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Relationships among Non-Neoplastic Histopathological Features, Kidney Function, Proteinuria, and Other Clinical Factors in Patients Undergoing Nephrectomy

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Keywords
Nephrosclerosis · Proteinuria · Hypertension · Obesity · Estimated glomerular filtration rate · Nephrectomy

Abstract

Introduction: The non-neoplastic kidney parenchyma from nephrectomies is often overlooked in routine examinations. We aimed to evaluate the associations between global glomerulosclerosis (GS), interstitial fibrosis (IF), or arteriosclerosis (AS) and estimated glomerular filtration rate (eGFR), dipstick proteinuria, and other clinical factors. ***Methods:*** We performed a cross-sectional analysis of 781 patients with nephrectomy. We used regression models with and without interaction factors. The tested exposures were GS, IF, or AS, and the outcome measures were GFR and dipstick proteinuria. ***Results:*** In multivariable analyses, increasing degrees of GS, IF, or AS were significantly associated with lower eGFR and proteinuria ($p < 0.05$ for each). Obesity and hypertension (HTN) modified the association between eGFR and degrees of GS, whereas proteinuria and cardiovascular disease (CVD) modified the association between eGFR and degrees of AS (p for interaction <0.05). Compared with GS <10%, GS >50% was associated with lower eGFR in patients with (−45 mL/min/1.73 m^2) than without (−19 mL/min/1.73 m^2) obesity, and GS >50% was associated with lower eGFR in patients with (−31 mL/min/1.73 m^2) than without (−16 mL/min/1.73 m^2) HTN. Compared with AS <26%, AS >50% was associated with lower eGFR in patients with (−11 mL/min/1.73 m^2) than without (−6 mL/min/1.73 m^2) proteinuria, and AS >50% was associated with lower eGFR in patients with (−23 mL/min/1.73 m^2) than without (−7 mL/min/1.73 m^2) CVD. ***Conclusion:*** Greater degrees of each GS, IF, and AS are independently associated with proteinuria and lower eGFR. Obesity, HTN, proteinuria, and CVD modify the relationship between eGFR and specific histopathological features of nephrosclerosis.

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Introduction

Nephrosclerosis is a general term that entails chronic histopathological fibrotic changes in one or more of the compartments of the kidney including glomeruli, global glomerulosclerosis (GS), tubule-interstitium, interstitial fibrosis (IF), tubular atrophy (TA), vasculature, and arteriosclerosis (AS). The extent of these chronic changes varies with age and is highly prevalent (>50%) in older individuals [1]. Nephrosclerosis is associated with lower estimated glomerular filtration rates (eGFR) in patients with suspected glomerular diseases undergoing kidney biopsy [2] and in individuals from the general population undergoing nephrectomy due to renal tumors who usually do not have a suspected kidney disease and frequently have comorbidities such as type 2 diabetes or hypertension [3–5].

Chronic histopathological changes such as GS, IF, and AS are also associated with proteinuria in living kidney donors [1] and in patients undergoing native kidney biopsy [2], but studies in tumor nephrectomy are scarce. One study showed an unadjusted association between IF and proteinuria [5], and a recent study showed an independent association between GS and proteinuria [6]. Whether all chronic histopathological changes (GS, IF, AS) are associated with proteinuria independent of eGFR and other clinical factors is unknown. Furthermore, whether proteinuria mediates the relationship between GS, IF, or AS and eGFR or whether proteinuria modifies the relationship between chronic histopathological features and eGFR is unknown.

In this study, we aimed to evaluate the association of nephrosclerosis features with lower eGFR and proteinuria and to determine whether the association with lower eGFR varies by the presence of proteinuria in nephrectomy patients. Additionally, we evaluated the modifying effects of hypertension, obesity, and cardiovascular disease (CVD) on the relationship between chronic histopathological changes and lower eGFR.

Materials and Methods

Study Population

A total of 813 patients that underwent nephrectomy were evaluated from 2013 to 2017. We excluded 32 patients with end-stage kidney disease (ESKD) on dialysis. We included 781 patients with nephrectomies (42% partial and 58% radical) in this study. The most common reason for nephrectomy was malignancy in 627 (80%), followed by benign conditions in 142 (18%), and trauma in 12 (2%) patients.

