Trends in the incidence and outcomes of end stage kidney disease from specific causes and the ability of measures of kidney function to predict mortality in community dwelling individuals.

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Summary of Contents

There are two broad themes in this research thesis. The first is an exploration of the ability of measures of kidney function and urinary protein excretion to predict death based on non-parametric methodology known as classification tree recursive partitioning. In the second part of the thesis, the clinical epidemiology of kidney failure from various rare diseases is characterised including trends in incidence, mortality and kidney transplant in the United States based on national registry data.

Declaration

I declare that this thesis, which I submit to NUIGalway for examination is my own personal effort. I took reasonable care to ensure that the work is original and to the best of my knowledge is in compliance with copyright law.

Acknowledgements

I would like to sincerely thank Prof Rob Foley for introducing me to the world of coding and data science, and teaching me something new everyday. I would also like to thank my supervisors Prof Martin O'Donnell and Prof Joe Eustace for all their support and advice throughout the years.

List of published manuscripts and abstracts related to this thesis

1. End Stage Kidney Disease from Scleroderma in the United States, 1996-2012. Sexton DJ, Reule S, Foley RN. ***Kidney International Reports***. In press **2017**.
2. End-Stage Renal Disease from Multiple Myeloma in the United States, 2001-2010. Reule, S, Sexton DJ, Solid CA, Chen S, Collins AC, Foley, RN. ***Journal of the American Society of Nephrology***. **2016**
3. End Stage Renal Disease from HIV-Associated Nephropathy in the United States, 2001-2010. Sexton DJ, Reule S, Solid C, Collins AJ, Foley RN. ***JAMA Internal Medicine; 2014*** *Mar 3. doi:10.1001.*
4. ESRD from Lupus Nephritis in the United States 1995-2010. Donal J Sexton, MB, Scott A Reule, MD, Craig Solid, PhD, Shu-Cheng Chen, MS, MPH, Allan J. Collins, MD, Robert N. Foley, MB. ***Clin J Am Soc Nephrol, feb 6 2015. CJASN***.
5. ESRD from Haemolytic Uremic Syndrome in the United States 1995-2010. Donal J Sexton, MB, Scott A Reule, MD, Craig Solid, PhD, Shu-Cheng Chen, MS, MPH, Allan J. Collins, MD, Robert N. Foley, MB. ***Hemodialysis International****, Feb 17 2015.*
6. End-Stage Renal Disease Attributed to Acute Tubular Necrosis in the United States, 2001 to 2010. Foley RN, Sexton DJ, Reule S, Solid C, Shu-Cheng C, Collins AJ. **American Journal of Nephrology** 2015.
7. End Stage Renal Disease from Autosomal Dominant Polycystic Kidney Disease in the United States, 2001-2010. Reule S, Sexton DJ, Solid C, Shu-Cheng C, Collins AJ, Foley RN. ***The American Journal of Kidney Disease****; 2014.*

Abstracts

1. ESRD in Nonagenarians in the United States, 1995 Through 2010. Donal J. Sexton, Scott Reule, Robert N. Foley. ASN Kidney Week 2015.
2. End-Stage Renal Disease from Membranous Nephropathy in the United States, 1995 to 2010 Robert N. Foley, Scott Reule, Donal J. Sexton. ASN Kidney Week 2015.
3. ESRD from Scleroderma in the United States 1995-2010 Donal J. Sexton, Scott Reule, Robert N. Foley. ASN Kidney Week 2015.
4. Intermittent Abnormal Kidney Function and Mortality in Community Dwelling Individuals Donal J. Sexton, Scott Reule, Robert N. Foley. ASN Kidney Week 2015.
5. Kidney Function and Mortality Risk in Community Dwelling Individuals: Hierarchical Importance of Threshold Values Donal J. Sexton, Scott Reule, Robert N. Foley. Div of Renal Diseases and Hypertension, Dept of Medicine, Univ of Minnesota, Minneapolis, MN. ASN Kidney week 2014.
6. End Stage Renal Disease due to HIVAN in the United States 2000-2010. Sexton DJ, Reule S, Solid C Chen SC, Collins AC, Foley RN. ASN Kidney Week 2013.
7. End Stage Renal Disease due to Lupus Nephritis in the United States 2000-2010. Sexton DJ, Reule S, Solid C Chen SC, Collins AC, Foley RN. ASN Kidney Week 2013.
8. End-Stage Renal Disease Due to Multiple Myeloma in the United States, 2000-2010. Reule S, Sexton DJ, Solid C Chen SC, Collins AC, Foley RN. ASN Kidney Week 2013.

9. End-Stage Renal Disease from Autosomal Dominant Polycystic Kidney Disease in the United States, 2000-2010. Reule S, Sexton DJ, Solid C Chen SC, Collins AC, Foley RN. ASN Kidney Week 2013.

Awards related to the work presented in this thesis

2013:

- Awarded the Health Research Board of Ireland Research Training Fellowship for Health Care Professionals as *Principal Investigator*.
- Awarded the *American Society of Nephrology (ASN) Travel Grant, ASN Kidney Week 2013*. (Advances in Geriatric Nephrology).

2015:

- Awarded the *Dimitrios Oreopoulos Geriatric Nephrology Travel Support grant* by the American Society of Nephrology at ASN Kidney Week 2015.
- The ASN Training Program Directors Executive Committee invited me to present in the Fellows Poster Discussion session on Sat Nov 7.

2017:

- Awarded the *Vincent Dolan Medal* for best clinical research presentation at the Irish Society of Nephrology Annual Scientific Meeting 2017.

- *Awarded an American Society of Nephrology (ASN) travel grant to attend* the "Advances in Research Conference: Precision Medicine in Renal Diseases" and ASN Kidney Week 2017.

Grants awarded which funded the work presented in this thesis

- The Irish Nephrology Society Research Bursary 2012.

- The HRB Research Training Fellowship for Health Care Professionals.

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List of Abbreviations

ACR; Albumin to creatinine ratio,

APOL-1; apoliprotein L1,

AOR; adjusted odds ratio,

AHR; adjusted hazard ratio,

ACE; Angiotensin-converting-enzyme,

AIR; adjusted incidence ratio,

AIDS; acquired immunodeficiency syndrome,

ANZDATA; The Australia and New Zealand Dialysis and Transplant Registry.

aHUS; atypical hemolytic uremic syndrome,

BP; blood pressure

BMI; body mass index,

CKD: Chronic kidney disease,

CKD-EPI; Chronic Kidney Disease Epidemiology Collaboration formula for estimating glomerular filtration rate,

CVD; Cardiovascular disease,

CRP; C-reactive protein,

Creat; serum creatinine,

Diastolic; diastolic blood pressure,

eGFR; estimated glomerular filtration rate,

ESRD; End Stage Renal Disease [also described as End Stage Kidney Disease (ESKD)]

HDL; high-density lipoproteins,

HTN; hypertension,

HIVAN; HIV associated nephropathy,

HIV; Human immunodeficiency virus,

HAART; highly active anti-retroviral,

HUS; Hemolytic Uremic Syndrome,

HD; haemodialysis,

KDIGO; Kidney Disease: Improving Global Outcomes (KDIGO),

LDL; low-density lipoprotein,

LN; lupus nephritis,

MMF, mycophenolate mofetil,

NHANES: National Health and Nutrition Examination Survey,

PSU; primary sampling unit,

PD; peritoneal dialysis,

RRT; renal replacement therapy,

ROC curve; Receiver operating characteristics curve,

Sn; Sensitivity,

Sp; Specificity,

SLE; systemic lupus erythematosus,

SIR; standardised incidence ratio,

SD; scleroderma,

SRC; scleroderma renal crisis,

UOR; unadjusted odds ratio,

UAE; Urinary albumin excretion**,**

USRDS; United States Renal Data System,

USPSTF ; United States Preventive Services Task Force,

US; United States,

WHR; waist-hip ratio,

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Chapter 1: Introduction

Kidney disease and the potential for screening

As per the National Foundation Kidney Outcomes Quality Initiative (NKF-K/DOQI) and Kidney Disease: Improving Global Outcomes (KDIGO) guidelines chronic kidney disease is defined as the presence of kidney damage or decreased function for three or more months. Kidney damage refers to abnormalities such as increased urinary albumin excretion, reduced estimated glomerular filtration rate (eGFR), and/or abnormal renal biopsy or findings on imaging. In practice, the vast majority of patients defined as having CKD are based on urinary albumin excretion (UAE) of greater than 30 mg/g and/or an eGFR < 60 ml/min/1.73m^2. CKD as defined by these criteria and thresholds is associated with amongst other factors cardiovascular disease and premature mortality. [1-3]

In 2003 Coresh et al analysed a nationally representative sample of 15,625 non-institutionalized adults residing in the United States aged over 20 years from NHANES III to estimate CKD prevalence.[4] The prevalence of CKD in the US was 11% based on creatinine based assessment using the Cockcroft-Gault equation, 3.3% had stage 1 (defined as persistent albuminuria and normal eGFR), 3% had stage 2 (persistent albuminuria and eGFR 60-89 ml/min/1.73m^2), 4.3% stage 3 (eGFR 30-59 ml/min/1.73m^2), 0.2% had stage 4 and 0.2% stage 5 or renal failure. Aside from hypertension and diabetes, age was a predictor of CKD and 11% of adults older than 65 years without hypertension or diabetes had stage 3 CKD or worse.

