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Partial Nephrectomy vs. Radical Nephrectomy in Patients With Small Renal Tumors: Is There a Difference in Mortality and Cardiovascular Outcomes?

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Abstract

Purpose—Radical nephrectomy (RN), compared with partial nephrectomy (PN), increases the risk of chronic kidney disease, a significant risk factor for cardiovascular (CV) events and death. Given equivalent oncologic efficacy in patients with small renal tumors (RTs), RN may result in overtreatment. We analyzed a population-based cohort of patients to determine if RN is associated with an increase in CV events and mortality compared with PN.

Materials and Methods—Using Surveillance, Epidemiology, and End Results (SEER) cancer registry data linked with Medicare claims, we identified 2991 patients older than 65 years of age treated with RN or PN for RTs 4 cm or smaller between 1995 and 2002. Primary end points of CV events and overall survival were assessed using Kaplan-Meier survival estimation, Cox proportional hazards regression, and negative binomial regression.

Results—A total of 2547 (81%) patients underwent RN and 556 (19%) underwent PN. During a median follow-up of 4 years, 609 patients had a CV event and 892 patients died. Adjusting for preoperative demographic and comorbid variables, RN was associated with an increased risk of overall mortality (hazard ratio [HR] 1.38, P<0.01) and a 1.4 times greater number of CV events after surgery (P<0.05). RN, however, was not associated with an increased risk of time to first CV event (HR 1.21, P=0.10) or CV death (HR 0.95, P=0.84).

Conclusion—RN, currently the most common treatment for small RTs, may be associated with significant, adverse treatment effects compared with PN. PN should be considered for most patients with small RTs.

Keywords

Radical Nephrectomy; Partial Nephrectomy; Mortality; Cardiovascular Events

Introduction

In 2008 there will be approximately 54,400 newly diagnosed cases of renal tumors (RTs) in the United States.[1] For nearly two decades, the incidence has been steadily rising, largely

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attributed to the incidental detection of small, localized tumors from widespread use of abdominal imaging for unrelated conditions.[2] This has resulted in a downward stage migration, with small incidental RTs (≤4 cm, T1a) now accounting for the largest proportion of newly diagnosed renal masses.[3]

As expected, the increased incidence of RTs has been mirrored by an increase in the number of surgical procedures performed to remove these tumors.[4] What has been unanticipated, however, is the continuing increase in mortality observed among these patients after surgery, including patients with RTs ≤ 4 cm.[4] Assuming that complete surgical removal of small localized RTs is generally curative, the mortality rates of patients with small RTs should be declining, not rising.

This seemingly paradoxical trend has drawn attention to the significance of comorbid conditions and competing causes of mortality in patients undergoing surgical treatment for RTs, and has demonstrated a need to reassess the treatment effects from removal of these tumors.[4] One mechanism by which the surgical treatment of RTs may adversely influence non-onocologic outcomes is through the development of chronic kidney disease (CKD) after surgery. CKD is associated with the development of kidney failure, as well as cardiovascular (CV) disease and premature death.[5, 6]

Although radical nephrectomy (RN) is a significant risk factor for the development of CKD in patients with RTs,[7] it continues to be the most common procedure performed for patients with small RTs in the United States and abroad.[8, 9] This widespread utilization of RN may result in overtreatment of many of these tumors, contributing to the rising overall mortality seen in these patients, particularly individuals with small RTs who are unlikely to die of renal cancer. To investigate this hypothesis, we examined a population-based cohort of patients with RTs ≤4 cm to determine whether RN is associated with increased risk of CV events and death compared with partial nephrectomy (PN).

Materials and Methods

Data

Our sample was obtained from Surveillance, Epidemiology, and End Results (SEER) cancer registry data linked with Medicare claims. SEER, a consortium of population-based cancer registries sponsored by the National Cancer Institute, currently includes 17 registries covering approximately 26% of the population.[2] For all incident cancers in their coverage areas, the SEER registries collect information regarding site and extent of disease, first course of treatment, and sociodemographic characteristics, with active follow-up for date and cause of death.[2] For cancer patients aged 65 and older residing in SEER areas, Medicare claims have been linked to SEER files. Medicare is the primary health insurer for 97% of Americans 65 years and older, covering inpatient hospital care (Part A) and outpatient care and physician services (Part B). Compared with the US elderly population, the SEER-Medicare population has similar age and sex distributions, but has a smaller proportion of non-whites, and individuals in SEER-Medicare are more likely to live in urban areas and affluent areas.[2]