Measures

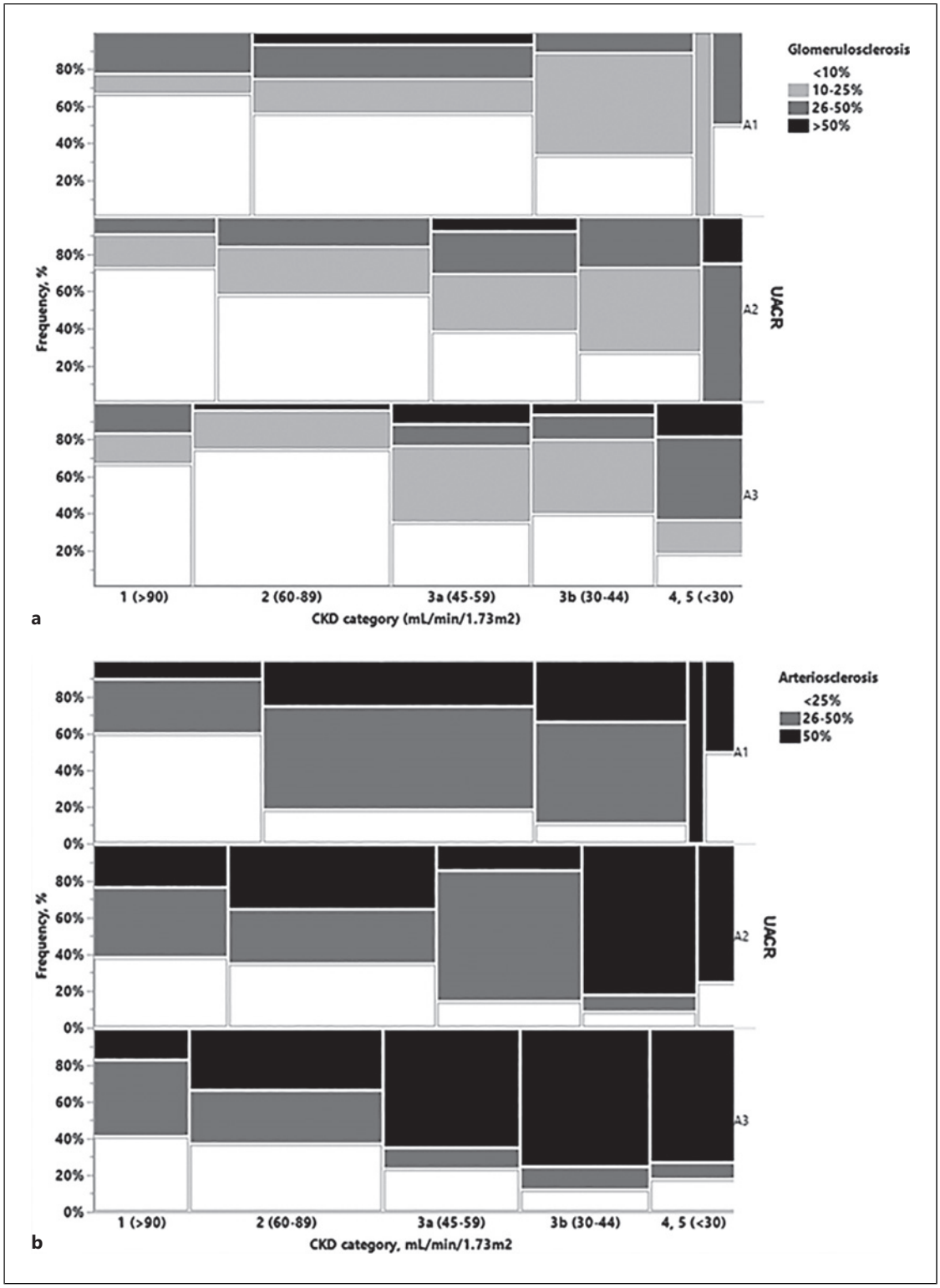
Pathological Evaluation

In 2013, the surgical pathology grossing and reporting protocol for nephrectomies in our institution was modified as follows: (a) inclusion of additional sampling of non-tumoral renal parenchyma; (b) staining for Hematoxylin-eosin (H&E), periodic acid-Schiff (PAS), trichrome, and silver of non-tumoral renal parenchyma; and (c) addition of the expanded checklist for reporting from the Renal Pathology Society recommendations [7]. Standardized morphologic evaluation of non-neoplastic renal parenchyma was performed on two to three micron-thick slides from paraffin-embedded tissue. In radical nephrectomy cases, pathology residents or pathology assistants chose the non-neoplastic section from regions grossly uninvolved by tumors, and in partial nephrectomy cases, the genitourinary pathologist who signed out the cases chose the slide containing as many glomeruli as possible and as far away from the tumor. All samples were reviewed by one of two trained nephropathologists (NPs) and reported as addendum. GS, IF, TA, and AS were described in pathology reports in categories according to the Banff classification [8]. GS was also described as the percentage of globally sclerosed glomeruli (GS%) calculated using the number of GS divided by the total glomeruli seen on light microscopy. When the number of glomeruli available to review was too many to count, the GS% was estimated after reviewing 100 glomeruli in a continuous section.

Primary exposures were the degrees of each chronic fibrotic histopathological features including GS, IF, and AS. The reported percentage of GS was reclassified using a semiquantitative approach [2, 9]: none to minimal (<10%), mild (10–25%), moderate (26–50%), and severe (>50%) to align with proposed standardized grading of chronic changes and to compare our results with similar prior studies. We reported GS% without adjusting for age [10], because our multivariable analyses included age in all the models. AS categories based on the Banff's criteria were reclassified only into three groups: mild (0–25%), moderate (26–50%), and severe (>50%), as previously proposed [9]. IF remained categorized as none (0–5%), mild (5–25%), moderate (26–50%), and severe (>50%). IF was not reported in 45 specimens. We only reported IF because TA was not consistently described in biopsy reports. IF is often associated with TA, and it is a surrogate measure of IFTA. We also report categories of each chronic histopathological feature according to the reasons for nephrectomy.

eGFR and Proteinuria

Primary clinical outcomes were pre-nephrectomy eGFR and dipstick proteinuria. We estimated GFR by the CKD Epidemiology Collaboration (CKD-EPI) 2009 equation [11], using the serum creatinine closest to the day of nephrectomy (including the same day but before nephrectomy) and up to 90 days before surgery. The eGFR was categorized according to KDIGO CKD guideline as follows: >90, 60–<90, 30–<60, 15–<30, and <15 mL/min/m^2. Proteinuria by dipstick (closest to the day of nephrectomy and up to 90 days before surgery) was categorized as follows: 0 = negative or <10 mg/dL, 1 = trace or 10 mg/dL, 2 = 1+ or 30 mg/dL, 3 = ≥2+ or 100 mg/dL. We defined proteinuria by dipstick as ≥ trace or 10 mg/dL. Subsequently, proteinuria by dipstick was converted to urine albumin to creatinine ratio (UACR) using the equation developed by Sumida et al. [12], and albuminuria was categorized as follows: A1 = <30 mg/g, A2 = UACR of 30–299 mg/g, A3 = UACR = ≥300 mg/g, as illustrated in Figure 1.