Agodoa et al conducted a randomized trial comparing the effect of amlodipine to Ramipril on the rate of change of eGFR in hypertensive nephrosclerosis based on mixed-effects models with three primary protocol specified comparisons [Ramipril vs Metoprolol, amlodipine vs Metoprolol and low vs usual mean arterial pressure (MAP)].[5] The participants in this trial were African Americans with an eGFR 20-65 ml/min/1.73m^2 with hypertension (N=1094). The trial showed a reduced composite endpoint of reduction in eGFR, ESRD or death. One difficulty with this is that it likely over-represented those with quite low eGFR, and in light of recent evidence of hypertension in African

Americans, likely included patients with true identifiable kidney disease from a nephropathy which we now know is likely related to mutations in gene encoding apoliprotein L1 (APOL-1). [6] Therefore external validity of these findings for the general population may be limited. If the trial had been limited to those with higher eGFR, the investigators would likely need a larger sample size, given the fact that the rate of ESRD is a rare event in those with mild reductions in eGFR. Progression was worse in those with higher urinary protein excretion in this trial. Which of urinary ACR or reduced eGFR are more important in terms of the association with adverse events appears to depend on the context in which these tests are used.[7]

Another prospective randomized trial compared strict vs conventional blood pressure control in 87 non-diabetic patients aged 25-75 years with CKD and found a slow overall mean rate of decline in eGFR. Participants were mainly African Americans (68/87) with long standing hypertension and eGFR < 70 ml/min/1.73m^2 and had a normal urine sediment. [8] This study likely included patients with advanced disease, which may have driven these results. For those with pre-existing diabetes the loss of kidney function or rate of decline in eGFR appears to be sharper.[9-11]

The PREVEND study (Prevention of Renal and Vascular End-Stage Renal Disease) was a longitudinal study initiated in 1997 looking at the impact of albuminuria on the development of renal and cardiovascular disease in the general population. Investigators studied whether proteinuria was associated with a reduction in eGFR to below the 60 ml/min/1.73m^2 threshold over follow up. The authors excluded those with eGFR < 60 ml/min/1.73m^2 at baseline and looked at whether albuminuria was associated with de novo development of impaired renal function (N=872). At 4 years of follow up 4.2% were found to have a GFR < 60 ml/min/1.73m^2, these patients were older, had higher blood pressure, higher cholesterol, glucose and urinary albumin.[12] Iseki et al assessed the development of end stage kidney disease (ESKD) in Japan over approximately 18 years using data from 106,177 screened patients aged 20-98 years. The authors found a graded association between dipstick proteinuria and ESKD, adjusted Odds Ratio of 1+ proteinuria of 1.93 (1.53-2.41, P<0.001) in men and 2.42 (1.91 to 3.06, P<0.001) in women. The authors propose that this evidence warrants screening for

asymptomatic proteinuria, however one must be aware that the absolute rates of ESKD were rare, with 1.4% 18yr ESRD incidence.[13]

Ishani et al aimed to estimate the risk of ESRD over 25 years. 12,866 men at high risk for heart disease from the Multiple Risk Factor Intervention Study (MRFIT) were enrolled (1973-1975) followed through 1999. Investigators identified cases of ESKD and death through linkage with the United States Renal Data System (USRDS) dataset and vital status from the National Death Index. [14] Predictors of ESKD were dipstick proteinuria of 1+ or ≥ 2+ (hazard ratio [HR] 3.1 [95% confidence interval (CI) 1.8 to 5.4] and 15.7 [95% CI 10.3 to 23.9] respectively) and an eGFR of < 60 ml/min per 1.73 m^2 (HR 2.4; 95% CI 1.5 to 3.8). Other baseline measures that independently predicted ESKD included age, cigarette smoking, blood pressure, low HDL cholesterol, and fasting glucose.[14 15]

Collectively the available data suggests that there is an annual decline in renal function, which appears to be exaggerated in those with diabetes, hypertension and proteinuria. Although the findings of these studies may be used by some to advocate for CKD screening, the heterogeneous nature of the study populations, and the low event rate of ESKD leave me unconvinced, particularly when ESKD is the primary event of interest. Although these studies suggest that markers of kidney function in the abnormal range is associated with adverse outcomes, what is not known, and a topic which is the focus of some of our studies, is the association of these markers within the normal range. In our study based on NHANES mortality data we looked at mortality prediction within the normal range of kidney function.

Current approaches to predicting mortality risk in the community

Risk stratification is an important tool in helping to decide who is at risk of certain events in both the short and long term even amongst those who are not known to have overt disease at the time of screening. While management decisions (e.g. who to treat with risk factor modification) based on risk are less complex when the subject is at low or high risk, many patients will also fall in the intermediate risk category, which creates uncertainties and adds to the complexity of decision-making.

Current prediction models for mortality are mainly based on the prediction of cardiovascular disease, and many are suboptimal for accurate individual-level prediction. Improvement of these models/approaches and enhancement/refinement of these risk scores, including the use of novel predictors, is desperately needed to optimize approaches to mortality reduction. ACR and eGFR provide an opportunity to add to the traditional risk factors and create a novel model, which could conceivably improve the discrimination of existing models.[16]

Given that cardiovascular disease (CVD) is the most common cause of death in CKD, mortality prediction based on cardiovascular event prediction models may be of particular applicability in CKD. Investigators have focused on novel predictors of CVD such as CRP and serum Fibrinogen in an attempt to improve CVD prediction. Disappointingly in a high quality study of people without known CVD, the estimation of CRP and Fibrinogen will prevent only one additional event over a 10-year period for every 400-500 people screened.[17] The addition of fibrinogen or CRP to established risk prediction does not result in a measureable improvement in the predictive accuracy.[18 19]

Evidence is also emerging for methods of CVD risk prediction aimed at the detection of subclinical disease such as pulse wave velocity, carotid intima-media thickness, flow-mediated vasodilation and radiological detection of aortic and cerebrovascular calcifications. However these methods are logistically problematic and unlikely to be practical or cost effective for screening of very large sections of the population.[20 21] Given the association between CKD, cardiovascular disease and premature mortality we hypothesised that measures of kidney function may have added discriminatory ability for mortality in community dwelling individuals.

CKD and CV risk.

As noted above, CKD is relatively common, particularly at older age, with a prevalence as high as 38% in those > 70 years. [22] The prevention of complications is limited by awareness since > 90% of those with CKD by current definitions are unaware. [23] Reduced GFR has been convincingly demonstrated to be associated with CVD independent of traditional risk factors in diverse study populations such as the Heart Outcomes and Prevention Evaluation study[24], the Cardiovascular Health Study [25], the

Hypertension Optimal Study [26] and the Atherosclerosis Risk in Communities study. [27] In a pooled meta-analysis of 1.1 million people with normal GFR, those with trace proteinuria had a hazard ratio of 1.78 for CV mortality and 1.44 for all-cause mortality[28]. The magnitude of increased risk attributable to trace proteinuria was approximately equal to that of smoking, which reaffirms its public health importance. As a result of this evidence, many advocate for screening for CKD in the general population.

A simple screening test for CKD is an attractive way to improve detection and awareness and possibly reduce mortality in the long run. In a healthy population, almost 9 out of 10 people have ACR < 30 mg/g [28], which makes it an attractive biomarker for CKD and CV screening. Urinalysis receives relatively little attention in the evaluation of apparently healthy individuals. However, even small quantities of albumin in the urine indicate increased risk for CVD, and all-cause mortality, which increases in a continuous fashion with increased proteinuria, and is further, amplified in the setting of reduced eGFR. [29-31] Urinary ACR is a powerful predictor of renal and cardiovascular outcomes across all age groups in people with and without diabetes [32 33 34] in community-based cohorts [31 35].

The CKD Prognosis Consortium published a large individual-level meta-analysis**.** This study included 2,051244 participants from 33 general population or high risk (of vascular disease) cohorts and 13 CKD cohorts from Asia, Australasia, Europe, and North/South America, conducted in 1972-2011 with a mean follow up time of 5.8 years.[34] Mortality and ESKD risks were higher at lower eGFR and higher albuminuria regardless of age. This metanalysis documents that the threshold for increased risk of mortality and ESKD is at 60 ml/min/1.73m^2, the threshold used for defining CKD across all age groups.

ACR and eGFR as CVD prediction tools

The potential for ACR and eGFR to improve prediction is promising since they are already in common clinical usage, are relatively inexpensive, can be determined in general practice and in large-scale studies. They are independent predictors of CVD even after adjustment for traditional predictors used in current models. [33 34] Unlike traditional risk factors microalbuminuria reflects actual low-level end organ damage or endothelial dysfunction. Microalbuminuria is defined as a level of urinary albumin excretion ≥

30mg/g. The SI equivalent of this threshold is 3 mg/mmol.

Measurement of urinary ACR may be viewed as a routine non-invasive test as part of clinic, office or bedside evaluation. Detection of CKD supports the introduction of blood pressure and lipid control, diabetes testing, smoking cessation and increased weight loss and exercise.

Prognostic prediction models are based on prospective cohort studies, we used NHANES, in which large numbers of disease-free participants submit to comprehensive baseline testing and are followed for a time for the development of the event.[36] Our study may provide more definitive evidence from a large-scale high quality study based on samples representative of the general population.

Overall aim:

The aim of our study based on NHANES was to further elucidate the ability of simple tests such as the urinary ACR and eGFR to predict all-cause mortality in community dwelling individuals. Data describing how ACR and eGFR can be used together to predict mortality are limited and the threshold levels of microalbuminuria and eGFR predictive of increased mortality risk in community dwelling as distinct to selected study populations are unclear. The ability of urinary ACR or eGFR to predict or out rule all cause mortality in non-institutionalised individuals is also relatively uncharacterised. We proposed to elucidate these test characteristics.

Whether ACR screening should be advocated for the general public hinges on whether it adds value to patients and can prolong life. However this debate cannot be fully informed without a complete knowledge of the characteristics of the test being used. We aimed to establish the thresholds for maximal (Sensitivity/Specificity) values of these tests for all cause mortality.

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Summary of the statement by United States Preventive Services Task Force *(USPSTF) on Chronic Kidney Disease:*

The following are the summary points of the USPSTF statement on the topic of screening for chronic kidney disease:

- As of 2012, The USPSTF could not find any studies on the accuracy of screening with serum creatinine or urinary albumin for chronic kidney disease (CKD) defined as eGFR less than 60 ml/min/1.73m2 or albuminuria that persists at least 3 months.[1]
- Few studies provide some information about reliability and false-positive results, and no studies directly evaluate the effectiveness of screening for CKD.
- Treatment of early stages of CKD is targeted at associated conditions, primarily using medications to control hypertension, diabetes, and cardiovascular disease.
- There are few studies on early treatment of CKD stages 1 to 3 in persons without chronic diseases (such as hypertension, diabetes, and cardiovascular disease). [1]
- Evidence shows that identification and treatment of CKD may affect management decisions and health outcomes in patients with established chronic disease, including diabetes, cardiovascular disease, and hypertension, but there is insufficient evidence that identification and early treatment of CKD in asymptomatic adults without these conditions results in improved health outcomes.[1]
- The USPSTF found no studies on the direct harms of screening for CKD. Convincing evidence shows that some harm occurs from medications used to treat comorbid medical conditions associated with early CKD, such as diabetes, hypertension, and cardiovascular disease.
- Although undiagnosed CKD in its early stages is common and there are potential beneficial disease management interventions for persons with chronic diseases, the USPSTF found insufficient evidence on screening

accuracy, benefits of early treatment in the general population (that is, persons without chronic disease), and harms of screening.

