizations, 6.6 hospital days and 4.0 outpatient nephrology visits per patient-year at risk. Cardiac disease/hyperten-

Table 5. Relative risk of outpatient nephrology visits among patients with chronic kidney disease

Variables	Generalized estimating equation	
	Univariate RR (95% CI)	Multivariate RR (95% CI)
Age *per year increase*	1.00 (1.00, 1.00)	1.00 (0.99, 1.00)
Male *vs. female*	0.94 (0.78, 1.13)	0.97 (0.80, 1.16)
White *vs. non-white*	0.89 (0.72, 1.10)	0.89 (0.72, 1.11)
Diabetes	1.10 (0.90, 1.35)	0.99 (0.82, 1.20)
Creatinine *per mg/dL increase*	0.99 (0.98, 1.00)	
GFR *per mL/min/1.73 m^2 decrease*	1.06 (0.98, 1.14)	
Hematocrit *per % increase*	0.98 (0.96, 0.99)[a]	
Abnormal Ca-PO_4 metabolism	1.40 (1.21, 1.61)[a]	
Erythropoietin use *vs. non-use*	1.54 (1.23, 1.92)[a]	1.47 (1.11, 1.82)[a]
Oral iron use *vs. non-use*	1.38 (1.08, 1.75)[a]	
Vitamin D use *vs. non-use*	1.34 (1.04, 1.74)[a]	

[a] Significant associations

sion was the most common primary diagnosis of hospitalizations, and progression of CKD/acute kidney failure was the most common secondary cause of hospitalization. Multivariate analyses incorporating changes in covariates over time (generalized estimating equation) revealed that older age and presence of cardiac disease were associated with a higher risk of hospitalization, while higher serum albumin and higher hematocrit were associated with a lower risk of hospitalization. In addition, higher albumin, higher hematocrit and ACE inhibitor use were associated with lower risk of subsequent hospital days. Only erythropoietin use was associated with a higher risk of outpatient nephrology visits.

The results confirm that hospital utilization among patients with CKD is high. We have previously shown that the dialysis population at our institution had 2.2 hospitalizations and 14.8 hospital days per patient-year at risk [8], which was similar to that among U.S. hemodialysis patients between 1996 and 1998, who had 1.9 hospitalizations and 14 hospital days per patient-year at risk [5]. In the general population, there were 0.31 hospitalizations and 1.9 hospital days per person in 1998 [12]. Hospital utilization among CKD patients was thus three times higher than among patients in the general population above the age of 15 years in a similar era and is in all likelihood even higher than we described, as hospitalizations outside of NEMC were not reliably captured. The causes of hospitalization among CKD patients in our study were similar to those in the U.S. dialysis population, with the exception of vascular access hospitalizations, which are a frequent cause of hospitalization among dialysis patients, and were rare in the current CKD cohort [5, 8]. Cardiac complications were the leading cause of hospitalization among CKD patients, accounting for 24.5% of all admissions, and this diagnostic category was also the second most common secondary cause of hospitalization in our cohort. Furthermore, the prevalence of certain comorbid conditions in our CKD cohort was comparable to the prevalence in the U.S. dialysis population: cardiovascular disease (40 vs. 58.8%), cerebrovascular disease (12 vs. 8%), and peripheral vascular disease (14 vs. 14%) [3]. The higher hospital utilization among patients with CKD compared to the general population and the similarity in the comorbid conditions and the causes of hospitalization between patients with CKD and ESRD patients, confirm the hypothesis that the complications and comorbidity observed in ESRD manifest themselves well before the onset of ESRD.

The results of this study in part support earlier findings regarding risk factors for hospital utilization among patients with kidney failure. Previous studies have demonstrated an association between age, gender, race, cardiac disease, peripheral vascular disease, serum albumin and hematocrit levels, and resource utilization among dialysis [8, 13, 14] and pre-dialysis [15] patients. Older age has been identified as an independent predictor of hospitalization in the ESRD population [13] and among patients identified as likely to progress to ESRD [15]. In addition, older age is associated with increased morbidity and mortality among ESRD patients [16–19]. The current analyses incorporating changes in age over time also identified an independent association between age and a higher risk of hospitalization.

Comorbid conditions such as cardiovascular disease, ischemic heart disease and peripheral vascular disease have been shown to be associated with increased hospitalizations among ESRD [8, 14] and pre-dialysis [15] patients. In the current study, cardiovascular comorbidity was strongly associated with an increased risk of hospitalization; however, the relationship was attenuated in the multivariate analyses. This may reflect a stronger influence of other factors such as use of ACE inhibitors and level of albumin and hematocrit (see paragraphs to follow), or an interplay between these factors and cardiovascular disease. Alternatively, these factors may serve as markers for other unmeasured comorbid conditions that affect risk of hospital utilization.

The benefit of ACE inhibitors in retarding the progression of kidney disease is fairly well established [20–22]. Although this study was not designed to evaluate this outcome, the analyses did reveal a lower risk of hospital utilization among patients recorded as using an ACE inhibitor in both the traditional Cox proportional hazards model and the generalized estimating equation model assessing risk of subsequent hospital days. Given the high prevalence of ischemic and other cardiac diseases in this patient population, it may be postulated that ACE inhibitors reduce the risk of hospital utilization by modification of cardiovascular risk factors, although the interaction between ACE inhibitor use and cardiovascular diseases was not significant. This may in part

be explained by imperfect capture of cardiovascular conditions. Alternatively, ACE inhibitor use may be a surrogate for other factors that were not recorded, or may simply reflect better access to care and improved management of other conditions. That is, patients presenting regularly for care are more likely to be prescribed recommended therapies.