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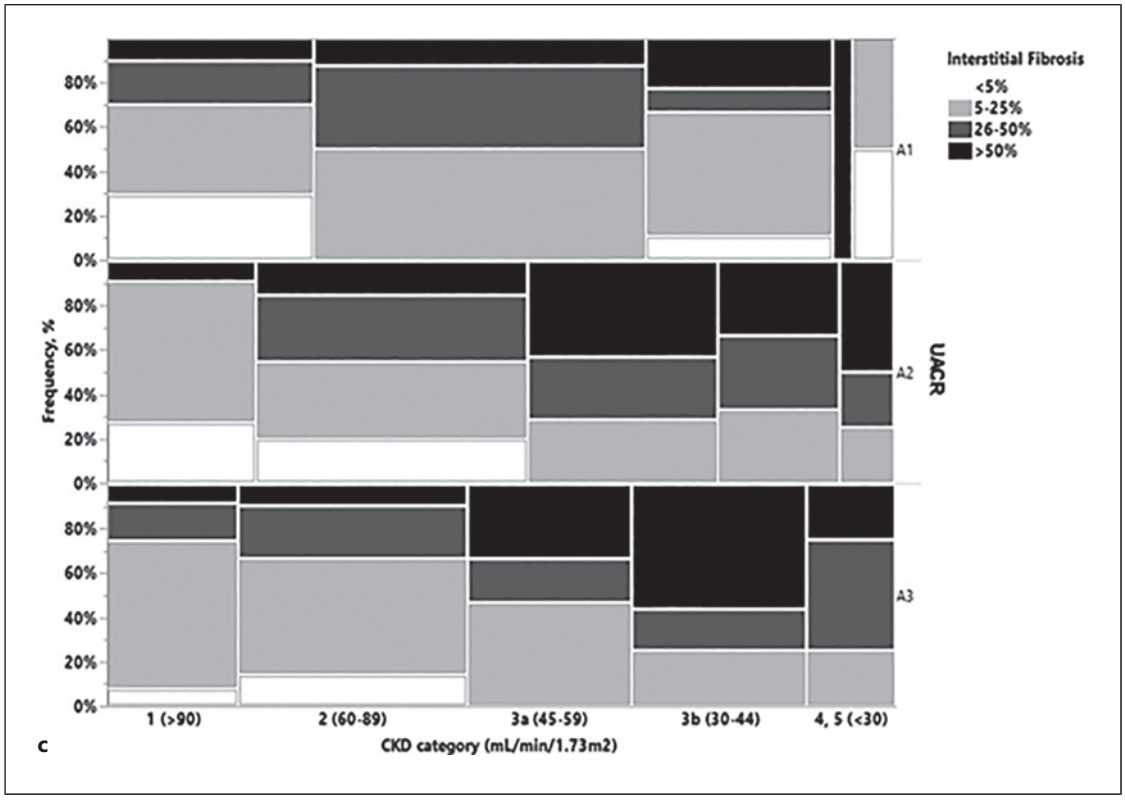

Fig. 1. Degrees of histopathological features according to categories of eGFR and proteinuria. **a** Frequency of GS by CKD stage and UACR. **b** Frequency of AS by CKD stage and UACR. **c** Frequency of IF by CKD stage and UACR. CKD, chronic kidney disease; UACR, albumin to creatinine ratio; GS, glomerulosclerosis; IF, interstitial fibrosis; AS, arteriosclerosis.

Clinical Factors

Clinical, demographic, and pathological data were collected by chart review. Baseline characteristics prior to nephrectomy included demographics, history of hypertension, type 2 diabetes, obesity, CVD, body mass index (BMI), smoking status, use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), the reason for nephrectomy, and tumor size. CVD was defined as the history of coronary artery disease (CAD), congestive heart failure (CHF), stroke, or peripheral vascular disease (PVD).

Statistical Analysis

Baseline continuous variables with normal distribution were reported as mean (standard deviation [SD]); non-normally distributed variables were reported as median (interquartile range [IQR]). Categorical variables were reported as frequencies and proportions. To assess the association between chronic fibrotic histopathological features and eGFR or proteinuria, we used linear and logistic regression models, respectively. Histopathological features were entered in these models in degrees, as stated above. Models were adjusted for factors thought to be clinically associated with eGFR and proteinuria, including age, gender, race (white vs. non-white), ethnicity (Hispanic vs. non-Hispanic), type 2 diabetes, hypertension, CVD, current or prior use of tobacco, obesity (BMI $\geq$30 kg/m^2), and use of ACEi or ARBs. To assess the modifying effect of important clinical factors on the relationship between chronic fibrotic histopathological features and eGFR, additional models included interaction terms between the chronic histopathological changes and obesity, hypertension, proteinuria, or CVD. Only significant interactions were reported, and subgroups were illustrated in Figure 2. Sensitivity analyses excluded nephrectomies with suboptimal specimens (non-neoplastic renal parenchyma less than 5 mm from the tumor) that may affect histological readings due to a tumor compression effect [13] and nephrectomies due to urothelial carcinomas because of their association with proteinuria [14]. Two-sided p values <0.05 were considered to represent a statistically significant association. We performed analyses using SAS software, version 9.4 (SAS Institute, Cary, NC, USA). The study was approved by the institutional review board at the University of Miami.