- Therefore, evidence to assess the balance of benefits and harms of screening for CKD in the general asymptomatic adult population is insufficient.

Reference

1. United States Preventive Services Task Force. Final recommendation statement chronic kidney disease (CKD): Screening, August 2012.

United States Preventive Services Task Force Statement on CKD

I am largely in agreement with statement by the USPSTF, at this point in time there is an absence of evidence to suggest that identifying CKD by screening reduces ESKD or ultimately mortality, and we don't have a definitive treatment for early CKD outside of primary and secondary prevention of cardiovascular disease. Overall the prevalence of CKD by current thresholds in the population is relatively uncommon. However since the performance of tests to detect CKD, depends on the prevalence of CKD within the population being tested perhaps there might be higher yield gleaned from focusing our attention on those with identifiable high-risk association attributes, which would include diabetes, older age, those with obesity, hypertension, and cardiovascular disease.

In a screening scenario at a population level, generally there are a limited number of opportunities to test, however to abide by the definition of CKD requires documentation of the persistence of these abnormalities at three months to account for the inherent variability in serum creatinine and urinary albumin on repeated testing.

We felt that as highlighted by the USPSTF statement, additional studies focusing on the test characteristics of eGFR and urinary ACR are warranted. Since CKD by the current thresholds is a relatively uncommon event at the population level and most individuals with early CKD die prematurely before developing ESRD, we decided to investigate the concept that perhaps alternative applications of eGFR and ACR as

continuous measures may be more informative in the community as a method of identifying high risk individuals rather than identifying only individuals above or below the defined cut offs of eGFR and ACR.

When evaluating eGFR and ACR in the community it is important to be aware of the clinical factors and comorbid conditions associated with chronic kidney disease.

High-risk groups for CKD

Diabetes

Diabetic nephropathy represents the most common cause of ESKD in the United States.[2] Kramer et al described the cross sectional prevalence of CKD and diabetic retinopathy in community dwelling NHANES III participants aged 40 years or more with type 2 diabetes, and found a cross sectional prevalence of: 13% (N=171/1197) for CKD, 19% for microalbuminuria (defined as urinary albumin excretion between 30 to 300 mg/day) and 28% for retinopathy. Retinopathy and albuminuria were absent in 30% of participants with an eGFR < 60 ml/min/1.73m^2.[3]

In addition approximately 20-30% of patients with type I diabetes mellitus will have moderate albuminuria after an average of 15 years, and many will progress inexorably to more severe proteinuria and eventually to ESRD. [4 5] However the natural history of macroalbuminruia and ESRD may be changing given the widespread use of renin angiotensin system blockade and intensive glycaemic control. [6]

Older age

It is well established that renal function declines with age. [7] However by 70 years of age it appears that as much as 50% of individuals may meet criteria for CKD by current eGFR thresholds.[8] Whether these individuals truly have kidney disease or merely that kidney function is a manifestation of accrued insults over a lifetime, comorbidities and the ageing process, is unknown. However it appears that the association of elevated mortality risk in those meeting the CKD threshold in eGFR in this segment of the population is consistent with other younger segments. [9] However as suggested by the

Kidney Disease: Improving Global Outcomes (KDIGO) group, it may be necessary to identify different and tailored eGFR thresholds for older age groups. [10] This is perhaps another area where our study of mortality discrimination by classification tree methodology is relevant since we evaluated all possible thresholds of eGFR and ACR for mortality in different age subgroups as well as the overall sample.

Hypertension

The relationship between CKD and hypertension is multifactorial, since hypertension has long been considered to be a cause of CKD and ESRD, a cause of progression of CKD as a result of any primary disease to ESRD, and as a major mediator of cardiovascular events and death in CKD.

The biopsy corollary of kidney disease caused by hypertension is hypertensive nephrosclerosis.[11] This has traditionally been the default diagnosis ascribed to cases of ESRD where the cause was not immediately apparent. However in certain subgroups such as African Americans, "hypertensive nephropathy" is know believed to be more accurately defined as APOL-1 related disease with hypertension as a secondary consequence rather than a primary consequence of hypertension. [12-14] Some investigators propose a different definition of hypertensive nephrosclerosis now, subdivided into "arteriosclerosis" in non-African American races and in African Americans "APOL1 related disease" given that up to 70% of non-diabetic glomerulosclerosis in African Americans are strongly associated with two coding renal-risk variants in APOL1. [15]

Nonetheless hypertension is common in those with CKD. Coresh et al analysed NHANES III data, which is predominately comprised of individuals of white race and found a cross sectional prevalence of CKD of approximately 64% in those with modified hypertension i.e. carried a diagnosis of hypertension and were prescribed treatment. [16] However although amongst the ESRD population, "hypertensive nephrosclerosis" is a frequent cause of ESRD, in non African Americans in particular, the absolute risk of worsening renal function from "hypertensive nephrosclerosis" appears to be relatively low. [11] The length of follow up in these studies is a limitation, since the lag for ESRD development or death may be quite long, leaving us to rely on surrogate markers such as, the 7-year incidence of a doubling in serum creatinine in this study.

A retrospective cohort study from a hypertension clinic with approximately 13 years of follow up attempted to address the issue of CKD incidence over time, and reported that 14.6% of this cohort developed CKD over follow up. Although this study was retrospective in nature, it was based on creatinine clearance data rather than eGFR, which is strength of the study. [17] Overall, although the theory of hypertension causing ESRD has recently been challenged, particularly in African Americans, hypertension prevalence in kidney disease is high and appears to consistently associate with progression of advanced CKD to ESKD, and with cardiovascular disease and mortality in all stages of CKD.

Cardiovascular disease

The interplay of CKD with cardiovascular disease is complex. CKD is thought to be associated in a causal manner with cardiovascular disease, while the majority of deaths in early CKD appear to result from cardiovascular disease. [18-20] In addition, those with concomitant cardiovascular disease are thought to be at risk of progression of CKD regardless of the cause of the CKD. Both reduced eGFR and albuminuria are known to be associated with cardiovascular disease; which is believed to be independent of the often co-existing hypertension, diabetes, smoking and obesity. Studies undertaken both in the general population and in CKD cohorts support this association. [18-20]

Manjunath et al looked at data from the Atherosclerosis Risk in Communities (ARIC) Study in order to try to isolate the independent association of reduced eGFR with kidney disease and found a graded association with progressively lower eGFR. ARIC was a prospective cohort study of participants aged 45-64 years. Over a mean follow up of 6.2 years, 6.3% (965) experienced atherosclerotic cardiovascular events overall, and patients with an eGFR 15-59 ml/min/1.73m^2 had a hazard ratio of atherosclerotic cardiovascular disease of 1.38 (1.02, 1.87), N=444. [20]

The same investigator undertook a similar analysis using data from the Cardiovascular Health Study (CHS), a cohort of subjects aged 65 years or older at baseline. The data from 4893 participants were included with mean age of 73.4 years. 11.2% died and 25.1% experienced a cardiovascular event over 5.05 years of follow up.

Each 10-ml/min/1.73m^2 reduction in eGFR was associated with de novo cardiovascular disease of adjusted hazard ratio 1.07 (1.01, 1.12). [19]

The Heart Outcomes and Prevention Evaluation (HOPE) study was a randomized trial enrolling over 9000 participants at high risk for cardiovascular disease.[21] In this trial, microalbuminuria was associated with increased risk of the composite primary outcome of MI, stroke and CV death, both with and without diabetes in a graded manner of urinary albumin excretion.

The Losartan Intervention For Endpoint reduction (LIFE) study was a multicentre cohort study assimilated from an original double blind randomized controlled trial enrolling over 8000 patients with hypertension randomized to losartan or atenolol. [19] In non-diabetic patients with hypertension and left ventricular hypertrophy, the risk of the composite outcome increased with degree of albuminuria. For every 10-fold increase in urinary ACR, the hazard ratio (HR) for cardiovascular mortality increased by 97.7% (CI, 66.5% -235%), by 75.2% (CI, 54% to 99.4%) for all cause mortality, by 51.0% (CI, 28.8% to 76.9%) for stroke and by 45% (CI 19.9%-75.4%) for myocardial infarction, P<0.001 for all comparisons.[22]

A number of studies in the general population have tried to address the association of urinary protein excretion with adverse outcomes. The Prevention of Renal and Vascular Endstage Disease (PREVEND) study from the Netherlands sent a postal questionnaire to all inhabitants in one city aged 28-75 (N=85421) in order to collect information about cardiovascular risk factors and sent participants a container to submit an early morning urine collection for assessment of urinary albumin excretion. [20] Investigators found a dose-response relationship between degree of urinary protein excretion and both cardiovascular and non-cardiovascular death, with the increase being significantly higher for cardiovascular mortality than for non-cardiovascular mortality (P=0.01). [23] A 2-fold increase in UAC was associated with a relative risk of 1.29 (95% CI 1.18 to 1.40) for cardiovascular mortality and 1.12 (95% CI 1.04 to 1.21) for non-cardiovascular mortality. [23]

Another study from the Netherlands used a nested case-control design to investigate the associations between micro albuminuria and cardiovascular morbidity and mortality in a cohort of 12,239 postmenopausal women in Utrecht, with urinary albumin

measured in 561 cases and 557 controls. Follow up from 1976 through 1995 produced 168,513 person-years of follow up. The age-adjusted rate ratio (95% CI) between those in the highest quintile of urinary albumin and those without detectable albuminuria was 4.4 (2.6 to 7.6).[24]

Race/ethnicity

Data from NHANES suggest that African Americans, Hispanics and Native Americans are more prone to higher rates of diabetes, which may account for some of the higher ESRD risk in these populations. A longitudinal observational study from 1995 through 1998 looked at 62,432 diabetic patients comprised by 12% Asian, 14% African Americans, 10% Latinos and 64% White race. Adjusted hazard ratios for ESRD were 2.03 for African Americans, 1.85 for Asians, and 1.46 for Latinos in comparison to white race respectively (P<.01). [25]

Based on USRDS data it is well recognised that African American race comprise a disproportionate percentage of the ESRD population in comparison to other races.[2] The APOL-1 risk genotype found predominately in African Americans is associated with HIV associated nephropathy, lupus nephritis, hypertensive renal disease and focal segmental glomerulosclerosis (FSGS), as well as with progression of these causes of CKD to ESRD in the US.