Lower serum albumin levels have been shown to be associated with increased hospital utilization [8, 14] and mortality [16, 23] in the ESRD population. In the current study, higher serum albumin was independently associated with a lower risk of hospital utilization, but was not associated with frequency of outpatient nephrology visits. Albumin is considered a marker of nutrition, and hence, it could be inferred that well nourished patients are at lower risk of adverse outcomes. However, other non-nutritional factors are also important determinants of albumin level. It is a negative acute phase reactant, and acute or chronic medical conditions have an impact on its synthesis [24]. Thus, the independent association of serum albumin may be the reflection of underlying disease severity. Consequently, although low serum albumin levels may serve to identify patients at greater risk for hospitalization, whether closer surveillance and interventions targeted at improving serum albumin levels would lead to less morbidity remains to be proven.

We found a significant association between hematocrit levels and the risk of hospitalization and hospital days. Higher hematocrit levels have been shown to be associated with a lower risk of hospitalization among patients with ESRD [6] and CKD [15], and with a lower mortality among patients with ESRD [25]. The impact of anemia may possibly be attributed to its relationship with cardiovascular complications, given the high morbidity associated with cardiovascular conditions in this population. Alternatively, other comorbid conditions leading to anemia, for which anemia serves as a marker, also may contribute to hospitalizations.

There is paucity of information on the factors associated with outpatient utilization among patients with chronic kidney disease. In a recent study of dialysis patients at our center, diabetes, younger age, Caucasian race and late referral to nephrology (that is, first nephrology visit less than 4 months prior to the initiation of dialysis) were shown to be independently associated with higher number of outpatient nephrology visits [8]. In the current study, only erythropoietin use was significantly associated with outpatient utilization. This may simply reflect that erythropoietin administration occurs most often at the physician's office and thus involves frequent visits. Alternatively, patients presenting more frequently for care are more likely to be diagnosed with a condition requiring treatment and thus to have the initiation of specific therapies. Thus, similarly as with ACE inhibitor use, erythropoietin use may reflect better access to care.

Levels of kidney function examined as either serum creatinine level or estimated GFR were not significantly associated with any of the measures of resource utilization evaluated in the current study. This is in contrast to the study by Holland and Lam, which noted that patients with serum creatinine levels >3.4 mg/dL had a 64% increased risk of hospitalization compared to patients with lower serum creatinine levels in univariate analysis. However, this relationship was not seen in multivariate analyses [15]. Serum creatinine may not be as strong a marker for other undefined conditions as has been speculated. If this were indeed the case, risk stratification primarily based on level of kidney function without taking into consideration other comorbid conditions may be misguided, and may potentially result in misallocation of resources.

To our knowledge, most investigators evaluating the association between risk factors and clinical or economic outcomes among patients with CKD or ESRD have generally assessed only the impact of baseline factors on subsequent outcomes. The GEE methodology used in this study incorporates potentially changing covariates in the analysis of repeated outcomes. This may provide a more accurate assessment of the particular factor's impact, or alternatively provide more accurate adjustment, especially as some factors, such as albumin and hematocrit, may be expected to change with time and advancing kidney disease.

The results of this study must be interpreted with its limitations in mind. It is a retrospective study with variable ascertainment of data and follow-up. Specifically, medications recorded in the chart may not reflect the actual use of the medication, thus the impact of medications on outcomes must be considered with caution. Hospitalizations outside of NEMC were not reliably captured, and only nephrology visits were analyzed, as we were primarily interested in nephrology-specific care. Thus utilization is actually higher than we described. In addition, the study is based in a tertiary care center, the patient population was predominantly Caucasian, and there was a relatively high prevalence of Asians and low prevalence of African Americans due to our center's location in the Chinatown district of Boston. The relative under-representation of African American is related to the overall demographic mix representative of the patients at our institution, and is not a selection bias of the study. Finally, a majority of the patients had some form of managed care insurance. These limitations may lead to under- or overestimation of the hospitalization risk, or to a lack of generalizability.

Despite these limitations, this study provides an overview of the resource utilization among patients with CKD in the United States and identifies potential factors associated with increased utilization. Targeting these factors with timely interventions could translate into re-

duced morbidity and mortality, and potentially reduced hospital utilization and cost. Future prospective studies are required to determine potential causal relationships between improvements in these modifiable factors and morbidity and resource utilization.

ACKNOWLEDGMENTS

This project was supported by the National Institutes of Health: F32 HS 00143 (Dr. Kazmi), 1KO8 DK 02745 (Dr. Kausz), and T32DK07777 (Dr. Abichandani), and Amgen, Inc. Drs. Pereira and Kausz serve on Amgen's Medical Advisory Board. We gratefully acknowledge the contributions of Drs. James A. Strom, Geetha Narayan, Martin Gelman, Sally Hood and Tony Dash, who provided access to their clinic records, and two Tufts University medical students, Alicia Krol and Nancy La Vine, who assisted in reviewing charts to identify the patients with CKD.

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