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Global glomerulosclerosis with nephrotic syndrome; the clinical importance of age adjustment

Musab S. Hommos, M.B.B.S.¹, Caihong Zeng, Ph.D.², Zhihong Liu, M.D.², Jonathan Troost, Ph.D.³, Avi Rosenberg⁴, Matthew Palmer⁵, Walter K Kremers, Ph.D.⁶, Lynn D. Cornell, M.D.¹, Fernando C. Fervenza, M.D., Ph.D.¹, Laura Barisoni, M.D.⁷, and Andrew D. Rule, M.D.¹

¹Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Rochester, MN, USA

²National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China

³Division of Nephrology, Department of Pediatrics and Communicable Diseases, C.S. Mott Children's Hospital, University of Michigan, Ann Arbor, MI, USA

⁴Department of Pathology, Johns Hopkins University, Baltimore, MD, USA

⁵Department of Pathology University of Pennsylvania, Philadelphia, PA, USA

⁶Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

⁷Department of Pathology, University of Miami, Miami, Miller School of Medicine, FL, USA

Abstract

Globally sclerotic glomeruli (GSG) occur with both normal aging and kidney disease. However, it is unknown whether any GSG or only GSG exceeding that expected for age is clinically important. To evaluate this, we identified patients with a glomerulopathy that often presents with nephrotic syndrome (focal segmental glomerulosclerosis, membranous nephropathy, or minimal change disease) in the setting of the Nephrotic Syndrome Study Network (NEPTUNE), China-Digital Kidney Pathology (DiKiP), and the Southeast Minnesota cohorts. Age-based thresholds (95th percentile) for GSG based on normotensive living kidney donors were used to classify each patient into one of three groups; no GSG, GSG normal for age, or GSG abnormal for age. The risk of end-stage renal disease or a 40% decline in glomerular filtration rate during follow-up was then compared between groups. Among the 425 patients studied, 170 had no GSG, 107 had GSG normal for age, and 148 had GSG abnormal for age. Compared to those with no GSG, the risk of kidney disease progression with GSG normal for age was similar but was significantly higher with GSG abnormal for age. This increased risk with GSG abnormal for age remained significant after

Corresponding author: Andrew Rule, 200 first street SW, Rochester, MN 55905, Phone: 507-266-1045, rule.andrew@mayo.edu.

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DISCLOSURE

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adjustment for interstitial fibrosis, arteriosclerosis, age, hypertension, diabetes, body mass index, glomerulopathy type, glomerular filtration rate, and proteinuria. Thus, in patients with glomerulopathy that often presents with nephrotic syndrome, global glomerulosclerosis is clinically important only if it exceeds that expected for age.

Keywords

global glomerulosclerosis; age-based threshold; FSGS; membranous nephropathy; minimal change disease; nephrotic syndrome

INTRODUCTION

Nephrosclerosis is a term often used to describe chronic irreversible changes observed on kidney biopsy. These changes include global glomerulosclerosis, arteriosclerosis and arteriolosclerosis, interstitial fibrosis and tubular atrophy (IFTA).¹ These histological findings also predict a worse renal prognosis in patients with chronic kidney disease (CKD).^{2–7} Accordingly, nephrologists often utilize these “chronic changes” to inform patients about their prognosis and to guide their management.⁸ However, some degree of nephrosclerosis can also be observed with normal healthy aging in the absence of kidney disease.^{9–12} Recent grading systems for chronic changes are not age-calibrated, but acknowledge uncertainty as to whether age-related changes are of prognostic importance.⁸

A recent study used carefully screened living kidney donors data to calculate the upper reference limit (95th percentile) for the number of globally sclerotic glomeruli (GSG) at a given age and number of glomeruli on a biopsy. (<https://qxmd.com/calculate/glomerulosclerosis-on-biopsy-2015>).¹³ The clinical relevance of determining whether or not the amount of GSG on a patient’s biopsy is abnormal is unclear. In particular, is any global glomerulosclerosis of prognostic significance or just glomerulosclerosis that is abnormal for age? For example, 3 of 20 glomeruli being globally sclerosed would be a biopsy finding commonly expected for a healthy 60 year-old (95th percentile would be 4 globally sclerosed glomeruli) but abnormal for a 20 year-old (95th percentile would be 1 globally sclerotic glomeruli)(Table 1). The older patient may only have a gradual process of age-related nephrosclerosis of limited clinical relevance, whereas the younger patient may have a more rapid glomerular loss from an underlying disease with an increased risk of kidney failure. However, validation of these age-based reference limits has not yet been performed in a diseased population. Whether glomerulosclerosis is prognostically important independent of other clinical characteristics and biopsy findings is also unclear.