However the higher risk of CKD in African Americans is likely multifactorial, including reduced access to healthcare and socioeconomic factors, which might predispose to suboptimal management of CKD and possibly even higher ESRD. However these factors may not explain the disproportionate ESRD entirely, and there is likely a combination of pathophysiological processes at work also.[26]

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CHAPTER 2 METHODOLOGY

NHANES

Stratified random sampling: In the National Health and Nutrition Examination Survey (NHANES) the National Center for Health Statistics performed mobile examinations in trailers moving around from town to town within one area. In NHANES II, a decision was made that it was logistically possible only to sample a certain number of locations throughout the country, and therefore many subjects needed to be recruited in each location. Within each location each city or country was stratified into districts for sampling with groups of houses sampled within each district with oversampling of certain households such as locations with higher Hispanic population. Stratified sampling may lead to increased precision for the given sample size.[1]

Sampling weights

NHANES data includes strata identifiers, PSU primary sampling unit identifiers, and sampling probability weights related to health care assessment and specific weights for blood test sampling, and fasting blood test sampling. Analyses using this data are required to incorporate these strata, cluster and sampling weights. SAS statistical package has a number of procedures designed to incorporate inverse probability weights to account for sampling probability within the population. For our analysis we used the following procedures in SAS: surveymeans (to calculate the mean for continuous variables while accounting for the complex survey design of the data), surveyfreq (for cross-tabulation while accounting for the complex survey design of the data), surveylogistic (to conduct logistic regression while accounting for the complex survey design of the data), surveyreg (to conduct linear regression analysis while accounting for the complex survey design of the data), and surveyPhreg (to examine time to event models accounting for the complex survey design of the data).

Sampling weights are important in design-based analyses because unequal sampling can bias associations between variables, and must be adjusted for in the analysis. The counter argument is that since regression models use adjustment for confounders as a way of removing distorted associations it is possible that a regression model might not require sampling weights.[2] This is outlined by DuMouchel and Duncan:[3] Fitting regression models with sampling weights will typically reduce precision, however although perhaps less precise we incorporated the stratum, cluster and sampling probability weights in all of our analysis of NHANES data in order to maximize the representativeness of our findings for the US population.

Study Design

Population NHANES

NHANES samples are multistage, cross-sectional, stratified, clustered probability samples of the non-institutionalized US civilian population.[4] NHANES III was a survey performed in two phases, 1988-1991 and 1991-1994; and now 1999-2002 as recommended by the National Center for Health Statistics, both subpopulations were combined in this study.[1] Older people, Mexican Americans, and non-Hispanic African Americans were systematically oversampled.

The National Health and Nutrition Examination Survey (NHANES) is a program of studies designed to assess the health and nutritional status of adults and children in the United States. The survey is unique in that it is the largest survey that combines interviews and physical examinations. NHANES is a major program of the National Center for Health Statistics (NCHS) in the United States. NCHS is part of the Centers for Disease Control and Prevention (CDC) and has the responsibility for producing vital health statistics for the US population.

The NHANES program began in the early 1960s and has been conducted as a series of surveys focusing on different population groups or health topics. The survey examines a nationally representative sample of about 5,000 persons each year. These persons are located in counties across the country, 15 of which are visited each year. The

NHANES interview includes demographic, socioeconomic, dietary, and health-related questions. The examination component consists of medical, dental, and physiological measurements, as well as laboratory tests administered by highly trained medical personnel. Smoking, alcohol consumption, sexual practices, drug use, physical fitness and activity, weight, and dietary intake are studied. Data on certain aspects of reproductive health, such as use of oral contraceptives and breastfeeding practices, are also collected.[1]

The sample for the survey is selected to represent the U.S. population of all ages. To produce reliable statistics, NHANES deliberately over-samples persons 60 years and older, African Americans, and Hispanics. Since the United States has experienced dramatic growth in the number of older people during this century, the aging population has major implications for health care needs, public policy, and research priorities. All participants visit the physician. Dietary interviews and body measurements are included for everyone. All but the very young have a blood sample taken and will have a dental screen. Depending upon the age of the participant, the rest of the examination includes tests and procedures to assess the various aspects of health listed.[1]

Measurements

The kinetic alkaline picrate method was used to measure serum creatinine in NHANES (White Sands Research Center, Alamogordo, New Mexico) with a Roche/Hitachi 737 analyzer (Roche Diagnostics, Indianapolis, Indiana). Serum creatinine measurements was then aligned to standardized creatinine measured at the Cleveland Clinic Research Laboratory (Cleveland, Ohio). Standardized creatinine values (in mg/dL) were calculated from actual creatinine as follows: standardized creatinine = 0.960 x actual creatinine - 0.184.[5]

The CKD Epidemiology Collaboration (CKD-EPI) formula was used to calculate eGFR (mL/min/1.73 m^2), using the following functions:[6] **see Table 1**.

Table 1.

Race and serum creatinine	eGFR equation
African American, female, Scr ≤ 0.7	$GFR_{CKD\text{-}EPI} = 166 \times (Scr/0.7)^{-0.329} \times (0.993)^{age}$

African American, female, Scr > 0.7	$GFR_{CKD\text{-}EPI} = 166 \times (Scr/0.7)^{-1.209} \times (0.993)^{age}$
African American, male, Scr ≤ 0.9	$GFR_{CKD\text{-}EPI} = 163 \times (Scr/0.9)^{-0.411} \times (0.993)^{age}$
African American, male, Scr > 0.9	$GFR_{CKD\text{-}EPI} = 163 \times (Scr/0.9)^{-1.209} \times (0.993)^{age}$
White or other race, female, Scr ≤ 0.7	$GFR_{CKD\text{-}EPI} = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{age}$
White or other race, female, Scr > 0.7	$GFR_{CKD\text{-}EPI} = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{age}$
White or other race, male, Scr ≤ 0.9	$GFR_{CKD\text{-}EPI} = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{age}$
White or other race, male, Scr > 0.9	$GFR_{CKD\text{-}EPI} = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{age}$

Urinary albumin and creatinine concentrations were measured at the University of Minnesota, Minneapolis, Minnesota, from spot urine samples by the modified kinetic Jaffe method (Synchron AS/Astra Analyzer, Beckman Coulter, Fullerton, California). Current smokers were defined by affirmative answers to the questions "Do you now smoke cigarettes?" and "Have you smoked at least 100 cigarettes in your life?" Hypertension, diabetes and cardiovascular disease (myocardial infarction, heart failure, or stroke) were defined by self-report.

Matching Methodology

Mortality ascertainment is based upon the results from a probabilistic match between NHANES III and National Death Index death certificate records.[7] Linkage of the NHANES III survey participants with the National Death Index provides the opportunity to conduct a vast array of outcome studies designed to investigate the association of a wide variety of health factors with mortality.[1] The NHANES III Linked Mortality File contains mortality follow-up data for NHANES III survey participants (1988-1994) through December 31, 2006. This is the second mortality follow-up of the NHANES III survey participants. The previous NHANES III Linked Mortality File provided mortality data through December 21, 2000.[1] Mortality status is also ascertained primarily through probabilistic record matching with the National Death Index (NDI). National Center for Health Statistics employed a matching methodology for the NHANES III Linked Mortality File that is similar, but not identical, to the standard methodology offered by the National Death Index. To protect confidentiality, the public use file is subjected to data perturbation techniques that introduce statistical noise into the dataset to reduce the risk of identification.[5] Synthetic dates are substituted for actual dates of death for selected

deceased participants, whereas information regarding vital status are not perturbed. A validation study has shown that mortality hazards ratios from the public access, perturbed dataset closely correspond with those from the restricted access, unperturbed dataset[5 8].

Statistical Consideration

Sample size

The 2006 NHANES linked mortality public-use files contains 20,024 eligible participants with 14,664 assumed alive and 5360 assumed deceased, with approximately 2511 deaths due to cardiovascular disease. The 1999-2000 linked mortality public-use files contained 5444 eligible participants with 600 assumed deceased.

Statistical considerations

A type I error rate of <0.05 was considered statistically significant. SAS, v9.1.3 (Cary, NC, USA) and R statistics package, were used for data analysis.

To compare participants included and excluded from our study, NHANES-recommended analytical procedures were followed, and the sampling weights implicit in this complex sample survey design were employed; specifically, we used WTPFEX6, SDPPSU6, and SDPSTRA6 as weight, cluster, and stratum variables, respectively, and used SAS v9.1.3 (Cary, North Carolina). WTPFEX6, SDPPSU6, and SDPSTRA6 represent the variables as they appear in the NHANES data files which are then incorporated into the analytic procedures to account for the complex survey design of NHANES.

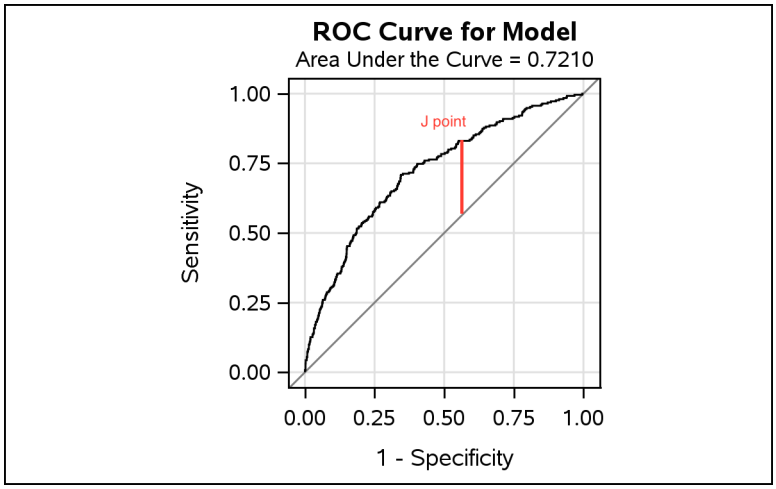
We used classification tree methodology to discern the thresholds of ACR and eGFR for maximal sensitivity and specificity for mortality. Classification tree analysis is a nonparametric decision tree prediction model that has the ability to efficiently segment populations into meaningful subgroups.[9] Classification trees are used to predict membership of cases or objects in the classes of a categorical dependent variable from their measurements on one or more predictor variables.[10 11] The goal of classification trees is to predict or explain responses on a categorical dependent variable. The ability of

classification trees to perform univariate splits, examining the effects of predictors one at a time, has implications for the variety of types of predictors that can be analysed.
To establish diagnostic and prognostic rules and to determine high-risk groups in clinical and epidemiological analysis, researchers often turn to tree-based methods or recursive partitioning. This may be because in clinical medicine, the methods have more affinity with the way clinicians make decisions—they logically demarcate clusters of signs and symptoms.[11]

In our study based on NHANES data, successive subgroups were defined by threshold values showing maximum (Sensitivity/Specificity) for predicting death. This was performed with the exclusion of variables used at parent nodes in subsequent child nodes and without exclusion of variables used at parent nodes in subsequent child nodes, and we repeated this analysis with and without the exclusion of age after the parent nodes.