Results

Baseline characteristics of the 781 patients are presented in Table 1. The majority were male and white, 45% were Hispanics, and only 12% were self-identified as

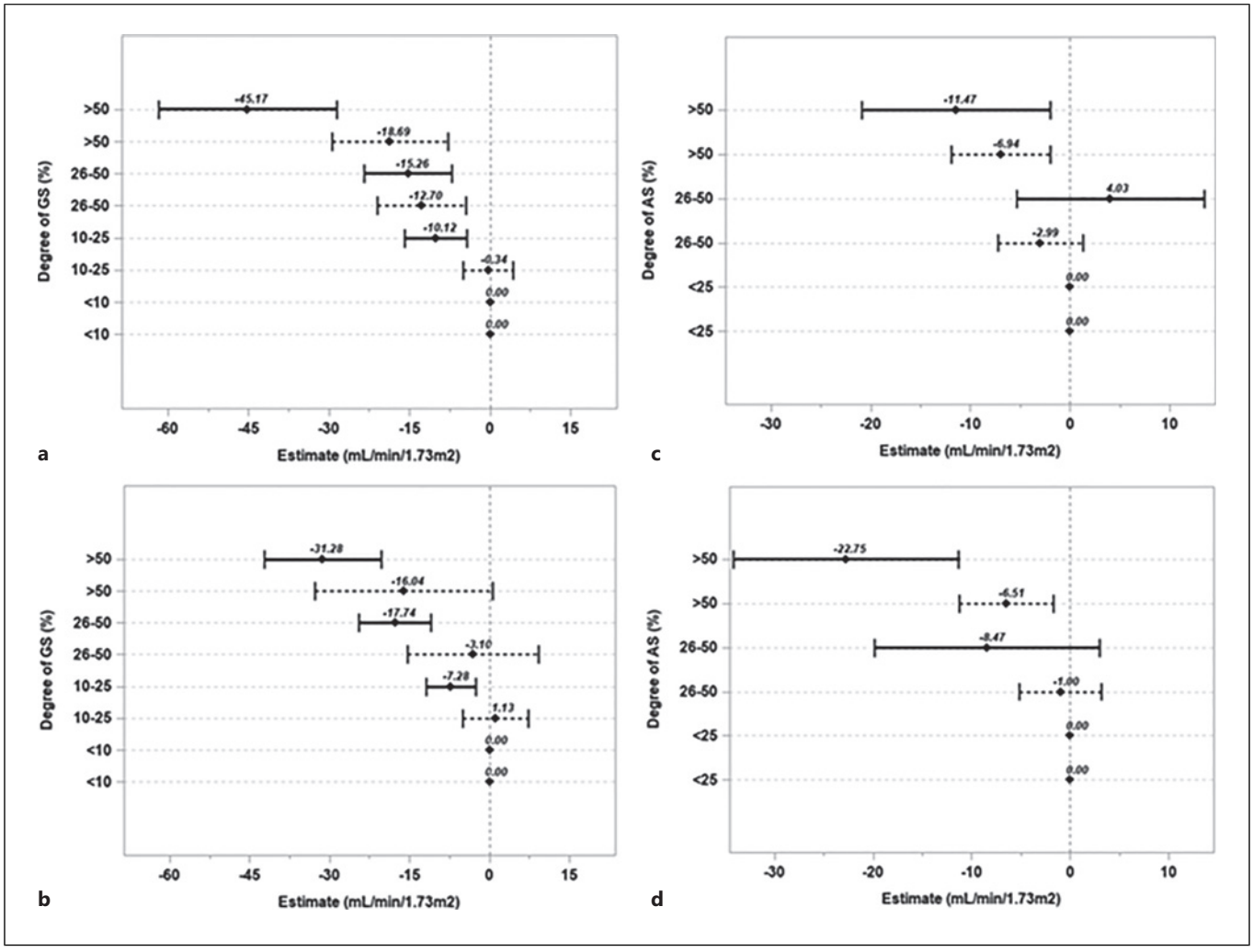

Fig. 2. The effect modification of clinical factors on the relationship of GS and AS with eGFR. **a** Effect of GS on eGFR in patient with and without obesity. **b** Effect of GS on eGFR in patient with and without hypertension. **c** Effect of AS on eGFR in patient with and without proteinuria. **d** Effect of AS on eGFR in patient with and without cardiovascular disease. Dashed-line corresponds to the group without the clinical factor and solid-line corresponds to group with the clinical factor present. Linear regression was used for the outcome eGFR and primary exposure GS when stratified by obesity (**a**), and hypertension (**b**). The model was adjusted by age, gender, cardiovascular disease (CVD), and proteinuria. Linear regression was used for the outcome eGFR and primary exposure AS when stratified by proteinuria (**c**) and CVD (**d**). The model was adjusted by age, gender, ethnicity, and hypertension.

non-white. Twenty-eight percent had an eGFR lower than 60 mL/min/1.73 m^2, and 26% had proteinuria. Fifty-nine percent of patients had hypertension, 38% had obesity, 24% had type 2 diabetes and had a history of smoking, and 41% were on ACEi or ARBs. 301 (40%) patients had ≥10% GS, 612 (83%) had >5% IF, and 486 (63%) had ≥25% AS. Online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000534339) presents categories of GS, IF, and AS according to the reasons for nephrectomy. The degrees of chronic histopathological changes were, in general, proportionally distributed among the different reasons for nephrectomy. However, severe IF and AS were present in about 50% of those with pyelonephritis.

Figure 1 shows the frequencies of histopathological features according to the KDIGO classification of CKD by eGFR and UACR. Greater severity of GS, IF, and AS was present in association with higher levels of albuminuria and lower eGFR. In higher risk KDIGO CKD stages (G4–G5, A3), 37% of patients had moderate or severe GS, whereas 65% and 82% had moderate or severe IF and AS, respectively. In lower risk KDIGO CKD stages (G1–G2, A1), 76%, 58%, and 35% had none or mild GS, IF, and AS, respectively. However, some patients in earlier eGFR