To validate the prognostic utility of age-based reference limits for glomerulosclerosis, we assessed the risk of kidney disease progression as predicted by glomerulosclerosis in three different cohorts of patients defined by a glomerulopathy on biopsy that often presents with nephrotic syndrome. Our primary objective was to compare the risk of kidney disease progression between patients with no GSG, GSG normal for age, and GSG abnormal for age. Our secondary objective was to determine whether GSG abnormal for age is predictive of kidney disease progression independent of other clinical and biopsy characteristics, and across different populations.

RESULTS

There were a total of 425 patients studied; 183 patients from the Nephrotic Syndrome Study Network (NEPTUNE) cohort, 129 from the China-Digital Kidney Pathology (China DiKiP) cohort, and 113 patients from Southeast (SE) Minnesota cohort (Figure 1). Baseline characteristics for each cohort and the overall cohort are summarized in Table 2. The prospective NEPTUNE cohort had up to 5 years of follow-up with 28% leaving the study (2% died); the prospective China DiKiP cohort had up to 4.6 years of follow-up with 18% leaving the study (0.5% died); and the historical SE MN cohort had up to 22 years of follow-up with 29% lost to follow-up in the medical record (12% died). Compared to the NEPTUNE and SE Minnesota cohorts, the China DiKiP cohort was younger; had a lower body mass index, less hypertension, and less diabetes; had higher estimated glomerular filtration rate (eGFR); had more minimal change disease (MCD) and less focal segmental glomerulosclerosis (FSGS); and had a lower incidence of CKD progression. The NEPTUNE and SE Minnesota cohorts were more similar.

The mean $\pm$ SD of total number of glomeruli present on biopsy was 24 ± 17 glomeruli (16% had < 10 glomeruli with the fewest being 3 glomeruli, 31% had 10–19, 26% had 20–29, and 27% had > 29 glomeruli). By global glomerulosclerosis category, 170 patients (40%) had no GSG, 107 patients (25%) had GSG normal for age, and 148 patients (35%) had GSG abnormal for age. Since GSG abnormal for age was defined using the 95th percentile threshold in healthy kidney donors, this exceeds what would be expected in a healthy population (35% vs. expected 5%, $p < 0.0001$). By primary diagnosis, FSGS (56% vs. expected 5.0%, $p < 0.0001$) and membranous nephropathy (MN) (19% vs. expected 5.0%, $p < 0.0001$) had more GSG than expected in healthy population, but MCD (6.5% vs. expected 5.0%, $p = 0.53$) did not. The %GSG showed substantial overlap between patients with GSG normal for age and patients with GSG abnormal for age for each of the three diagnoses (Figure 2).

Table 3 compares the characteristics between those with no GSG, GSG normal for age, and GSG abnormal for age. Presence of GSG normal for age compared to no GSG was associated with older age, hypertension, diabetes, and lower eGFR. In multivariable analysis adjusting for each other clinical characteristic, only older age (odds ratio = 1.07 per year, $p < 0.001$) independently associated with GSG normal for age compared to no GSG. Presence of GSG abnormal for age compared to no GSG was associated with older age, higher body mass index (BMI), hypertension, diabetes, lower proteinuria, and lower eGFR. In multivariable analysis including each of these clinical characteristics (age, BMI, hypertension, diabetes, proteinuria, and eGFR), only lower eGFR ($p < 0.0001$) and lower proteinuria ($p = 0.01$) independently associated with GSG abnormal for age compared to no GSG. Other biopsy findings (IFTA, arteriolar hyalinosis, and arteriosclerosis) were higher in those with GSG (normal or abnormal for age) compared to no GSG. The amount of IFTA were markedly more severe with GSG abnormal for age compared to GSG normal for age, whereas arteriosclerosis and arteriolar hyalinosis were only slightly more severe with GSG abnormal for age compared to GSG normal for age.

The risk of CKD progression was not different in those with GSG normal for age compared to no GSG (HR=1.0, $p=0.98$) but was higher in those with GSG abnormal for age compared to no GSG (HR=3.7, $p<0.0001$) (Figure 3). In a sensitivity analysis limited to NEPTUNE, classifying GSG as abnormal for age using digitally scanned and annotated images versus using clinical biopsy reports showed good agreement ($\kappa = 0.66$, $p<0.0001$). Although the annotated images (rigorous method) detected more glomeruli (mean 27 vs. 18, $p<0.0001$) and more GSG (mean 5 vs. 3, $p<0.0001$) than the biopsy report (convenient method), the percentage of glomeruli that were GSG between the two methods showed minimal difference (21% by annotated images vs. 20% by biopsy report, $p=0.03$) and was highly correlated ($r=0.90$). Furthermore, the risk of CKD progression with GSG abnormal for age compared to no GSG or GSG normal for age was similar by annotated images (HR=2.4, $p=0.0008$) or by pathology report (HR=2.5, $p=0.0006$) (Supplemental Figure 1).