The metric of Max (Sn/Sp) which is [Max (Sensitivity + Specificity)] at a given cut point in the continuous variable has its origin in receiver operating characteristic methodology, and is equivalent to Youden's J index [Max ((Sensitivity + Specificity) -1)] (See Figure 1).[12] When the threshold value for a continuous diagnostic variable changes the proportions of true positives and false positives also change. These proportions are the sensitivity and 1-specificity. A perfect test would obviously equate to a sensitivity and specificity of 1. The performance of a diagnostic variable can be estimated by calculating the area under the ROC curve (AUROC), which has a maximal value of 1 and is the sum of the areas of the trapeziums. For our classification tree we calculated the Max (Sensitivity/Specificity), which is essentially equivalent to the J point (Youden's index) [12] of the ROC curve, and then used the highest-ranking J point to choose the threshold in the variables of interest for subsequent recursive partitioning. We then wrote a macro loop in SAS to perform the recursive partitioning based on the highest-ranking J point of all variables included in the analysis.

Figure 1. Receiver operating characteristic (ROC) curve showing the J point of the curve.



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Assessment of prediction models performance.

Assessment of the performance of prediction models is based on four main concepts [1] the overall accuracy of the score, the ability of the score to discriminate between those who do and do not experience the event, the correct calibration of the score (Goodness of fit), and the external validity of the score.[1] Many of the existing mortality prediction tools are based on cardiovascular disease and cardiovascular risk factors incorporating traditional risk factors of hypertension, dyslipidaemia and smoking among others. When the current risk prediction models are subjected to scrutiny on these terms their weaknesses become highlighted and the need for improved model development reinforced.

Measures such as the concordance index (or the C-statistic) which is the proportion of all usable pairs of patients in whom the predictions and outcomes are concordant are commonly used to compare model performance.[2] One of its advantages is that it evaluates models and not individual variables. The c statistic is the most widely reported measure of model discrimination for current cardiovascular disease (CVD) risk prediction models.[1 3 4] The C statistic is a function of both the sensitivity and specificity of the model across all of its values, and it represents the ability of the score to discriminate (future) cases from non-cases. [1 3 4] It indicates the probability that a randomly selected patient who develops the disease (a "case") will have a higher risk score than a randomly selected non-case, which is essentially equivalent to the area under the ROC curve.[5] Other measures of model performance include the Net reclassification index (NRI) which can be both categorical and continuous, and the Integrated Discrimination Improvement (IDI), overall accuracy, and the misclassification rate.[3 4]

The majority of existing predictive models are based on logistic regression and time to event models. Performance of these models is mainly based on discrimination and calibration. However while these models may give overall estimates of risk, individual level prediction is more difficult. One of the benefits of classification tree methodology is that it may map out various subgroups delineated by risk, such that the characteristics of individuals within this groups may help to identify risk factors for the outcome of interest.

The general theme of our study of classification tree methodology was to entertain

alternative methods of analysing data to investigate mortality discrimination. Many of the indices of model performance mentioned above yield overall summary measures of the model performance, and identify variables which are important associations with the outcome of interest. However in contrast to classification and regression trees, there is little information on the interplay between variables and the conditional interaction between these variables and the outcome. In particular the interplay of variables within different subgroups of the entire sample is not explored in the same conditional manner as a classification and regression tree. As can be seen in our classification trees, the Max(Sn/Sp) of each variable for mortality was not only investigated in the overall cohort but also within each subgroup created by the recursive partitioning algorithm. In my view this may add additional information to outcome prediction. For example perhaps systolic blood pressure is more important for predicting mortality in older individuals while Body Mass Index may be more important in younger people, yet we cannot discern this readily from standard model performance metrics without sub-setting the data.

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Recursive partitioning methods and machine learning methods

Decision trees are non-parametric tools for data exploration and to assist in decision-making, which can both explain and predict a quantitative variable in the form of a regression tree or a qualitative variable in the form of a classification tree from quantitative and/or qualitative explanatory variables.[1] These trees consist of a sequential algorithm based on classification and regression [2] which constructs individual cases with classes generated using binary rules constructed from explanatory variables so that the individuals from a given class might be as homogenous as possible in terms of the response variable.[1] The trees are composed of leaves and nodes.

In our studies rather than using machine learning methods we created a set of macros in SAS which identified the J point for all-cause mortality for each variable of interest and then ranked the variables in order of magnitude of J and then split the sample into a relevant group based on this threshold and then repeated the methodology from there on downward to the terminal node.

Another interesting way to think of classification and regression trees is to realize their characteristic feature is that the space occupied by all predictor variables is partitioned into a set of rectangular spaces where observations with similar response values are grouped.[3] A potential limitation of tree based methods, and particularly when single trees are used, is the instability of the tree when applied in different cohorts, or on different samples taken from the same cohort. This is a result of the fact that the exact cut point used for the recursive partition as well as the selection of the splitting variable, depend strongly on the particular distribution of observations in the learning sample.[3] To combat this problem, other methods such as the ensemble methods have emerged which average the results of many tree models to generate more externally valid models.[4] Essentially these methods perform the same analysis on smaller segments of the data file and use a voting system from the results of each segment in order to generate the overall results of the analysis. However in our study we are using a specific predefined cut point i.e. the Max (Sensitivity/Specificity) in order to split the sample and subsequent subsamples, and ranked the Max(Sn/Sp) to determine the "most important" variable

which may not be as susceptible to these problems outlined in terms of which variables to choose and which thresholds within these variables are subsequently chosen.

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Chapter 3

Project Title: "The Ability of Urinary Albumin Excretion and Estimated Kidney Function to Predict Short Term All Cause mortality in Community Dwelling Individuals".

What is the ability of urinary albumin to creatinine ratio and eGFR to predict all-cause mortality in community dwelling individuals as part of a risk-triage paradigm?

Ref:

Urinary albumin to creatinine ratio and estimated glomerular filtration rate and mortality risk discrimination in community dwelling individuals.
Sexton DJ, Reule S, Foley RN. In progress

Urinary albumin to creatinine ratio and estimated glomerular filtration rate and mortality risk discrimination in community dwelling individuals.

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Abstract

Introduction

We attempted to identify threshold values of measures of kidney function to maximally discriminate all-cause mortality in community dwelling individuals and to compile a hierarchical rank for these thresholds while also considering classic mortality risk factors.

Methods

We retrospectively identified estimated glomerular filtration rate (eGFR) (CKD-EPI equation), and urinary albumin-creatinine ratio (ACR) thresholds to maximize sensitivity and specificity (Max Sn/Sp) for death in community dwelling NHANES III participants from 1988 to 1994 with mortality follow up through December 31st 2006. We used classification tree methodology to rank thresholds in addition to; age, sex, race, smoking status, systolic and diastolic blood pressure, serum low (LDL) and high density (HDL) lipoproteins, body mass index (BMI), waist-hip ratio (WHR), high sensitivity C-reactive protein, self reported hypertension, diabetes, and cardiovascular disease. We limited our analysis to those aged ≥ 20 years, with both serum creatinine and urinary ACR measurements (n = 6285).

Results

Mean (SD) age was 47.4 (19) years, eGFR 99.9 (24) ml/min/1.73m^2 and median (25-75th centile) ACR 6.1 (3.6-11.9) mg/g. 10.5% were of African American race, 4% were Hispanic ethnicity, and 53.1% were female. Mean follow up was 13.4 years. The overall prognostic discrimination of the optimum eGFR threshold of 94 ml/min/1.73m^2 was (0.77/0.71) and exceeded those for other parameters apart from age, while the optimal threshold for ACR of 8 mg/g (0.61/0.72) exceeded that for all variables apart from age and systolic blood pressure. Max Sn/Sp for current established thresholds defining a diagnosis of chronic kidney disease were (0.01/0.99) for eGFR

of ≤ 30ml/min/1.73m2, (0.2/0.99) for ≤ 60 ml/min/1.73m^2 and (0.2/0.95) for an ACR of 30 mg/g. In a classification tree including dichotomizing variables with exclusion of variables used at parent nodes in subsequent nodes; age 54 years was initially selected, with WHR and ACR appearing in the second round.

Conclusion

Albumin-creatinine ratio and eGFR may be at least as useful for mortality risk triage as most other classic risk factors in community dwelling adults.

Introduction

Chronic kidney disease (CKD) is common in the general population and associated with adverse health outcomes such as myocardial infarction, heart failure, stroke, end stage renal disease and death.[1 2] Although screening for CKD is thought by many to be of upmost importance in the prevention of these adverse health outcomes, the United States Preventive Services Task Force recently concluded that there was insufficient evidence to recommend screening based on current evidence. [3] Much of this current evidence is based on arbitrary thresholds to define chronic kidney disease including an eGFR $\leq$ 60 ml/min/1.73m^2 and or ACR $\geq$ 30 mg/gr on two separate occasions three months apart.[4] These thresholds are based on evidence suggesting the location of inflection points for adverse event risks at these thresholds. [4 5]

Although these established thresholds appear to be useful in risk discrimination, analogous to other clinical parameters proposed as screening tools such as LDL cholesterol and systolic blood pressure,[6 7] other thresholds along the continuum of kidney function may also provide additional useful information. Current thresholds for CKD are likely disregarding this information. [8] It is also possible that thresholds of optimal sensitivity and specificity for kidney function and adverse outcomes differ in different demographic subgroups and could perhaps be more malleable than a strict definition applied to all groups.