Patient Selection

In the linked SEER-Medicare database, we identified all first primary renal-cortical tumors (*ICD-O-2 Topography* codes C64, C64.9) diagnosed between 1995 and 2002. The cohort was restricted to patients aged 66 and older whose primary tumor was less than or equal to 4 cm (pT1a). We excluded patients whose diagnoses were made only at the time of death, patients who were in a managed care plan during the course of treatment, and patients who lacked Part A or Part B Medicare coverage.

Surgery

Although SEER records information on cancer-directed surgery, it does not identify procedure dates. Therefore we defined the type and date of renal surgery based on Medicare claims within the first 6 months after cancer diagnosis. Using *Current Procedural Terminology (CPT)* codes and *ICD-9-Clinical Modification (ICD-9-CM)* procedure codes, we classified definitive renal surgery as either RN (*CPT* codes 50220, 50225, 50230, 50545, 50546; *ICD-9-CM* codes: 5551, 5552, 5553, 5554) or PN (*CPT* codes: 50240, 50280, 50290, 50542, 50543; *ICD-9-CM* codes 5531 5539, 554). If a patient had a claim for RN within 30 days after a claim for PN, type of surgery was categorized as RN. Patients were excluded from the study if they had no claim for definitive renal surgery within 6 months of diagnosis, if they had a claim for RN more than 30 days after a claim for PN, or if they had a claim for PN preceded by a claim for RN.

Outcomes

Primary end points of the analysis were CV events, CV deaths, and all-cause mortality after renal surgery. CV events, based on claims for inpatient care, included myocardial infarction, ischemic stroke, transient ischemic attack, percutaneous coronary intervention, coronary artery bypass graft surgery, and hospitalization for a diagnosis of acute angina, congestive heart failure, coronary artery disease, or peripheral vascular disease. Diagnosis and procedure codes identifying these events were adapted from a prior study of CV events in patients with CKD.[5]

Date of death was identified from Medicare enrollment records, with follow-up for vital status through December 31, 2004. CV deaths, identified from the underlying cause of death reported on the state death certificate, included deaths attributed to diseases of the heart (*ICD-9*: 390-398, 402, 404, 410-429; *ICD-10*: I00-I09, I11, I13, I20-I51), hypertension without heart disease (*ICD-9*: 400-401, 403; *ICD-10*: I10, I12), or cerebrovascular diseases (*ICD-9*: 430-438; *ICD-10*: I60-I69).

Predictors of Surgery

We examined several variables hypothesized to predict type of surgery and potentially confound the relationship between surgery and the primary end points. Demographic characteristics, from SEER and Medicare records, included age at diagnosis, race, marital status, urban-rural location, and area-level socioeconomic status.

Comorbidity was defined in two ways. In one set of analyses we used the Romano modification of the Charlson comorbidity index,[10, 11] based solely on inpatient claims during the year prior to surgery. In separate analyses we identified specific medical conditions based on diagnosis codes in inpatient, outpatient, and physician claims during the year prior to surgery.

Statistical Analysis

Unadjusted associations between type of renal surgery and patient characteristics were examined using chi-square statistics. We used multivariable logistic regression to estimate the adjusted effects of each characteristic on the likelihood of receiving RN versus PN. Odds ratios (OR), 95% confidence intervals, and two-sided P values were calculated for each predictor.

The relationship between type of surgery and each primary end point was evaluated in a time-to-event framework. In all analyses, the time origin was the date of surgery. In analysis of the time to first CV event, patients who died without experiencing an event were censored at the time of death. In analysis of the time until CV death, patients were censored if they died of non-CV causes. We constructed Kaplan-Meier survival curves stratified by type of surgery, and we used multivariable Cox proportional hazards regression to assess the effect of surgery type on the hazard of each end point, controlling for demographic characteristics and

comorbidity. The effect of surgery type on the total number of CV events per person-time at risk was assessed using negative binomial regression. We also evaluated interactions between type of surgery and patient characteristics, including preexisting comorbid conditions. All analyses were performed using SAS software (Cary, NC).