Given the lack of a detectable difference in CKD progression between no GSG and GSG normal for age, these two categories were combined for subsequent analysis. The risk of CKD progression with GSG abnormal for age versus no GSG or GSG normal for age remained significant even after adjustment for biopsy findings, the primary diagnosis, or clinical characteristics (Table 4). Findings were similar when GSG abnormal for age was only compared to GSG normal for age (supplemental table 1). Subgroup analysis did not find evidence that the risk of CKD progression with GSG abnormal for age differed between women and men ($p=0.23$ for statistical interaction), differed between ages <40 years and 40 years ($p=0.35$ for statistical interaction), differed between FSGS and MN ($p=0.12$ for statistical interaction), differed between the 3 sites ($p=0.51$ for statistical interaction), or differed between total number of glomeruli on biopsy ($p=0.98$). Analysis restricted to those with only 1 or 2 GSG more than the upper reference limit for age versus no GSG or GSG normal for age revealed the risk of CKD progression remained.

DISCUSSION

In this study, we demonstrated that in patients with glomerulopathy commonly presenting as nephrotic syndrome (MCD, MN and FSGS), global glomerulosclerosis on the baseline kidney biopsy was only predictive of CKD progression when it exceeded the age-specific 95th percentile for global glomerulosclerosis in healthy adults.¹³ Glomerulosclerosis exceeding that expected for age informs prognosis independent of other clinical and biopsy characteristics (including commonly reported IFTA scores). This finding was robust showing consistency between different cohorts, different methods for counting glomeruli, and different number of glomeruli. This study validates age-based thresholds developed in normotensive living kidney donors applied to patients with MCD, MN, and FSGS. Clinicians can now more clearly delineate whether the amount of global glomerulosclerosis on a biopsy is age-related (of little clinical significance) or disease-related (increased risk for CKD progression).

An age-based approach to CKD has been considered controversial,^{14,15} but is supported by both structural and epidemiological studies.¹⁶ Precedence already exists for age-based thresholds in CKD. By using age-based thresholds for number of renal cysts, nephrologists avoid misdiagnosing age-related cysts in older patients as autosomal dominant

polycystic kidney disease.^{17,18} Similarly, the use of age-based thresholds can help nephrologist differentiate “normal” age-related global glomerulosclerosis of little clinical relevance from disease-related global glomerulosclerosis that portends to a worse prognosis. We found that the patients with MCD only had glomerulosclerosis to the extent expected for their age, consistent with their low risk of CKD progression.¹⁹ Qualitative characterization of globally sclerotic glomeruli can be useful since glomerulosclerosis from some diseases will have the appearance of solidification (e.g. diabetic nephropathy and amyloidosis) rather than the deflating, ischemic appearance that characterizes age-related glomerulosclerosis.²⁰ Nonetheless, distinguishing subtypes of global glomerulosclerosis and inferring an etiology is not always possible.

This age-based quantitative approach to global glomerulosclerosis complements the qualitative approach often employed by pathologists. This quantitative approach can be rapidly applied without additional techniques or skills. Prior studies have demonstrated that glomeruli are more accurately counted using rigorous digital annotation compared to what is reported in clinical practice.²¹ The accuracy of the “convenient” counting method used in clinical practice is limited by visual-spatial memory of the pathologist across multiple histologic levels.²¹ Yet, the percentage of glomeruli that are GSG and prognosis with GSG abnormal for age is similar between both methods. Thus, the “convenient” method for counting glomeruli used in clinical practice is valid for determining whether the number of GSG is abnormal for age.

Age was the only independent risk factor for having GSG normal for age rather than no GSG, suggesting that age-related glomerulosclerosis is not simply due to comorbidities such as diabetes and hypertension that become more prevalent with age. Age-related glomerulosclerosis did not occur in isolation; it was associated with an increase in IFTA, arteriosclerosis, and arteriolar hyalinosis that can together be described as age-related nephrosclerosis.²² The underlying mechanism is likely ischemia to the glomeruli (capillary wrinkling, global deflation, pericapsular fibrosis and capsule thickening) induced by arteriosclerosis that leads to global glomerulosclerosis and atrophy of the attached tubules.²³ This nephrosclerosis leads to a 50% loss of nephrons from a healthy 20 year-old to a healthy 70 year-old.²⁴ Thus, it is important not to misinterpret age-related glomerulosclerosis and nephrosclerosis as “chronic changes” from the underlying kidney disease that led to the biopsy.