We therefore set out to identify thresholds in markers of kidney function in addition to established parameters of public health importance, particularly those advocated in screening community dwelling individuals to simultaneously maximize both sensitivity and specificity for all cause mortality in community dwelling individuals using classification tree methodology.[8]

Methods

Our objectives were to identify thresholds in eGFR and ACR with maximal sensitivity and specificity for death among adult NHANES III participants through December 31st 2006. We calculated max(Sens/Spec) using the formula max(sensitivity proportion + specificity proportion). Mean follow up was 13.4 years. To utilize classification tree methodology in order to

rank thresholds of kidney function while also considering classic mortality risk factors, particularly those proposed in community screening such as LDL cholesterol and systolic blood pressure. NHANES is a multistage, cross sectional, stratified, cluster probability sample of the non-institutionalized population in the US. NHANES III was conducted in two phases, the first from 1988-1991 and the second from 1991-1994 under the recommendation of the National Center for Health Statistics. [9]

Physical examinations and blood and urine collections were performed at mobile examination centers and participants were also interviewed in their homes. For this study, we limited the study population to participants examined in a mobile examination center after 12h fasting, aged ≥ 20 years, with serum creatinine and urinary albumin–creatinine measurements with mortality follow up data available. Serum creatinine was measured by the kinetic alkaline picrate method at the White Sands Research Center (Coulston Foundation) laboratory (Alamogordo, NM, USA) with a Roche/Hitachi 737 analyzer (Roche Diagnostics, Indianapolis, IN, USA). Serum creatinine measurements were aligned to standardized creatinine measured at the Cleveland Clinic Research Laboratory (Cleveland, OH, USA).[10] Standardized creatinine values (in mg/dl) were calculated from actual creatinine, as follows: standardized creatinine = 0.960 × actual creatinine − 0.184.

For GFR estimates, the Chronic Kidney Disease Epidemiology Collaboration formula was used as follows [11] :

African American and female and (creat ≤ 0.7) then eGFR = 166 x $(creat/0.7)^{(-0.329)}$ x $(0.993)^{Age}$;

African American and female and creat > 0.7 then eGFR = 166 x $((creat/0.7)^{(-1.209)}$ x $(0.993)^{Age}$;

African American and Male and (creat ≤ 0.9) then eGFR = 163 x $(creat/0.9)^{(-0.411)}$ x $(0.993)^{Age}$;

African American and Male and creat > 0.9 then eGFR = 163 x $(creat/0.9)^{(-1.209)}$ x $(0.993)^{Age}$;

White or other race and female and (creat ≤ 0.7) then eGFR = 144 x $(creat/0.7)^{(-0.329)}$ x $(0.993)^{Age}$;

White or other race and female and creat > 0.7 then eGFR = 144 x $(creat/0.7)^{(-1.209)}$ x $(0.993)^{Age}$;

White or other race and male and (creat ≤ 0.9) then eGFR = 141 x $(creat/0.9)^{(-0.411)}$ x $(0.993)^{Age}$;

White or other race and male and creat > 0.9 then eGFR = 141 x (creat/0.9)$^{(-1.209)}$ x (0.993)^{Age}.

Results

Characteristics of the study population (NHANES III) are shown in table 1 along with descriptive statistics and correlations with age. There was a preponderance of individuals of white race. Common comorbidities included hypertension (22.5%) and current smoking (25.3%) while established cardiovascular disease (5.0%) and diabetes (3.8%) were less common. Mean (se) age was 44.4 (0.6) years, 53.1% were female, mean BMI was 26.4(0.14) kg/m^2, systolic BP of 121.3(0.5) mmHg, and diastolic of 73.6 (0.24) mmHg. Mean eGFR was 99.8 (0.67) ml/min/1.73m^2 and ACR was 6.1(3.6-11.9) mg/g. Almost all variables displayed in table 1 were associated with age apart form HDL cholesterol. (Table 1)

15.7% (N=1409) of the study population died over a mean of 13.49 years, a rate of 17 per 1000 person years. Sensitivity and specificity values for eGFR and ACR for mortality are shown in Figure 1.

In terms of multi-colinearity, Variance Inflation Factors (VIFs) for age and each of the individual variables of interest included: eGFR 3.6, sex 2.3, race 1.23, BMI 1.4, ACR 1.1, LDL 1.14, HDL 1.22, systolic BP 1.95, diastolic 1.5, WHR2.0, CRP 1.1, serum glucose 1.16 and serum creatinine 3.38.

Correlations with *eGFR included (R2 and P value):* sex 0.10 P<0.001, race 0.21 P<0.001, ACR -0.10 P<0.001, age 0.79 P<0.001, LDL -0.27 P<0.001, HDL 0.01 P=0.047, systolic BP -0.48 P<0.001, diastolic BP -0.13 P<0.001, WHR -0.34 P<0.001, CRP -0.05 P<0.001, serum glucose -0.17 P<0.001, serum creatinine -0.67 P<0.001.

For systolic BP, correlations included (R2 and P value): 0.48 P<0.001 eGFR, -0.17 P<0.001 sex, -0.048 P<0.001 race, BMI 0.17 P<0.001, ACR 0.14 P<0.001, 0.59 P<0.001, LDL 0.23 P<0.001,

HDL -0.01 P=0.38, diastolic 0.51 P<0.001, 0.39 P<0.001 WHR, 0.07 P<0.001 for CRP, 0.23 P<0.001 for serum glucose, 0.28 P<0.001 for serum creatinine.

When looking at the population in its entirety, the highest rank Max(Sens/Sp) was age 54 years with a sensitivity of 80.9% and specificity of 79.1%, and a prevalence of 30% (Table 2). We then used this threshold to divide the population and again examined thresholds of mortality discrimination for all variables of interest with and without the inclusion of age. We continued this recursive partitioning method repeatedly, based on the highest ranking Max(Sens/Sp) within each subgroup to create defined nodes and leaves of the classification tree both with age included and excluded separately. In the overall analysis, eGFR at a threshold of 94 ml/min ranked second after age in the entire cohort with a max sensitivity/specificity of 77%/71% and a prevalence of 37%. This was superior to systolic blood pressure at a threshold of 127 mmHg and urinary albumin: creatinine ratio at a threshold of 8mg/g. These were followed by parameters associated with the metabolic syndrome such as WHR (72%/57%) and serum glucose (68%/59%). In those aged less than 54, age ranked highest amongst variables for Max(Sn/Sp), at a threshold of age 43 years (64%/75%) followed by WHR (67%/62%) and BMI (59% /67%). However with the exclusion of age WHR was ranked highest at the threshold of 92, with an age adjusted OR of 1.9 (1.4,2.5) for mortality P<0.001, followed by BMI of 27 kg/m^2 adjusted OR 1.42(1.11,2.0) P<0.001 and systolic BP of 116 mmHg adjusted OR 1.6 (1.1,2.2) P=0.001. With binary partitioning at age greater than 53 years, with age included, the highest ranked variable was again age at a threshold of 67 years. However with age excluded, ACR at the 12 mg/g threshold was ranked highest in terms of Max(Sn/Sp) (53%/76%) and age adjusted OR of 2.1(1.6,2.4) P<0.001. In the partitioned subgroup defined by aged 54-67 years, age at 75 years was ranked highest (57%/77%), however with age excluded the ACR threshold of 9 mg/g ranked highest (66%/58%) with an age adjusted OR of 1.6 (1.1,2.2) P<0.001. With the partition defined by age <= 54, age at the 43 years threshold was ranked highest (64%/75%), however with age excluded WHR of 92 ranked highest (67%/62%) with an age adjusted OR of 2.6(2,3.5) P<0.001.

The discriminatory ability for mortality (c statistic) at each node of the recursive partitioning tree is reported in table 3, with results presented separately for both age included and excluded. These were compared to the reference group with the lowest mortality risk over follow up. In general the mortality discrimination was higher in models incorporating age. While ranking Max(Sn/Sp) thresholds for mortality, eGFR featured frequently in the models excluding age but not in the trees also considering age. Variables which featured commonly in both trees incorporating and excluding age included smoking, BMI, systolic BP, hypertension and serum glucose. A full description of the mortality associations of the given thresholds of each variable at each node can be seen in the supplementary tables.

Discussion

Our objective was to identify optimal cut points in measures of kidney function that maximally discriminate longer-term mortality, and aimed to establish the hierarchical significance of these measures in addition to traditional risk factors. We were particularly interested in the comparison to parameters advocated for population screening programs such as cholesterol and blood pressure. In terms of kidney function, established thresholds of risk for adverse outcomes are based on studies identifying likely inflection points of increased risk. [4]

However whether these thresholds are ideal for screening populations at risk is a matter of debate, since many arbitrary thresholds inherently tend to maximize either sensitivity or specificity. Perhaps thresholds based on a metric, which maximizes both sensitivity and specificity simultaneously, may be informative, particularly if these thresholds afford equal merit to both false positive and false negative values.[8 12] Since in a population CKD screening scenario, with an ultimate aim of reducing mortality, an individual is as likely to yield a false positive as a false negative for any test, perhaps thresholds for screening which give equal weighting to both results ought to be advocated, particularly since opportunities for repeated testing are likely to be limited. Our study suggests that thresholds in eGFR and ACR other than those currently used to

diagnose CKD, give as close as possible to this equal weighting, and often these thresholds appeared to lie well within the established normal range for these parameters. Therefore perhaps current thresholds are disregarding much of this useful information.

Recursive partitioning methods such as the classification trees presented in this study are a useful tool in predictive modelling since they are associated with few assumptions regarding the data distribution. The application of these tools in population risk stratification studies incorporating kidney function appears to be limited in the existing literature.

Measures of kidney function (eGFR) and urinary albumin excretion (ACR) performed well overall, and could perhaps be used in addition to established public health parameters to aid in mortality discrimination in community dwelling individuals. In classification trees considering age in addition to other parameters ACR appeared in the third round within the subgroup defined by age 54-67 years and in the final node of this tree for those with hypertension aged 44-54. In trees excluding age from the parent nodes, ACR appeared in the second round and eGFR appeared in the third round in three out of four possible nodes. That is eGFR and ACR ranked higher in terms of Max (Sn/Sp) at these points than other health parameters studied.
We looked at mortality over approximately 13 years, considering kidney function in addition to and in the absence of traditional mortality risk factors, and attempted to rank the optimal thresholds for each variable. Overall, age was the most discriminatory variable for all cause mortality. Since age is included in the calculation of eGFR it is also possible that some of the discriminatory ability associated with eGFR was attributable to the contribution by age.