Results

Patient Characteristics and Predictors of Treatment

The study cohort included 2991 patients with definitive surgery for a RT of 4 cm or smaller diagnosed between 1995 and 2001. Five hundred fifty-six patients (18.6%) had PN and 2435 patients (81.4%) had RN. The demographic and clinical characteristics of all patients are shown in Table 1. Patients receiving PN were more likely to be younger, male, married, and treated more recently. No differences were noted in type of surgery based on urban vs. rural residence, area-level socioeconomic status, or race. In unadjusted analysis, comorbidities between the two cohorts were similar except for preoperative renal disease ($P<0.01$) and cerebrovascular disease ($P<0.05$) (Table 1).

Adjusting for demographic characteristics and preexisting comorbid conditions, factors predictive of RN included age at surgery (OR 1.43, $P<0.001$), female gender (OR 1.31, $P<0.05$), and cerebrovascular disease (OR 1.41, $P<0.05$). Factors predictive of PN included a more-recent year of surgery (OR 0.84, $P<0.0001$) as well as preexisting renal disease (OR 0.66, $P<0.01$) (Table 2).

Primary End Point Analysis

Cardiovascular events—A total of 609 patients had at least one CV event after surgery, including 84 patients (15.1%) in the PN group and 525 patients (21.6%) in the RN group. Median follow-up time was 43 months overall and 48 months among patients who were alive at the end of follow-up. In the PN group, the 3-year and 5-year probabilities of freedom from a CV event were 86% and 82%, respectively. In the RN group, the 3-year and 5-year probabilities of freedom from a CV event were 82% and 75%. CV event-free survival, stratified by type of surgery, is depicted in Figure 1A. In unadjusted analysis, RN was associated with an increased risk of a CV event [hazard ratio (HR) 1.37, $P<0.01$]. Controlling for demographic characteristics and preexisting comorbid conditions, the risk of a CV event was greater in the RN cohort than the PN cohort, but did not reach statistical significance (HR 1.21, $P=0.1$). (Table 3) In the interest of parsimony, urban-rural residence and census-tract poverty were excluded from this and subsequent multivariable models, as they did not confound the relationship between type of surgery and the primary end points. Interactions between type of surgery and patient characteristics were not statistically significant.

Using negative binomial regression to estimate the effect of surgery type on the total number of CV events, accounting for per person-time at risk, we found a significant difference between groups. The incidence of CV events in the patients who received RN was 1.4 times greater than in the patients who received PN ($P<0.05$), controlling for demographic characteristics and comorbidity.

Cardiovascular deaths—Of the 892 deaths, 173 were attributed to CV causes. Twenty-seven patients (4.9%) in the PN group and 146 patients (6.0%) in the RN group died secondary to CV causes. Controlling for patient characteristics, type of surgery was not statistically significantly associated with the risk of CV death. Predictors of CV-related deaths included increased age, black race, and history of congestive heart disease (data not shown).

All-cause mortality—About 30% of the patients died during the study period, including 110 (19.8%) in the PN group and 782 patients (32.1%) in the RN group. The 3-year and 5-year survival probabilities were 87% and 74% after PN and 80% and 68% after RN. (Figure 1B) The median time to death after RN was 102 months (not reached in the PN group). In unadjusted analysis, RN was associated with a significantly increased risk of death from any cause (HR 1.46, P<0.001) Controlling for patient characteristics, RN remained a significant predictor of death from any cause (HR 1.38, P<0.001) (Table 4). Interactions between type of surgery and preexisting comorbid conditions were not statistically significant. Overall, 107 deaths (3.5%) were attributed to kidney cancer, including 8 (1.4%) in the PN group and 99 (4.0%) in the RN group.

Discussion

Despite many studies demonstrating equivalent oncology efficacy between RN and PN in treating RTs ≤ 4cm and select tumors ≤ 7 cm,[12-14] RN remains the most common form of treatment for newly diagnosed small RTs.[8, 9] In this study as well as other population-based studies, fewer than 1 in 5 patients with RTs ≤ 4 cm are treated with PN.[8]

During the last decade there has been a paradigm shift at specialized medical centers in the United States, where elective PNs now account for up to 60% of all nephrectomies.[15, 16] This trend toward organ preservation, similar to other solid malignancies such as breast cancer and soft-tissue sarcomas, is a result of improvements in surgical techniques, advances in the understanding of the biology of RTs, and an increasing awareness of the importance of preserving long-term kidney function.