We found that GSG abnormal for age was independently associated with both lower eGFR and lower proteinuria. It was also associated with much more severe IFTA than GSG normal for age, but only modestly more arteriosclerosis and arteriolar hyalinosis than GSG normal for age. The underlying glomerulopathy leads to excess glomerulosclerosis beyond that expected from ischemia with age-related arteriosclerosis and arteriolar hyalinosis. As glomeruli are lost due to the underlying glomerulopathy, the corresponding tubules become atrophic with surrounding interstitial fibrosis.²⁵ This, in turn, results in lower GFR. The association between lower proteinuria and more GSG may be due to loss of glomeruli to filter protein;²⁶ eGFR adjustment only partially accounts for this loss of glomeruli.

Prior studies have shown that “chronic changes” on kidney biopsy are associated with worse kidney outcomes.^{2,4,27} Many prior studies have emphasized the importance of interstitial fibrosis and did not find glomerulosclerosis to be an independent risk factor for CKD progression. One possible explanation is that these past studies have not differentiated global glomerulosclerosis that is normal for age from global glomerulosclerosis that is abnormal for age. In this study, the presence of GSG abnormal for age indicated worse prognosis independent of the amount of IFTA with IFTA categorized as commonly done in clinical practice: none-minimal, mild, moderate, or severe.

There are several potential limitations to this study. The age-based thresholds for global glomerulosclerosis were derived from healthy living donors who were mostly white;¹³ whether these thresholds should differ by race is unclear. Second, the China DiKiP cohort presented as younger, healthier, and with milder CKD than the other two cohorts. Since China DiKiP and NEPTUNE used similar study protocols, these differences are unlikely methodological but rather due to genetic and environmental differences between Chinese and American patients that requires further study. Third, there were differences between the cohorts in how glomeruli were counted, though we were able to show that findings were consistent between rigorous and convenient methods of counting glomeruli in the NEPTUNE cohort.²¹ Fourth, we studied IFTA using the semi-quantitative scale (none-minimal, mild, moderate, and severe) as commonly determined with visual inspection by pathologists. Whether a more quantitative granular classification of IFTA would change the findings is unclear.

In conclusion, this study validated the clinical utility of age-based global glomerulosclerosis thresholds. Specifically, we found that age-related glomerulosclerosis has minimal impact on the risk of CKD progression in patients with FSGS, MN, and MCD. In contrast, glomerulosclerosis abnormal for age was an independent risk factor for CKD progression. This finding highlights the need and clinical benefit of distinguishing kidney “pathology” that occur with healthy aging from that driven by a disease process. Secondary analyses of clinical trials are needed to determine if glomerulosclerosis exceeding that expected for age is an effect modifier for interventions to treat biopsied kidney disease.

METHODS

Study population

Three cohorts of patients with a biopsy proven glomerulopathy that often presents with nephrotic syndrome were studied: NEPTUNE, China DiKiP, and SE Minnesota cohorts. All three cohorts were limited to adult patients with a diagnosis of FSGS, MN, or MCD on biopsy with or without nephrotic syndrome. The NEPTUNE cohort is a North American multicenter consortium of 27 medical centers that are part of the National Institutes of Health Rare Disease Clinical Research Network and has prospectively followed patients after their first renal biopsy since 2010.²⁸ The China DiKiP cohort is a similar ongoing multicenter consortium in China (we used data from the Nanjing site) that also follows patients prospectively after their first renal biopsy since 2012. Both of these cohorts have study visits every 4 months for the first year and every 6 months after that. The SE Minnesota cohort is a historical cohort of adult residents in the 11 counties surrounding

Rochester, Minnesota, USA who had a kidney biopsy at the Mayo Clinic (the only regional provider of kidney biopsies) between 1993 and 2016 with passive follow-up per usual clinical care. Patients who had end-stage renal disease (ESRD) before the baseline diagnostic biopsy were excluded. This study was approved by the ethics committees and institutional review boards of NEPTUNE, Jinling Hospital (China DiKiP), and the Mayo Clinic (SE Minnesota).

Biopsy characteristics

The NEPTUNE and China-DiKiP renal biopsy sections were scanned into whole slide images and stored in a digital pathology repository. The digital renal biopsies were reviewed by study renal pathologists to digitally annotate all glomeruli in all sections (levels) available to calculate the total number of glomeruli and the number of GSG (rigorous method). The counts of GSG included glomeruli that could be described as either globally sclerotic or obliterated. In addition to the annotated counts, the NEPTUNE cohort also had available for analysis the total number of glomeruli and the number GSG as documented in the clinical biopsy report by the renal pathologist caring for the patient (convenient method). The SE Minnesota cohort pathology findings, including the number of glomeruli and the number of GSG, were only available from the clinical biopsy reports. All glomeruli were counted regardless of their location and no biopsies were excluded for having too few glomeruli.