Table 1. Baseline characteristics

Characteristic	*N* = 781
Age, years	60.3±14.3
Male	476 (61%)
Race	
White	687 (88%)
Non-white	94 (12%)
Ethnicity: hispanic or latino	354 (45%)
Diabetes	186 (24%)
Hypertension	459 (59%)
Cardiovascular disease	102 (13%)
Tobacco use	186 (24%)
Body mass index	29.3±6.1
Obese (BMI ≥30)	294 (38%)
ACEi or ARB use	323 (41%)
Dipstick protein	
<10 mg/dL	518 (74%)
Trace	39 (6%)
30 mg/dL	62 (9%)
>100 mg/dL	81 (11%)
eGFR, mL/min/1.73 m^2	75±25
eGFR category	
≥90 mL/min/1.73 m^2	232 (30%)
60–89 mL/min/1.73 m^2	327 (42%)
45–59 mL/min/1.73 m^2	125 (16%)
30–44 mL/min/1.73 m^2	67 (9%)
<30 mL/min/1.73 m^2	27 (3%)
Radical nephrectomy	449 (58%)
Reason for nephrectomy	
Renal cell carcinoma	513 (66%)
Urothelial carcinoma	97 (12%)
Other malignancy	17 (2%)
Benign pathology	142 (18%)
Trauma	12 (2%)
Tumor size	
≥4 cm	296 (58%)
<4 cm	212 (42%)
Nephrosclerosis	
GS, *N*	748
<10%	449 (60%)
10–25%	212 (28%)
26–50%	65 (9%)
>50%	22 (3%)
IF, *N*	736
<5	124 (17%)
5–25	407 (55%)
26–50	123 (17%)
>50	82 (11%)
AS, *N*	776
<26	290 (37%)
26–50	260 (34%)
>50	226 (29%)

Values for continuous variables given as means ± standard deviation and for categorical variables as number (percentage). BMI, body mass index; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate.

stages but with severe proteinuria (G1–G2, A3) already had moderate or severe GS (6%), IF (15%), and AS (47%).

In unadjusted and multivariable-adjusted linear regression analyses, greater degrees of GS, IF, and AS were significantly associated with lower eGFR. The results were qualitatively unchanged when further adjusting for proteinuria (Table 2, $p < 0.05$ for each). In univariable and multivariable-adjusted logistic regression analyses, greater degrees of GS, IF, and AS were significantly associated with proteinuria; the relationship remained statistically significant in the model that was further adjusted for eGFR (Table 2, $p < 0.05$ for each).

Older age, male gender, hypertension, CVD, and proteinuria were consistently and independently associated with lower eGFR in separate multivariable-adjusted linear regression analyses for severity of GS, IF, and AS (online suppl. Table 2, $p < 0.05$ for each). Obesity was independently associated with higher eGFR only in models that included severity of GS, whereas Hispanic ethnicity was associated with higher eGFR in models including severity of AS (online suppl. Table 2, $p < 0.05$ for each).

Obesity and hypertension modified the relationship between GS and lower eGFR (p for interaction <0.05 for each, Fig. 2, panels a, b). Remarkably, compared with the category of GS <10% as reference group, GS >50% was associated with lower eGFR of −45.17 mL/min/1.73 m^2 among patients with obesity versus −18.69 mL/min/1.73 m^2 in those without obesity. Likewise, compared with the category of GS <10% as the reference group, GGS >50% was associated with lower eGFR of −31.28 mL/min/1.73 m^2 among patients with hypertension versus −16.04 mL/min/1.73 m^2 in those without hypertension. Patients with hypertension had lower eGFR than patients without hypertension across all categories of GS (online suppl. Table 3), whereas patients with obesity had lower eGFR than patients without obesity only in the category of severe GS (online suppl. Table 3). The association between lower eGFR and GS did not vary by CVD or proteinuria (p for interaction >0.05). Proteinuria and CVD modified the relationship between lower eGFR and AS (p for interaction <0.05 for each, Fig. 2, panels c, d). Compared to AS ≤26%, AS >50% was associated with lower eGFR of −11.47 mL/min/1.73 m^2 in patients with proteinuria versus −6.94 mL/min/1.73 m^2 in those without proteinuria. Likewise, compared with the category of AS ≤26%, AS >50% was associated with lower eGFR of −22.75 mL/min/1.73 m^2 in patients with CVD versus −6.51 mL/min/1.73 m^2 in those without CVD. Lower eGFR was noted in patients with CVD compared to those without CVD and in patients with proteinuria

Table 2. Univariate and multivariate regression analyses between the degrees of histological features as primary exposures with eGFR and proteinuria as dependent variables, adjusted by demographic and clinical factors

Histopathological feature	eGFR			Proteinuria		
	univariate	multivariate *	multivariate + proteinuria**	univariate	multivariate	multivariate + eGFR***
	β (CI)	β (CI)	β (CI)	OR (CI)	OR (CI)	OR (CI)
GGS, %	***p* < 0.01**	***p* < 0.01**	***p* < 0.01**	***p* < 0.01**	***p* < 0.01**	***p* = 0.02**
<10	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
10–25	−11.92 (−15.68–−8.16)	−5.57 (−9.13–−2.02)	−4.93 (−8.62–−1.25)	1.28 (0.86–1.93)	1.12 (0.71–1.76)	1.01 (0.64–1.61)
26–50	−22.83 (−15.68–−8.16)	−18.39 (−24.05–−12.73)	−16.23 (−22.11–−10.35)	4.12 (2.34–7.24)	3.64 (1.93–6.87)	2.67 (1.37–5.23)
>50	−31.69 (−41.53–−21.84)	−28.53 (−37.21–−19.84)	−27.03 (−36.02–−18.05)	3.04 (1.22–7.58)	3.06 (1.16–8.11)	1.87 (0.66–5.29)
IF, %	***p* < 0.01**	***p* < 0.01**	***p* < 0.01**	***p* < 0.01**	***p* < 0.01**	***p* < 0.01**
<5	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
5–25	−8.47 (−13.07–−3.88)	0.90 (−3.40–5.21)	0.04 (−4.41–4.49)	1.42 (0.79–2.57)	1.21 (0.62–2.36)	1.20 (0.61–2.35)
26–50	−21.39 (−27.08–−15.70)	−9.08 (−14.45–−3.71)	−8.59 (−14.24–−2.94)	3.52 (1.82–6.82)	2.70 (1.26–5.78)	2.39 (1.11–5.17)
>50	−29.03 (−35.39–−22.67)	−17.26 (−23.14–−11.39)	−16.14 (−22.28–−9.99)	6.46 (3.22–12.95)	5.93 (2.72–12.94)	4.77 (2.14–10.64)
AS, %	***p* < 0.01**	***p* < 0.01**	***p* < 0.01**	***p* < 0.01**	***p* < 0.01**	***p* = 0.04**
<25	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
26–50	−8.89 (−12.82–−4.96)	−2.43 (−6.32–1.47)	−1.96 (−5.94–−2.02)	1.28 (0.83–1.97)	1.15 (0.70–1.87)	1.11 (0.68–1.82)
>50	−20.69 (−24.76–−16.61)	−9.52 (−13.77–−5.27)	−8.81 (−13.34–−4.49)	2.65 (1.74–4.06)	2.17 (1.32–3.59)	1.83 (1.09–3.07)