Several studies have demonstrated poor kidney functional outcomes in patients treated with RN rather than PN.[17, 18] Recently, we demonstrated that even in the setting of a normal baseline serum creatinine and two normally functioning kidneys, patients undergoing RN for a solitary small RT (≤4 cm) had a statistically significant greater risk of developing CKD after surgery (HR 3.8, P<0.0001). The 3-year probability of freedom from new onset of CKD was only 35% in patients who received RN compared with 80% in patients who received PN (P<0.0001).[7]

The clinical significance of iatrogenic CKD has been poorly studied and remains an investigational topic of great importance. Emerging evidence suggests that the type of treatment for small RTs may have a significant effect on morbidity and mortality. In a recent series from the Mayo Clinic, younger patients (<65 years of age) treated with RN instead of PN for pT1a tumors had a significantly increased risk of mortality after adjusting for preoperative variables associated with mortality.[16] In our study, we examined a population-based cohort of patients aged 65 years and older. Patients treated with RN instead of PN for small RTs developed significantly more CV events over time and had a significantly greater risk of death from any cause. No significant differences, however, were observed between the two groups in the hazard of either a first CV event or CV-related death.

Although these results seem incongruent, they are consistent with data from other studies examining the relationships between CKD, CV disease, and mortality. CKD may be a greater risk factor for *recurrent* CV events than for the onset of a first CV event.[19] In addition, CKD and CV disease appear to act as strong independent risk factors, as opposed to synergistic risk factors, for mortality.[20] Thus, it is not surprising to find that patients undergoing RN have an increase in the cumulative number of CV events and in all-cause mortality, but no increase in the risk of a first CV event or CV death.

Several limitations of this study warrant mention. The largest is the lack of randomization and the possible influence of selection bias on the observed differences in survival and CV events

between the cohorts. To minimize the effect of selection bias, we controlled for demographic and comorbid factors that would be expected to influence both treatment choice and outcomes. Unfortunately, the only way to eliminate this bias would be to prospectively randomize patients to RN or RN, a study many would consider unethical today.

Another limitation is the lack of information on pre- and postoperative kidney function. Although Medicare claims provided data on important and relevant comorbidities, serum creatinine levels for these patients were not available to determine which patients had preexisting CKD and which patients developed CKD after surgery. Without such data, the proposed pathway by which the type of surgery influences the risk of CKD and subsequently the risk of CV events and mortality can be inferred but not directly observed.

Despite these limitations, our results have important ramifications for the treatment of small RTs. It is becoming increasingly evident that goals of treatment for RTs, particularly small incidental RTs, extend well beyond tumor control. Surgeons must carefully consider each patient on an individual basis and understand not only the biology of the disease but also the consequences that the treatment may have on the survivorship of the patient. Given the potentially serious, detrimental long-term effects of RN, it is worth reassessing the current treatment standards for RTs, making PN the preferred treatment for many newly diagnosed small tumors.

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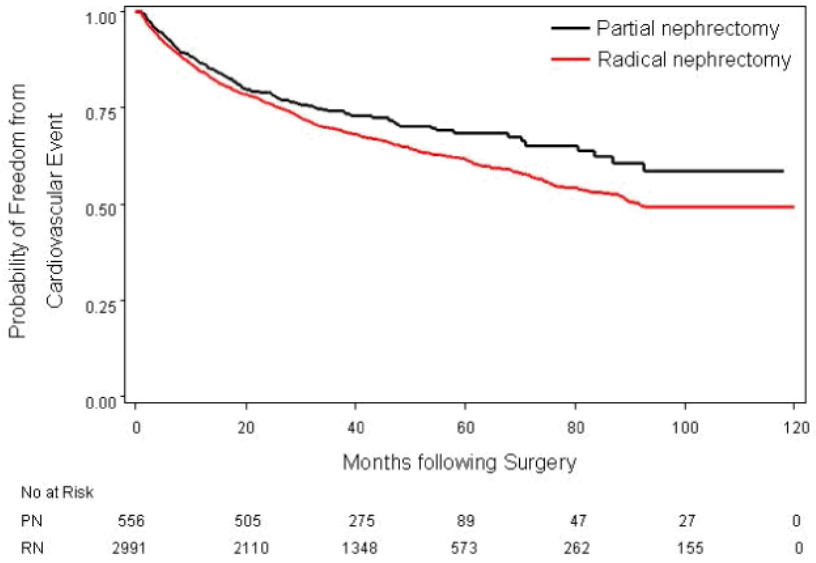
1a. Cardiovascular Events