The number of GSG was classified abnormal if it was more than the 95th percentile expected for a given age and number of glomeruli, as previously determined with 1847 normotensive healthy living kidney donors (ages 18–77 years) (table 1).¹³ As reference limits are not available for ages >77 years, patients who were older than 77 years used the same thresholds as the 75–77 year-old group. Using the number of GSG, all patients were subsequently divided into three categories: no GSG, GSG normal for age, and GSG abnormal for age. For each patient, the degree of interstitial fibrosis and tubular atrophy (IFTA) was classified into groups of 0= <10% (none-minimal), 1= 10–25% (mild), 2= 26–50% (moderate), and 3= >50% (severe) consistent with what is done in practice and what is recommended.⁸ Arteriosclerosis was defined as thickening of arterial intima with fibrosis. Arteriolar hyalinosis was defined as thickening of arteriolar wall with hyaline material. Both were scored semiquantitatively according to the following score: 0 =absent, 1=mild, thickening < 25%, 2= moderate, thickening 25–50%, 3=severe, thickening > 50%.

Clinical characteristics

For NEPTUNE and China DiKiP, clinical characteristics were determined at a study visit that included a survey, a clinical exam, and blood and urine samples just prior to the baseline biopsy. For SE Minnesota patients, clinical characteristics were abstracted from manual review of the medical records at the episode of care just prior to the baseline biopsy. These clinical characteristics included age, sex, race, body mass index, blood pressure, hypertension (BP >140/90 or use of anti-hypertensive medications), and diabetes mellitus (fasting glucose >126 mg/dl or use of insulin or oral hypoglycemics), kidney function measures included creatinine-based estimated glomerular filtration rate (eGFR) by the CKD-EPI equation and 24-h urine protein (estimated from spot urine protein to creatinine ratio or spot urine protein to osmolality ratio if timed collection was not available).

Outcome

The primary outcome was CKD progression defined by ESRD (initiation of dialysis or kidney transplantation) or an eGFR level 40% lower than baseline eGFR (a validated surrogate endpoint for ESRD).²⁹ All patients were followed for this event until the date of their last visit (study visit for NEPTUNE and China DiKiP and clinic visit for SE Minnesota).

Statistical Analysis

Clinical characteristics, biopsy findings, and outcomes were compared between patients with no GSG, GSG normal for age, and GSG abnormal for age. Categorical data was presented as count (%) and continuous data was presented as mean $\pm$ standard deviation or median [25%ile, 75%ile] for skewed data. p value was calculated using Fisher's exact test for categorical variables and Wilcoxon rank sum test for continuous variables. A sensitivity analysis limited to the NEPTUNE cohort compared glomerular counts and percentages based on annotated images versus the clinical biopsy report using the paired Wilcoxon signed-rank test. The risk of CKD progression with the three glomerulosclerosis categories based on annotated images versus these three glomerulosclerosis categories based on the clinical biopsy report was further assessed.

The risk of CKD progression in patients with GSG abnormal for age versus patients with no GSG or GSG normal for age was assessed using Cox proportional hazard models with censoring at the time of last visit. Separate models adjusted for biopsy findings, clinical characteristics, and kidney function measures. Subgroup analysis was also performed comparing the risk of CKD progression by sex, age group (40 vs <40 years), primary diagnosis, and each individual cohort. We further assessed whether only 1 or 2 GSG above these reference limits was still predictive of CKD progression. Data was analyzed using JMP[®] Pro, version 10.0.0. SAS Institute Inc., Cary, NC. A $p < 0.05$ was considered statistically significant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

China DiKip	China-Digital Kidney Pathology
CKD	chronic kidney disease
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FSGS	focal segmental glomerulosclerosis
GSG	globally sclerotic glomeruli
IFTA	interstitial fibrosis and tubular atrophy
MCD	minimal change disease
MN	membranous nephropathy
NEPTUNE	the Nephrotic Syndrome Study Network
SE Minnesota	southeast Minnesota

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Figure 1. Study sample

FSGS: focal segmental glomerulosclerosis. MN: membranous nephropathy. MCD: minimal change disease. ESRD: end-stage renal disease. GSG: globally sclerotic glomeruli

Figure 2. Distribution of % globally sclerotic glomeruli (GSG) for patients with focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), or minimal change disease (MCD) and any GSG on biopsy

The % globally sclerotic glomeruli (GSG) substantially overlap between patients with GSG normal for age and patients with GSG abnormal for age. There was 60% overlap for FSGS, 94% overlap for MN, and 73% overlap for MCD. Patients with no GSG (27% of FSGS, 43% of MN, and 77% of MCD) are not shown.