Our findings in this study are largely congruent with our previous study based on shorter mortality follow up.[8]

The performance of clinical parameters of established public health importance for mortality discrimination appears to vary according to the demographic subgroup within which it is applied in a conditional manner. Kidney function may be at least as important as established mortality risk factors in the risk triage of community dwelling individuals.

Table 1. Baseline characteristics of the NHANES III sample.

Characteristic n=6285	**Mean or % (s.e.) Median (25th-75th centile)**	**Correlation with age**	
		r	**P**
Age (years)	44.4 (0.56)	.	.
Women (%)	53.1 (0.9)	0.06	<0.001
Race (%)			
White	77.2 (1.5)	0 (reference)	
African American	10.2 (0.63)	0.06	<0.001
Hispanic	5 (0.49)	0.1	<0.001
Other	7.6 (1.1)	0.03	0.4
Hypertension (%)	22.5 (0.86)	0.32	<0.001
Diabetes (%)	3.8 (0.3)	0.16	<0.001
Cardiovascular disease (%)	5.0 (0.42)	0.31	<0.001
Current smoker (%)	25.3 (0.9)	0.18	<0.001
Systolic blood pressure (mmHg)	121.3 (0.5)	0.49	<0.001
Diastolic blood pressure (mmHg)	73.6 (0.24)	0.12	<0.001
Body mass index (kg/m^2)	26.4 (0.14)	0.05	<0.001
Waist-hip ratio	0.91 (0.002)	0.42	<0.001
LDL cholesterol (mg/dl)	127.4 (0.9)	0.28	<0.001
HDL cholesterol (mg/dl)	50.6 (0.4)	0.03	1
C-reactive protein (mg/l)	0.39 (0.001)	0.09	<0.001
Glucose (mg/dl)	99.1 (0.4)	0.24	<0.001
Creatinine (mg/dl)	1.06 (0.01)	0.3	<0.001
eGFR (ml/min per $1.73m^2$)	99.8 (0.67)	-0.79	<0.001
ACR (mg/g)	6.1 (3.6-11.9)	0.08	<0.001

Figure 1a: Albumin: creatinine ratio (ACR): sensitivity plotted against specificity for a range of ACR values.

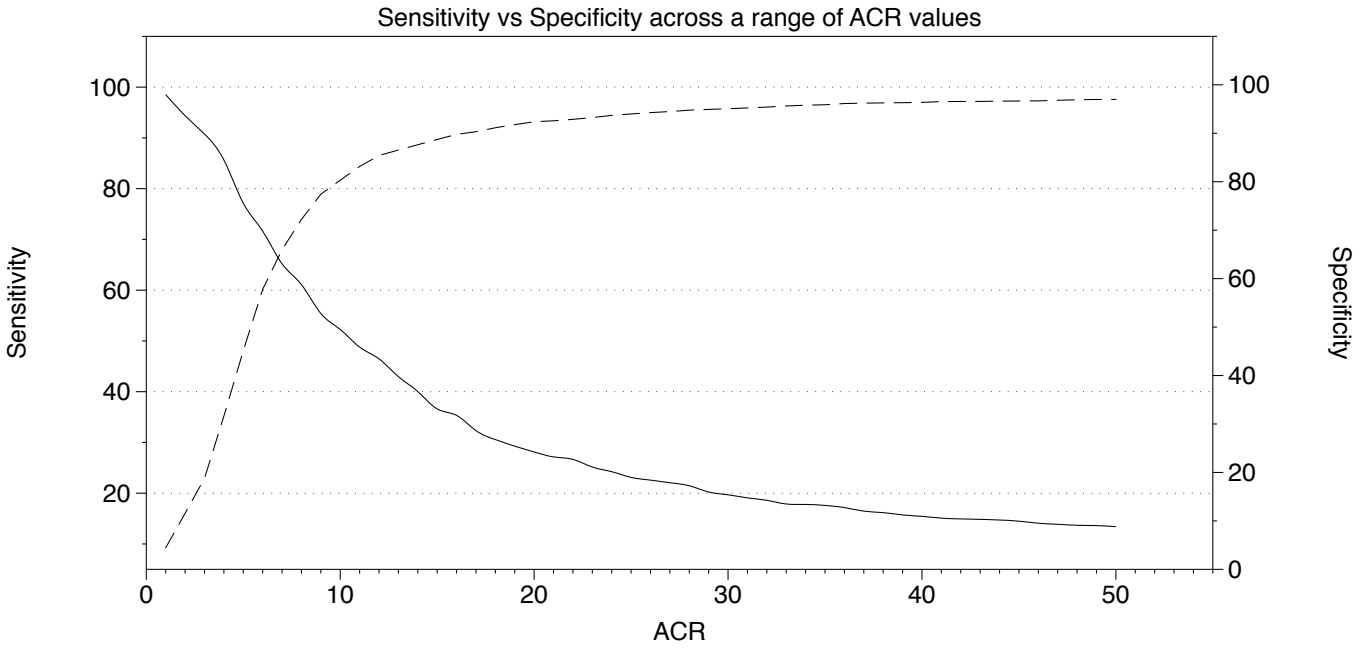

Figure 1b: Estimated Glomerular filtration rate (eGFR): sensitivity plotted against specificity for a range of values for eGFR.

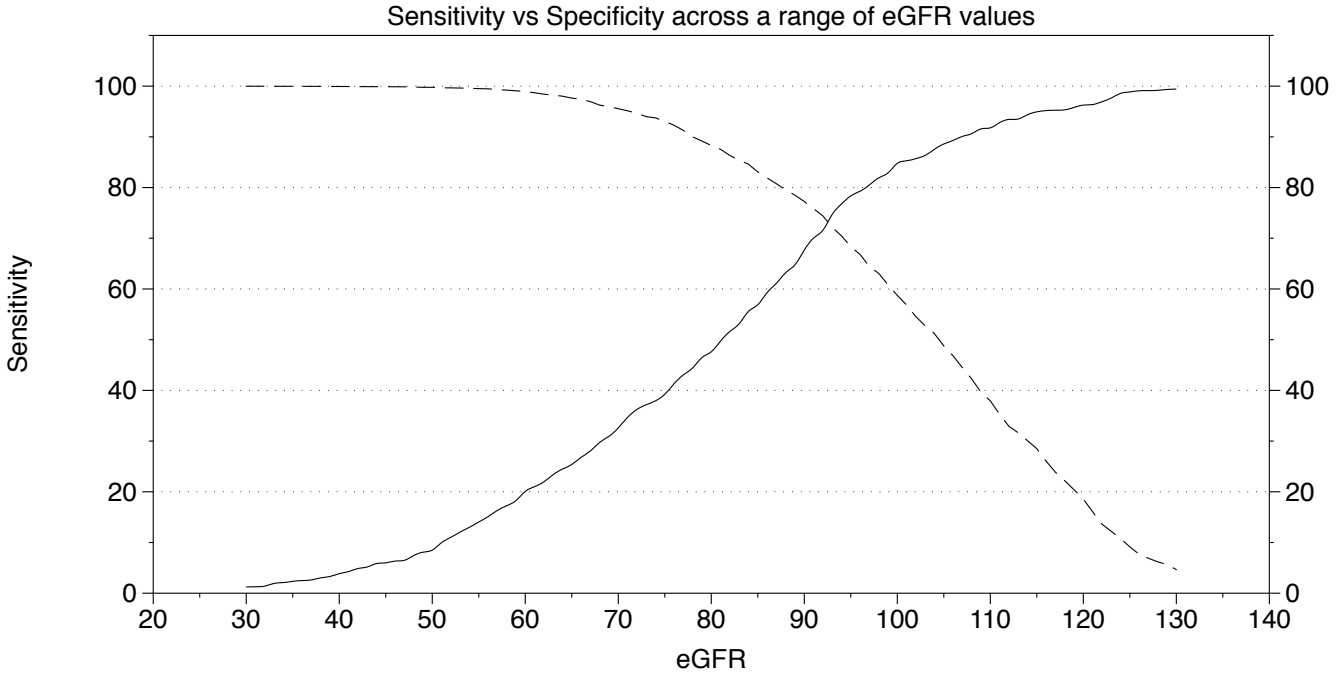

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Table 2. Threshold values for mortality discrimination ranked by Max(Sn/Sp) within each stratum of the NHANES III population.