1b. Overall Mortality (Death from Any Cause)

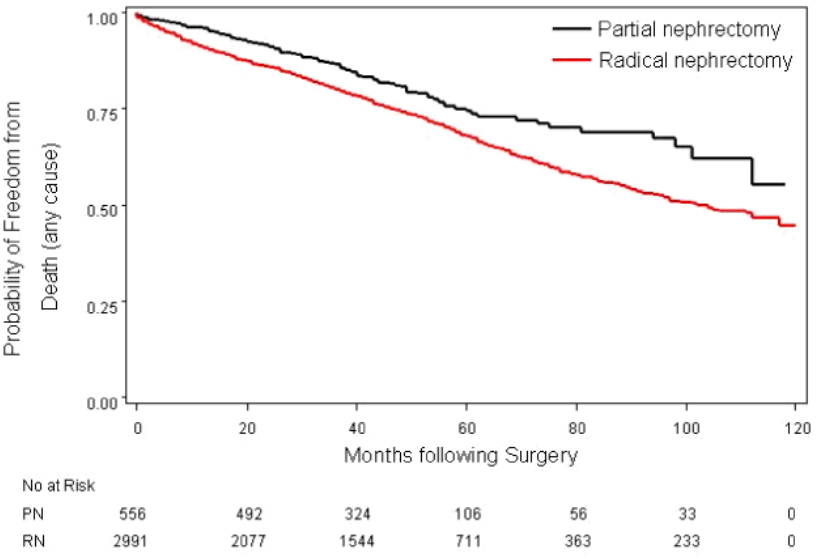


Figure 1. Kaplan Meier Estimates According to Surgery Type

Table 1

Characteristics of the Study Cohorts

Characteristic (N=2991)	PN (N=556)	RN (N=2435)	Total	P-value
Age				<0.001
66-69	22.4%	77.6%	691	
70-74	20.2%	79.8%	936	
75-79	17.7%	82.3%	815	
80-84	13.9%	86.1%	423	
85+	7.1%	92.9%	126	
Gender				<0.001
Male	20.5%	79.5%	1,713	
Female	16.0%	84.0%	1,278	
Marital Status				<0.05
Not Married	16.6%	83.4%	1,136	
Married	19.8%	80.2%	1,855	
Race				
White	18.5%	81.5%	2,575	NS
Black	20.0%	80.0%	230	
Other	17.7%	82.3%	186	
Urban vs. Rural Residence				NS
Urban	18.9%	81.1%	2,594	
Rural	16.9%	83.1%	397	
Year of Surgery				<0.001
1995	8.1%	91.9%	235	
1996	15.0%	85.0%	254	
1997	13.5%	86.5%	230	
1998	10.8%	89.2%	240	
1999	15.7%	84.3%	235	
2000	19.0%	81.0%	536	
2001	21.7%	78.3%	589	
2002	26.0%	74.0%	672	
Census Tract % Poverty Level				
Lowest Tertile	16.1%	83.9%	646	NS
Second Tertile	17.1%	82.9%	648	
Third Tertile	16.3%	83.7%	646	
Charlson-Romano Index				NS

Characteristic (N=2991)	PN (N=556)	RN (N=2435)	Total	P-value
0	18.8%	81.3%	2,320	
1	18.7%	81.3%	347	
2+	17.3%	82.7%	324	
Diabetes				
No	18.0%	82.0%	2,181	NS
Yes	20.1%	79.9%	810	
Acute Myocardial Infarction				
No	18.5%	81.5%	2,741	NS
Yes	20.0%	80.0%	250	
Congestive Heart Failure				
No	18.9%	81.1%	2,287	NS
Yes	17.5%	82.5%	704	
Cerebrovascular Disease				
No	19.3%	80.7%	2,517	<0.05
Yes	14.8%	85.2%	474	
Vascular Disease				
No	18.6%	81.4%	2,358	NS
Yes	18.5%	81.5%	633	
Renal Insufficiency				
No	17.9%	82.1%	2,717	<0.01
Yes	25.2%	74.8%	274	
Hypertension				
No	18.2%	81.8%	2,310	NS
Yes	19.8%	80.2%	681	