Incidence % (No. at Risk)

	0	5	10	15
GSG abnormal for age —	0% (148)	52% (11)	59% (4)	86% (2)
GSG normal for age - -	0% (107)	23% (18)	30% (12)	38% (4)
No GSG . . .	0% (170)	21% (15)	21% (10)	31% (5)

Figure 3. Cumulative incidence of ESRD or 40% decline in eGFR

There was no evident difference in risk of this outcome between patients with GSG normal for age and patients with no GSG (log-rank p-value 0.98). Patients with GSG abnormal for age had significant increase in this outcome compared to other patients (log-rank p-value < .0001). The risk at 5 years and beyond is determined by the SE Minnesota cohort.

Table 1

Upper reference limit (95th percentile) for number of globally sclerotic glomeruli (GSG) based upon age and number of glomeruli.

Age (years)	Number of glomeruli									
	1	2	3-4	5-8	9-16	17-32	33-48	49-64		
18-29	0.5	0.5	0.5	0.5	1	1	1	1		
30-34	0.5	0.5	0.5	0.5	1	1	1	1.5		
35-39	0.5	0.5	0.5	0.5	1	1.5	2	2		
40-44	0.5	0.5	0.5	1	1	2	2.5	3		
45-49	0.5	0.5	1	1	1.5	2	3	4		
50-54	1	1	1	1.5	2	3	4	5		
55-59	1	1	1.5	1.5	2	3.5	4.5	6		
60-64	1	1.5	1.5	2	2.5	4	5.5	7		
65-69	1	2	2	2.5	3	4.5	6.5	8		
70-74	1	2	2.5	3	4	5.5	7.5	9		
75-77	1	2	2.5	3	4	6	8	9.5		

Note: These 95th percentile thresholds were determined with quantile regression using 1847 healthy normotensive living kidney donors in the Aging Kidney Anatomy study.¹³ The percentage GSG for these thresholds decreases with more glomeruli biopsied. For example, a 70 year old patient with 5 glomeruli would have a 95th percentile of 60% (3/5) but with 49 glomeruli would have a 95th percentile of 18% (9/49). This occurs because the precision for distinguishing abnormal from normal improves when more glomeruli are biopsied.

Table 2

Characteristics of each cohort and the overall cohort

Characteristics	NEPTUNE (N=183)	China DiKiP (N=129)	SE Minnesota (N=113)	Overall (N=425)
	N(%), Mean $\pm$ SD, Median [25%, 75%ile]	N(%), Mean $\pm$ SD, Median [25%, 75%ile]	N(%), Mean $\pm$ SD, Median [25%, 75%ile]	N(%), Mean $\pm$ SD, Median [25%, 75%ile]
Demographics				
Male	113 (62%)	84 (65%)	65 (58%)	262 (62%)
Age, yr	46 $\pm$ 16.1	32 $\pm$ 12.4	50 $\pm$ 18.6	43 $\pm$ 17.5
Race				
White	112 (61%)	0 (0%)	96 (85%)	208 (49%)
Black	30 (16%)	0 (0%)	3 (3%)	33 (8%)
Asian	24 (13%)	129 (100%)	2 (2%)	155 (36%)
Other *	17 (10%)	0 (0%)	12 (10%)	29 (7%)
Comorbidities				
Body mass index, kg/m ²	29.7 $\pm$ 7	24.3 $\pm$ 6.0	31.4 $\pm$ 7.2	28.5 $\pm$ 7.3
Hypertension	118 (64%)	36 (28%)	70 (62%)	224 (53%)
Diabetes	13 (7%)	0 (0%)	13 (12%)	26 (6%)
Systolic BP, mmHg	125 $\pm$ 18.1	125 $\pm$ 12.7	136 $\pm$ 19.5	128 $\pm$ 17.6
Diastolic BP, mmHg	78 $\pm$ 11.8	78 $\pm$ 9.9	79 $\pm$ 12.6	78.2 $\pm$ 11.4
Laboratory studies				
24 hour urine protein, g/d	2.0 [0.9, 3.8]	5.1 [3.7, 7.8]	6.1 [3.1, 10.9]	3.9 [1.8, 7.5]
Serum creatinine, mg/dl	1.2 [0.9, 1.7]	0.8 [0.6, 0.9]	1.3 [0.9, 1.7]	1.0 [0.8, 1.5]
eGFR, ml/min/1.73m ² **	65.4 [41.7, 96.0]	117.0 [97.1, 127.3]	63.0 [34.2, 90.9]	81.2 [46.3, 112.7]
Diagnoses				
Focal and segmental glomerulosclerosis	106 (58%)	46 (36%)	55 (49%)	207 (49%)
Membranous nephropathy	51 (28%)	46 (36%)	45 (40%)	142 (33%)
Minimal change disease	26 (14%)	37 (28%)	13 (11%)	76 (18%)
Follow up duration				
Years	2.5 [1.0, 3.6]	3.5 [2.5, 4]	3.7 [1.4, 8.4]	3.0 [1.4, 4.0]
Outcome (CKD progression)				
ESRD or 40% decline in eGFR	59 (32%)	10 (8%)	40 (35%)	109 (26%)

Abbreviations: BP, blood pressure; China DiKiP, China Digital Kidney Pathology study; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; NEPTUNE, the Nephrotic Syndrome Study Network; SE Minnesota, Southeast Minnesota.