Linear regression was used for the outcome eGFR, and the estimate coefficient (confidence interval) (β [CI]) represents the association of independent variables with the outcome: either higher (positive) or lower (negative) eGFR in mL/min/1.73 m^2. Logistic regression was used for the outcome proteinuria, and the odds ratio (confidence interval) (OR [CI]) represents the association of independent variables with the outcome, respectively. Proteinuria was dichotomized as negative or positive (≥ trace by dipstick). eGFR, estimated glomerular filtration rate; GGS, global glomerulosclerosis; IF, interstitial fibrosis; AS, arteriosclerosis. *Multivariate model included age, gender, race, ethnicity, hypertension, diabetes, cardiovascular disease, current or prior tobacco use, obesity, and use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. **Multivariate + proteinuria model included all the variables in the multivariable model plus proteinuria. ***Multivariate + eGFR model included all the variables as in the multivariate model plus eGFR.

compared to those without proteinuria independently from the severity of AS (online suppl. Table 3). The association between lower eGFR and AS did not vary by HTN or obesity (p for interaction >0.05). The association between lower eGFR and IF did not vary by hypertension, obesity, CVD, or proteinuria (p for interaction >0.05).

We performed additional sensitivity analyses excluding 97 patients with urothelial carcinoma and 146 with suboptimal specimens (135 with partial and 11 with radical nephrectomy), and the results were qualitatively unchanged. Only AS was no longer associated with proteinuria after excluding suboptimal specimens (online suppl. Table 4, 5). This is probably due to a variation in arterial size captured in the nephrectomy versus the partial nephrectomy specimens.

Discussion

In this large and ethnically diverse cohort of patients who underwent tumor nephrectomies, we found that greater severity of GS, IF, and AS were associated with lower eGFR and proteinuria, independent of demographics and clinical characteristics. Moreover, we found

that obesity and hypertension modified the relationship between lower eGFR and severity of GS, whereas proteinuria and CVD modified the association between lower eGFR and AS. These results add further insight into understanding the pathophysiological mechanisms linking scarring in specific compartments of the kidney, clinical factors, and kidney dysfunction.

Several cross-sectional studies have reported associations between chronic fibrotic histopathological changes and kidney function [2, 3, 5, 6]. Previous studies have shown an independent association between lower eGFR and a higher percentage of GS (GS%) [6] and an unadjusted inverse correlation between eGFR and severity of GS, IFTA, and AS [5]. More recently, a large study [3] showed an independent association between greater degrees of GS, IFTA, and AS and lower eGFR. The results of our study using a cohort of highly prevalent Hispanic patients are consistent with these observations on nephrectomy patients, further supporting the association between fibrotic/sclerotic processes in specific compartments of the kidney and changes in eGFR.

Expanding to the current knowledge, we found that proteinuria remained strongly associated with lower eGFR, independent of other clinical factors and histopathological features. Patients with severe proteinuria and normal eGFR (KDIGO CKD stages G1–G2, A3) already had moderate or severe GS, IF, and AS at the time of the nephrectomy, and that greater severity of GS, IF, and AS is associated with proteinuria independent of eGFR and other clinical factors. Studies showing associations between histopathological features and proteinuria in patients undergoing nephrectomy are limited. A human study [5] reported an unadjusted association between proteinuria and IFTA, and a recent study showed an independent association between GS and proteinuria [6]. An autopsy-base population study [15] found an association between proteinuria and AS and GS. Progressive proteinuria and GS have also been described as being associated with podocyte depletion in mice [16]. These results raise the hypothesis of a direct rather than indirect effect of proteinuria on lower eGFR which corresponds with the well-established clinical association between proteinuria and kidney function decline [17, 18]. In contrast, a study of kidney biopsies in patients with hypertension showed that proteinuria accounted only minimally for the variability of GS [19]. Whether proteinuria is mechanistically linked to degrees of histopathological features in earlier stages of CKD remains unknown. Further longitudinal studies looking at the mechanisms of kidney function decline and the development of proteinuria are warranted. Furthermore, whether proteinuria plays a major role in the development of fibrosis in renal diseases as previously proposed [20] remains to be determined.

Our study showed that the associations between AS and lower eGFR were stronger in patients with proteinuria compared to those without proteinuria and that patients with versus without proteinuria have lower eGFR across different categories of AS. In line with our results, a recent study on patients with diabetic kidney disease reported a correlation between AS and proteinuria and that AS >50% was an independent predictor of renal outcomes [21]. Our study paves the way to further analyze the development of proteinuria as an intermediate factor in the progression of kidney disease associated to AS.

In contrast to prior tumor nephrectomy studies [3, 22], we found an association between hypertension and lower eGFR independent of histopathological features. Similarly, prior studies in the general population have shown an association between hypertension and lower eGFR, independent of clinical factors [23–25]. Furthermore, when the effect of hypertension and its interaction with GS on eGFR was tested, we found that the effect of these two factors depended on each other. These results concur with the proposed ischemic theory for hypertension-induced GS [26]. Whether GS is the consequence of hypertension or other factors such as Apolipoprotein L1 gene variants [27, 28] remains unclear. Further studies are needed to evaluate the underlying mechanisms of kidney dysfunction with GS and hypertension.