Abbreviation: NS, not significant

Table 2

Predictors of Surgery

Characteristic	Adjusted Odds Ratio	95% C I	P-value
Age (per year)	1.04	1.02 to 1.06	<0.0001
Gender			
Male	Reference		
Female	1.31	1.07 to 1.61	<0.05
Year of Surgery (per year)	0.84	0.8 to 0.89	<0.0001
Race			
White	Reference		
Black	1.02	0.71 to 1.47	NS
Other	1.07	0.72 to 1.60	NS
Urban vs. Rural Residence			
Urban	Reference		
Rural	1.24	0.92 to 1.67	NS
Marital Status			
Not Married	Reference	to	
Married	0.89	0.72 to 1.11	NS
Census Tract % Poverty Level			
Lowest	Reference		
Second Tertile	0.81	0.6 to 1.09	NS
Third Tertile	0.84	0.61 to 1.15	NS
Co-morbid Condition			
Diabetes	0.93	0.75 to 1.16	NS
Acute Myocardial Infarction	0.91	0.64 to 1.29	NS
Congestive Heart Failure	1.23	0.96 to 1.58	NS
Cerebrovascular Disease	1.41	1.06 to 1.89	<0.05
Vascular Disease	1.03	0.81 to 1.30	NS
Kidney Insufficiency	0.66	0.48 to 0.90	<0.01
Hypertension	0.87	0.68 to 1.10	NS

Note: Odds ratios are adjusted for all variable in table and for SEER registry

Abbreviation: NS, not significant

Table 3

Characteristics Associated with Time to 1st CV event

Time to 1st CV Event	Hazard Ratio	95% C.I.	P-value
RN vs. PN	1.21	0.96 to 1.53	NS
Age (per year)	1.04	1.03 to 1.06	<0.001
Female vs. Male	0.77	0.64 to 0.91	<0.01
Year of Diagnosis (per year)	0.90	0.86 to 0.93	<0.001
Race (Black vs. White)	1.47	1.13 to 1.92	<0.01
Race (Other vs. White)	0.77	0.54 to 1.10	NS
Rural vs. Urban	1.18	0.94 to 1.48	NS
Married vs. Not Married	1.04	0.87 to 1.24	NS
Diabetes	1.47	1.23 to 1.75	<0.001
Acute Myocardial Infarction	1.42	1.11 to 1.81	<0.05
Congestive Heart Failure	1.71	1.42 to 2.06	<0.001
Cerebrovascular Disease	1.57	1.29 to 1.91	<0.001
Vascular disease	1.28	1.06 to 1.54	<0.05
Kidney Disease	1.17	0.90 to 1.52	NS
Hypertension	1.42	1.18 to 1.70	<0.001

Abbreviation: NS, not significant

Table 4
Characteristics Associated with Time to Death (any cause)

Death (any cause)	Hazard Ratio	95% C.I.	P-value
RN vs. PN	1.38	1.13 to 1.69	<0.001
Age (per year)	1.06	1.05 to 1.08	<0.001
Female vs. Male	0.77	0.67 to 0.89	<0.001
Year of Diagnosis (per year)	0.97	0.94 to 1.00	NS
Race (Black vs. White)	1.20	0.95 to 1.51	NS
Race (Other vs. White)	0.63	0.46 to 0.87	<0.01
Rural vs. Urban	1.01	0.83 to 1.24	NS
Married vs. Not Married	0.81	0.70 to 0.93	<0.001
Diabetes	1.16	1.00 to 1.35	NS
Acute Myocardial Infarction	1.41	1.15 to 1.74	<0.001
Congestive Heart Failure	1.45	1.25 to 1.70	<0.001
Cerebrovascular Disease	1.14	0.96 to 1.35	NS
Vascular disease	1.19	1.02 to 1.40	<0.05
Kidney Disease	1.59	1.30 to 1.95	<0.001
Hypertension	1.23	1.05 to 1.43	<0.05

Abbreviation: NS, not significant