* Other includes multiracial, Native American, Alaskan, and unknown.

** eGFR using CKD-EPI equation

Table 3

Characteristics for the overall cohorts by globally sclerotic glomeruli (GSG) category

Characteristics	No GSG (N=170)	N(%), Mean $\pm$ SD, Median [25%, 75%ile]	GSG normal for age (N=107)	P value*	GSG abnormal for age (n=148)	P value**
Clinical characteristics						
Male	110 (65%)		66 (62%)	0.61	86 (58%)	0.25
Age, yr	35 $\pm$ 14.9		52 $\pm$ 17.5	<0.0001	45 $\pm$ 16.0	<0.0001
Body mass index, kg/m²	27.5 $\pm$ 7.2		28.8 $\pm$ 6.5	0.07	29.5 $\pm$ 7.9	0.03
Hypertension	54 (32%)		66 (62%)	<0.0001	104 $\pm$ 70%	<0.0001
Diabetes	2 (1%)		11 (10%)	0.0007	13 (9%)	0.002
Systolic BP, mmHg	125 $\pm$ 15.8		128 $\pm$ 18.9	0.22	130 $\pm$ 18.4	0.03
Diastolic BP, mmHg	78 $\pm$ 11.3		76 $\pm$ 11.9	0.23	80 $\pm$ 11.0	0.07
24 hour urine protein, g/d	4.7 [2.5, 8.3]		4.3 [2.1, 8.1]	0.43	2.4 [1.1, 4.8]	<0.0001
Serum creatinine, mg/dl	0.9 [0.7, 1.1]		1.0 [0.8, 1.4]	0.009	1.4 [1.0, 2.2]	<0.0001
eGFR, ml/min/1.73m²†	106.4 [74.0, 121.8]		78.0 [52.2, 103.8]	<0.0001	53.5 [32.2, 87.9]	<0.0001
Biopsy findings						
Number of Glomeruli	22 (11.9)		24 (14.4)	0.52	25 (22.2)	0.73
Number of GSG	0		1.6 (1)	<0.0001	8 (8.5)	<0.0001
Percentage GSG	0		9%	<0.0001	38%	<0.0001
Cortical IFTA 0–3				0.001		<0.0001
0	127 (75%)		62 (58%)		49 (33%)	
1	35 (20%)		29 (27%)		44 (30%)	
2 or 3	8 (5%)		16 (15%)		55 (37%)	
Arteriotar hyalinosis 0–3‡				0.001		<0.0001
0	130 (77%)		63 (60%)		77 (53%)	
1	38 (22%)		33 (31%)		52 (36%)	
2 or 3	1 (1%)		9 (9%)		17 (11%)	
Arteriosclerosis 0–3‡				<0.0001		<0.0001
0	113 (69%)		48 (46%)		41 (29%)	

Characteristics	No GSG (N=170)	GSG normal for age (N=107)	GSG abnormal for age (n=148)	P value [*]	P value ^{**}
	N(%), Mean $\pm$ SD, Median [25%, 75%ile]	N(%), Mean $\pm$ SD, Median [25%, 75%ile]	N(%), Mean $\pm$ SD, Median [25%, 75%ile]		
1	43 (26%)	29 (28%)	54 (39%)		
2 or 3	8 (5%)	27 (26%)	45 (32%)		
Primary Diagnosis					
Focal segmental glomerulosclerosis	55 (32%)	36 (34%)	116 (78%)	0.90	<0.0001
Membranous nephropathy	61 (36%)	54 (50%)	27 (18%)	0.02	0.0004
Minimal change disease	54 (32%)	17 (16%)	5 (4%)	0.003	<0.0001
Outcome (CKD Progression)					
ESRD or 40% decline in eGFR	26 (15%)	19 (18%)	64 (43%)	0.62	<0.0001

Abbreviations: BP, blood pressure; China DiKip, China Digital Kidney Pathology study; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GSG, globally sclerotic glomeruli; NEPTUNE, the Nephrotic Syndrome Study Network; SE Minnesota, Southeast Minnesota.

^{*} p value (Fisher's exact test or Wilcoxon rank sum test) comparing GSG normal for age vs. no GSG.

^{**} p value comparing GSG abnormal for age vs. no GSG.

[†] eGFR calculated using CKD-EPI equation.