We found that obesity was associated with higher eGFR independent of GS and that obesity modified the relationship between GS and eGFR across different degrees of GS such as the eGFR being higher in patients with versus without obesity in the group with GS <10% but lower in the group with GS >50%. Obesity is associated with hyperfiltration and glomerular hypertrophy and increases the risk for CKD and its progression to ESRD [29, 30], and in patients with obesity-related glomerulopathy [31], greater degrees of GS are associated with decline in kidney function. Whether GS is also part of a maladaptive process seen in obesity that overtime can cause lower eGFR or whether GS is a fibrotic process unrelated to obesity is unknown. Future studies should evaluate the underlying mechanisms of the joint effect of obesity and GS on eGFR.

We found that CVD is associated with lower eGFR, independent of other clinical factors and histopathological features, and that CVD modified the relationship between lower eGFR and AS. CKD is a well-known risk factor for CVD in the general population [32, 33], and in tumor nephrectomy [34]. Endothelial dysfunction, inflammation, oxidative stress, and atherosclerosis are some of the

proposed mechanisms [35]. Our findings extend the current knowledge by providing evidence of vascular damage in the form of AS in the pathophysiology of CVD.

Hypertension, CVD, obesity, and proteinuria are all modifiable risk factors for CKD progression; knowing their relationships with histopathological features and eGFR provides a better insight into understating the pathophysiological mechanisms leading to scarring and worsening kidney function. Future longitudinal studies should evaluate the effect on progressive eGFR decline of interventions modifying these clinical factors in patients undergoing nephrectomies, with the final goal of preventing progressive CKD.

Our study has the following limitations. (1) This is a cross-sectional study; therefore, we cannot establish causality. However, a standardized morphological evaluation of non-neoplastic renal parenchyma was systematically performed according to the Renal Pathology Society recommendations [7], allowing for the capture of information that may contribute to better characterizing CKD in nephrectomy patients [8]. (2) The evaluation of non-neoplastic kidney tissue from partial nephrectomies may be less representative of the status of the remaining kidney parenchyma and contralateral kidney. (3) We do not have data of proteinuria based on measured UACR. However, we report UACR predicted from urine dipstick protein that has been shown to be useful for staging and prognosis. [12]. The strengths of this study are as follows. (1) We included a large and highly diverse population. (2) We accounted for many important risk factors including type 2 diabetes, hypertension, CVD, obesity, proteinuria, and use of ACEi and ARBs.

In summary, we found that severity of GS, IF, and AS is independently associated with lower eGFR and proteinuria and that hypertension, obesity, CVD, and proteinuria modify the relationship between certain histopathological features and lower eGFR. Further longitudinal studies are needed to evaluate the underlying mechanisms of kidney function decline with histopathological features and the role of interventions improving modifiable risk factors such as hypertension, obesity, and proteinuria in slowing the progression of CKD in nephrectomies patients.

Statement of Ethics

This study followed the guidelines for human subjects and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study was approved by the University of Miami Institutional Review Board (Protocol Number 20170344) and granted waiver of informed consent.

Conflict of Interest Statement

All the authors declare no competing interests.

Funding Sources

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Author Contributions

Study design: L.A.B., J.S.B., G.C., and J.M.M. Data collection: L.A.B., J.S.B., F.I., O.I., and J.M.M. Statistical analysis: L.A.B., G.C., and T.E. Drafting the manuscript: L.A.B., J.S.B., and J.M.M. Critically revising the manuscript: G.C., A.F., L.B., D.B.T., Y.Z., T.E., and J.M.M.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

References

1 Rule AD, Amer H, Cornell LD, Taler SJ, Cosio FG, Kremers WK, et al. The association between age and nephrosclerosis on renal biopsy among healthy adults. Ann Intern Med. 2010;152(9):561–7.

2 Srivastava A, Palsson R, Kaze AD, Chen ME, Palacios P, Sabbisetti V, et al. The prognostic value of histopathologic lesions in native kidney biopsy specimens: results from the Boston Kidney Biopsy Cohort Study. J Am Soc Nephrol. 2018;29(8):2213–24.

3 Li P, Gupta S, Mothi SS, Rennke HG, Leaf DE, Waikar SS, et al. Histopathologic correlates of kidney function: insights from nephrectomy specimens. Am J Kidney Dis. 2021;77(3):336–45.

4 Denic A, Mathew J, Nagineni VV, Thompson RH, Leibovich BC, Lerman LO, et al. Clinical and pathology findings associate consistently with larger glomerular volume. J Am Soc Nephrol. 2018 Jul;29(7):1960–9.

5 Ellis RJ, Kalma B, Del Vecchio SJ, Aliano DN, Ng KL, Dimeski G, et al. Chronic kidney cortical damage is associated with baseline kidney function and albuminuria in patients managed with radical nephrectomy for kidney tumours. Pathology. 2019 Jan;51(1):32–8.

6 Denic A, Ricaurte L, Lopez CL, Narasimhan R, Lerman LO, Lieske JC, et al. Glomerular volume and glomerulosclerosis at different depths within the human kidney. J Am Soc Nephrol. 2019;30(8):1471–80.

7 Chang A, Gibson IW, Cohen AH, Weening JJ, Jennette JC, Fogo AB, et al. A position paper on standardizing the nonneoplastic kidney biopsy report. Clin J Am Soc Nephrol. 2012 Aug;7(8):1365–8.