Cortical interstitial fibrosis and tubular atrophy Values are N (%), mean $\pm$ SD, or median [25%, 75% percentile] (IFTA) was semi-quantified as: 0 (<10%), 1 (10–25%), 2 (26–50%), and 3 (>50%).

[‡] Arteriosclerosis was defined as thickening of arterial intima with fibrosis. Arteriolar hyalinosis was defined as thickening of arteriolar wall with hyaline material. Both were scored semiquantitatively according to the following score: 0 =absent, 1=mild, thickening < 25%, 2= moderate, thickening 25–50%, 3=severe, thickening > 50%.

Table 4

Risk of CKD progression (ESRD or 40% decline in eGFR) with globally sclerotic glomeruli abnormal for age vs having no globally sclerotic glomeruli or having globally sclerotic glomeruli normal for age

Analysis for predicting CKD progression with GSG abnormal for age	Hazard ratio (95% CI)	P value
Unadjusted	3.6 (2.4–5.3)	<.0001
Adjusted for		
Biopsy findings		
Interstitial fibrosis 0–3	2.6 (1.7–3.9)	<.0001
Arteriosclerosis 0–3 [‡]	3.1 (2.1–4.8)	<.0001
Arteriolar hyalinosis 0–3 [‡]	3.3 (2.2–4.9)	<.0001
Interstitial fibrosis, arteriosclerosis, and arteriolar hyalinosis	2.5 (1.6–3.9)	<.0001
Clinical characteristics		
Hypertension	2.9 (2.0–4.3)	<.0001
Diabetes	3.4 (2.3–5.0)	<.0001
Body mass index	3.2 (2.1–4.8)	<.0001
Age	3.5 (2.4–5.2)	<.0001
Primary diagnosis	2.4 (1.6–3.7)	<.0001
Hypertension, diabetes, body mass index, age and primary diagnosis	2.0 (1.3–3.2)	0.0017
Kidney function measures		
eGFR, ml/min/1.73 ²	2.2 (1.5–3.3)	0.0001
Proteinuria, g/day	3.5 (2.3–5.3)	<.0001
eGFR and proteinuria	2.3 (1.5–3.6)	0.0002
All biopsy, clinical characteristics and kidney function measures		
Interstitial fibrosis, arteriosclerotic, arteriolar hyalinosis, age, HTN, DM, BMI, primary diagnosis, eGFR, and proteinuria	1.8 (1.0–3.1)	0.04
Subgroups analysis by		
Sex[*]		
Men	2.9 (1.8–4.7)	<.0001
Women	5.6 (2.8–12)	<.0001
Age[*]		
< 40 years old	4.8 (2.4–9.9)	<.0001
40 years old	3.1 (1.9–5.1)	<.0001
Primary glomerulopathy[*]		
Focal segmental glomerulosclerosis	3.2 (1.9–5.4)	<.0001
Membranous nephropathy	1.3 (0.46–2.9)	0.63
Minimal change disease	N/A [‡]	N/A [‡]
Cohort[*]		
SE Minnesota	3.8 (2.0–7.4)	<.0001
NEPTUNE	2.4 (1.4–4.2)	0.0008
China DiKiP	1.6 (0.35–5.9)	0.50
Total number of glomeruli on biopsy[*]		

Analysis for predicting CKD progression with GSG abnormal for age	Hazard ratio (95% CI)	P value
Total glomeruli on biopsy 3–9	2.6 (1.2–6.2)	0.02
Total glomeruli on biopsy 10–19	3.9 (2.1–7.8)	<.0001
Total glomeruli on biopsy 20–29	3.2 (1.4–7.8)	0.009
Total glomeruli on biopsy >29	3.8 (1.6–9.3)	0.002
Restricted analysis		
GSG only slightly abnormal (1 or 2 GSG above the reference limit)	2.3 (1.3–3.8)	0.005

Abbreviations: China DiKiP, China Digital Kidney Pathology study; eGFR, estimated glomerular filtration rate; GSG, globally sclerotic glomeruli; NEPTUNE, the Nephrotic Syndrome Study Network; SE Minnesota, Southeast Minnesota.

* P > 0.05 for statistical interaction between subgroups.

[†] Not available (only 2 events in minimal change disease patients).

Cortical interstitial fibrosis and tubular atrophy (IFTA) was semi-quantified as: 0 (<10%), 1 (10–25%), 2 (26–50%), and 3 (>50%).

[‡] Arteriosclerosis was defined as thickening of arterial intima with fibrosis. Arteriolar hyalinosis was defined as thickening of arteriolar wall with hyaline material. Both were scored semiquantitatively according to the following score: 0 = absent, 1 = mild, thickening < 25%, 2 = moderate, thickening 25–50%, 3 = severe, thickening > 50%.