8 Racusen LC, Solez K, Colvin RB, Bonsib SM, Castro MC, Cavallo T, et al. The Banff 97 working classification of renal allograft pathology. Kidney Int. 1999;55(2):713–23.
9 Sethi S, D'Agati VD, Nast CC, Fogo AB, De Vriese AS, Markowitz GS, et al. A proposal for standardized grading of chronic changes in native kidney biopsy specimens. Kidney Int. 2017 Apr;91(4):787–9.
10 Kremers WK, Denic A, Lieske JC, Alexander MP, Kaushik V, Elsherbiny HE, et al. Distinguishing age-related from disease-related glomerulosclerosis on kidney biopsy: the Aging Kidney Anatomy study. Nephrol Dial Transpl. 2015;30(12):2034–9.
11 Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5;150(9):604–12.
12 Sumida K, Nadkarni GN, Grams ME, Sang Y, Ballew SH, Coresh J, et al. Conversion of urine protein-creatinine ratio or urine dipstick protein to urine albumin-creatinine ratio for use in chronic kidney disease screening and prognosis: an individual participant-based meta-analysis. Ann Intern Med. 2020 Sep 15;173(6):426–35.
13 Henriksen KJ, Chang A. The importance of nephropathology in kidney cancer. Semin Nephrol. 2020 Jan;40(1):69–75.
14 Jørgensen L, Heuch I, Jenssen T, Jacobsen BK. Association of albuminuria and cancer incidence. J Am Soc Nephrol. 2008 May;19(5):992–8.
15 Kubo M, Kiyohara Y, Kato I, Tanizaki Y, Katafuchi R, Hirakata H, et al. Risk factors for renal glomerular and vascular changes in an autopsy-based population survey: the Hisayama study. Kidney Int. 2003;63(4):1508–15.
16 Shi S, Yu L, Chiu C, Sun Y, Chen J, Khitrov G, et al. Podocyte-selective deletion of dicer induces proteinuria and glomerulosclerosis. J Am Soc Nephrol. 2008;19(11):2159–69.
17 Clark WF, Macnab JJ, Sontrop JM, Jain AK, Moist L, Salvadori M, et al. Dipstick proteinuria as a screening strategy to identify rapid renal decline. J Am Soc Nephrol. 2011;22(9):1729–36.
18 O'Donnell K, Tourojman M, Tobert CM, Kirmiz SW, Riedinger CB, Demirjian S, et al. Proteinuria is a predictor of renal functional decline in patients with kidney cancer. J Urol. 2016;196(3):658–63.
19 Marcantoni C, Ma L-J, Federspiel C, Fogo AB. Hypertensive nephrosclerosis in African Americans versus caucasians. Kidney Int. 2002;62(1):172–80.
20 Remuzzi G, Bertani T. Pathophysiology of progressive nephropathies. N Engl J Med. 1998;339(20):1448–56.
21 Zhang Y, Jiang Q, Xie J, Qi C, Li S, Wang Y, et al. Modified arteriosclerosis score predicts the outcomes of diabetic kidney disease. BMC Nephrol. 2021 Aug 18;22(1):281.
22 Quinn GZ, Abedini A, Liu H, Ma Z, Cucchiara A, Havasi A, et al. Renal histologic analysis provides complementary information to kidney function measurement for patients with early diabetic or hypertensive disease. J Am Soc Nephrol. 2021 Nov;32(11):2863–76.
23 Yu Z, Rebholz CM, Wong E, Chen Y, Matsushita K, Coresh J, et al. Association between hypertension and kidney function decline: the atherosclerosis risk in communities (ARIC) study. Am J Kidney Dis. 2019 Sep;74(3):310–9.
24 Kubo M, Kiyohara Y, Kato I, Tanizaki Y, Arima H, Tanaka K, et al. Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: the Hisayama study. Stroke. 2003;34(10):2349–54.
25 Fogo A, Breyer JA, Smith MC, Cleveland WH, Agodoa L, Kirk KA, et al. Accuracy of the diagnosis of hypertensive nephrosclerosis in african Americans: a report from the african American study of kidney disease (AASK) trial. AASK pilot study investigators. Kidney Int. 1997;51(1):244–52.
26 Hill GS. Hypertensive nephrosclerosis. Curr Opin Nephrol Hypertens. 2008 May;17(3):266–70.
27 Lipkowitz MS, Freedman BI, Langefeld CD, Comeau ME, Bowden DW, Kao WH, et al. Apolipoprotein L1 gene variants associate with hypertension-attributed nephropathy and the rate of kidney function decline in African Americans. Kidney Int. 2013 Jan;83(1):114–20.
28 Freedman BI, Cohen AH. Hypertension-attributed nephropathy: what's in a name? Nat Rev Nephrol. 2016 Jan;12(1):27–36.
29 D'Agati VD, Chagnac A, de Vries AP, Levi M, Porrini E, Herman-Edelstein M, et al. Obesity-related glomerulopathy: clinical and pathologic characteristics and pathogenesis. Nat Rev Nephrol. 2016 Aug;12(8):453–71.
30 Stenvinkel P, Zoccali C, Ikizler TA. Obesity in CKD: what should nephrologists know? J Am Soc Nephrol. 2013;24(11):1727–36.
31 Praga M, Hernandez E, Morales E, Campos AP, Valero MA, Martinez MA, et al. Clinical features and long-term outcome of obesity-associated focal segmental glomerulosclerosis. Nephrol Dial Transpl. 2001 Sep;16(9):1790–8.
32 Hui X, Matsushita K, Sang Y, Ballew SH, Fulop T, Coresh J. CKD and cardiovascular disease in the Atherosclerosis Risk in Communities (ARIC) study: interactions with age, sex, and race. Am J Kidney Dis. 2013 Oct;62(4):691–702.
33 Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004 Sep 23;351(13):1296–305.
34 Takeshita H, Yokoyama M, Fujii Y, Chiba K, Ishioka J, Noro A, et al. Impact of renal function on cardiovascular events in patients undergoing radical nephrectomy for renal cancer. Int J Urol. 2012 Aug;19(8):722–8.
35 Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: effects on the cardiovascular system. Circulation. 2007 Jul 3;116(1):85–97.