Sensitivity	Specificity	Threshold	P value	Variable	Prevalence	UOR	P	AOR	P
Overall population									
0.81	0.79	54	<.0001	Age	0.3				
0.77	0.71	94	<.0001	eGFR	0.37			1(0.8,1.2)	0.63
0.65	0.78	127	<.0001	SBP	0.29	2.3(1.8,3.1)	<.0001	1.5(1.3,1.8)	<.0001
0.61	0.72	8	<.0001	ACR	0.33	2.2(1.6,2.9)	<.0001	1.7(1.5,2)	<.0001
0.72	0.57	92	<.0001	WHR	0.48	2.6(2,3.5)	<.0001	1.5(1.3,1.8)	<.0001
0.68	0.59	96	<.0001	Glucose	0.45	2.1(1.6,2.8)	<.0001	1.3(1.1,1.5)	0.002
0.45	0.82	1	<.0001	HTN	0.23			1.3(1.1,1.6)	0.001
0.18	0.97	1	<.0001	CVD	0.05	6.4(3.4,12)	<.0001	2.6(2,3.3)	<.0001
0.42	0.74	111	<.0001	Creat	0.28	1.6(1.2,2.2)	0.002	1.3(1.1,1.6)	0.0003
0.4	0.76	22	<.0001	CRP	0.27	1.8(1.4,2.4)	<.0001	1.4(1.2,1.6)	<.0001
0.38	0.76	149	<.0001	LDL	0.26	1.6(1.1,2.2)	0.006	1(0.8,1.2)	0.85
0.64	0.48	1	<.0001	Smoking	0.25			2.2(1.9,2.6)	<.0001
0.46	0.64	27	<.0001	BMI	0.37	0.7(0.4,1.3)	0.23	1.1(0.9,1.2)	0.52
0.1	0.97	1	<.0001	Diabetes	0.04	2.7(1.6,4.5)	0.0002	1.6(1.2,2.1)	0.001
0.24	0.81	82	0.01	Diastolic	0.2	3.7(2.7,5)	<.0001	1.3(1.1,1.6)	0.001
0.3	0.75	40	0.001	HDL	0.26	1.5(1.2,2)	0.003	1.3(1.1,1.6)	0.0008
0.5	0.54	1	0.14	Sex	0.47	1.7(1.3,2.2)	0.0002	1.7(1.4,2)	<.0001
0.1	0.89	1	0.005	White	0.85	0.7(0.5,0.9)	0.01	0.7(0.6,0.9)	0.0004
0.1	0.89	1	0.23	AA	0.11	1.6(1.2,2.1)	0.002	1.5(1.2,1.8)	<.0001
0.02	0.96	1	0.01	Hispanic	0.04	0.6(0.3,1.4)	0.22	0.6(0.4,1.1)	0.09
Age <= 54 (age excluded)									
Sensitivity	**Specificity**	**Threshold**	**P value**	**label**		**UOR**	**P**	**AOR**	**P**
0.64	0.75	43	0.0001	Age	0.27				
0.67	0.62	92	0.0001	WHR	0.39	2.6(2,3.5)	<.0001	1.9(1.4,2.5)	<.0001
0.59	0.67	27	0.0001	BMI	0.35	0.7(0.4,1.3)	0.23	0.7(0.5,0.9)	0.008
0.67	0.58	116	0.0001	SBP	0.43	2.3(1.8,3.1)	<.0001	1.6(1.2,2.2)	0.001
0.38	0.86	1	0.0001	HTN	0.15	2.7(2,3.7)	<.0001	2(1.5,2.7)	<.0001
0.57	0.64	96	0.0001	Glucose	0.37	2.1(1.6,2.8)	<.0001	1.4(1.1,1.9)	0.01
0.29	0.91	86	0.0001	Diastolic	0.1	3.7(2.7,5)	<.0001	2.8(2,3.8)	<.0001
0.35	0.83	93	0.0009	eGFR	0.18	1.9(1.4,2.7)	<.0001	1(0.7,1.5)	0.9
0.68	0.48	1	0.0006	Smoking	0.26	2.9(2.1,3.9)	<.0001	2.4(1.8,3.2)	<.0001
0.36	0.8	30	0.0006	CRP	0.21	1.8(1.4,2.4)	<.0001	1.5(1.2,2.1)	0.003
0.27	0.86	11	0.0001	ACR	0.15	2.2(1.6,2.9)	<.0001	1.9(1.4,2.6)	<.0001
0.58	0.53	1	0.03	Sex	0.48	1.7(1.3,2.2)	0.0002	1.7(1.3,2.2)	<.0001
0.31	0.8	38	0.01	HDL	0.21	1.5(1.2,2)	0.003	1.6(1.1,2.1)	0.005
0.34	0.76	111	0.06	Creat	0.24	1.6(1.2,2.2)	0.002	1.5(1.1,2)	0.02
0.25	0.84	155	0.06	LDL	0.17	1.6(1.1,2.2)	0.006	1.1(0.8,1.6)	0.47

0.15	0.89	1	0.27	White	0.84	0.7(0.5,0.9)	0.01	0.6(0.5,0.8)	<.0001
0.15	0.89	1	0.02	AA	0.11	1.6(1.2,2.1)	0.001	1.8(1.3,2.3)	<.0001
0.05	0.99	1	0.002	CVD	0.01	6.4(3.4,12)	<.0001	4.1(2.2,7.9)	<.0001
0.05	0.98	1	0.01	Diabetes	0.02	2.7(1.6,4.5)	0.001	2(1.2,3.4)	0.01
0.03	0.95	1	0.57	Hispanic	0.05	0.6(0.3,1.4)	0.22	0.7(0.3,1.5)	0.32

Age > 54 (with age excluded)

Sensitivity	Specificity	Threshold	P value	label		UOR	P	AOR	P
0.72	0.7	67	0.0001	Age	0.88				
0.53	0.76	12	0.0001	ACR	0.2	2.5(2.1,3)	<.0001	2(1.6,2.4)	<.0001
0.59	0.64	135	0.0001	SBP	0.39	2.1(1.7,2.4)	<.0001	1.4(1.1,1.7)	0.001
0.29	0.92	63	0.0001	eGFR	0.84	4.3(3.4,5.4)	<.0001	1.8(1.4,2.3)	<.0001
0.47	0.68	104	0.0001	Glucose	0.73	1.5(1.2,1.7)	<.0001	1.6(1.3,1.9)	<.0001
0.22	0.91	1	0.0001	CVD	0.01	3.1(2.4,4)	<.0001	2.5(1.9,3.3)	<.0001
0.63	0.48	1	0.0008	Smoking	0.25	1.5(1.3,1.8)	<.0001	2.5(2,3.1)	<.0001
0.47	0.63	1	0.003	HTN	0.15	1.3(1.1,1.5)	0.003	1.2(1,1.5)	0.04
0.32	0.78	40	0.0002	CRP	0.26	1.4(1.2,1.7)	<.0001	1.8(1.4,2.2)	<.0001
0.29	0.8	121	0.0001	Creat	0.56	2(1.6,2.4)	<.0001	1.4(1.2,1.8)	0.001
0.6	0.49	95	0.0001	WHR	0.49	1.5(1.2,1.7)	<.0001	1.6(1.3,2)	<.0001
0.32	0.75	41	0.004	HDL	0.3	1.2(1,1.5)	0.02	1.4(1.1,1.7)	0.002
0.48	0.58	1	0.09	Sex	0.48	1.6(1.3,1.8)	<.0001	1.8(1.4,2.1)	<.0001
0.11	0.93	1	0.06	Diabetes	0.02	1.5(1.2,2)	0.002	1.6(1.2,2.1)	0.003
0.26	0.77	165	0.15	LDL	0.15	1(0.8,1.2)	0.8	1.1(0.9,1.4)	0.34
0.08	0.92	1	0.17	White	0.84	1.2(1,1.4)	0.09	0.8(0.6,1)	0.04
0.08	0.92	1	0.47	AA	0.11	0.9(0.7,1.1)	0.35	1.4(1.1,1.7)	0.008
0.04	0.99	105	0.48	Diastolic	0.72	1.5(0.5,4.4)	0.51	3.2(1,10.2)	0.05
0.01	0.99	40	0.77	BMI	0.26	1.4(0.8,2.7)	0.26	1(0.5,1.9)	0.95
0.01	0.96	1	0.01	Hispanic	0.05	0.5(0.3,0.9)	0.02	0.6(0.3,1.2)	0.16

Age > 54 & > 67 (age included)

Sensitivity	Specificity	Threshold	P value	label		UOR	P	AOR	P
0.57	0.77	75	0.0001	Age	0.46	5.7(4.3,7.6)	<.0001		
0.66	0.58	9	0.0001	ACR	0.58	1.6(1.2,2.2)	0.0001	1.6(1.2,2.2)	0.001
0.38	0.82	63	0.0001	eGFR	0.31	1.5(1.1,2.1)	0.01	1.5(1.1,2.1)	0.01
0.48	0.7	103	0.0001	Glucose	0.42	1.6(1.2,2.1)	0.0001	1.6(1.2,2.1)	<.0001
0.41	0.74	44	0.0001	HDL	0.36	1.6(1.2,2.2)	0.0001	1.6(1.2,2.2)	<.0001
0.24	0.89	1	0.0001	CVD	0.2	2.4(1.6,3.6)	<.0001	2.4(1.6,3.6)	<.0001
0.62	0.51	95	0.003	WHR	0.49	1.7(1.3,2.3)	0.0002	1.7(1.3,2.3)	<.0001
0.5	0.62	111	0.001	Creat	0.46	1.5(1.1,2)	0.004	1.5(1.1,2)	0.004
0.48	0.64	1	0.005	Sex	0.44	2.3(1.7,3)	<.0001	2.3(1.7,3)	<.0001
0.46	0.65	143	0.01	SBP	0.43	1.2(0.9,1.7)	0.13	1.2(0.9,1.7)	0.13
0.31	0.79	40	0.02	CRP	0.28	1.6(1.2,2.3)	0.002	1.6(1.2,2.3)	0.002
0.55	0.55	1	0.02	Smoking	0.24	2.2(1.6,2.9)	<.0001	2.2(1.6,2.9)	<.0001
0.12	0.95	1	0.01	Diabetes	0.1	1.9(1.2,3)	0.008	1.9(1.2,3)	0.008

0.41	0.66	149	0.13	LDL	0.39	1.1(0.8,1.4)	0.58	1.1(0.8,1.4)	0.58
0.46	0.59	1	0.2	HTN	0.44	1.1(0.8,1.5)	0.43	1.1(0.8,1.5)	0.43
0.19	0.83	82	0.6	Diastolic	0.18	1.5(1.1,2.2)	0.02	1.5(1.1,2.2)	0.02
0.75	0.27	23	0.61	BMI	0.74	1(0.7,1.4)	1	1(0.7,1.4)	1
0.07	0.94	1	0.67	White	0.92	0.9(0.6,1.2)	0.42	0.9(0.6,1.2)	0.42
0.06	0.94	1	0.7	AA	0.11	1.3(0.9,1.9)	0.14	1.3(0.9,1.9)	0.14
0.01	0.98	1	0.17	Hispanic	0.01	0.3(0.1,0.9)	0.03	0.3(0.1,0.9)	0.03
				Age <= 54 (age included)					
Sensitivity	**Specificity**	**Threshold**	**P value**	**label**		**UOR**	**P**	**AOR**	**P**
0.64	0.75	43	0.0001	Age	0.27	3.8(2.9,5)	<.0001		
0.67	0.062	92	0.0001	WHR	0.39	2.6(2,3.5)	<.0001	2.6(2,3.5)	<.0001
0.59	0.67	27	0.0001	BMI	0.35	0.6(0.4,0.7)	<.0001	0.6(0.4,0.7)	<.0001
0.68	0.58	116	0.0001	SBP	0.43	2.3(1.8,3.1)	<.0001	1.6(1.2,2.2)	0.001
0.38	0.86		0.0001	HTN	0.15	2.7(2,3.7)	<.0001	2(1.5,2.7)	<.0001
0.57	0.64	96	0.0001	Glucose	0.34	2.1(1.6,2.8)	<.0001	1.4(1.1,1.9)	0.01
0.29	0.91	86	0.0001	Diastolic	0.1	3.7(2.7,5)	<.0001	3.7(2.7,5)	<.0001
0.35	0.83	93	0.0009	eGFR	0.18	1.9(1.4,2.7)	<.0001	1(0.7,1.5)	0.9
0.68	0.48		0.0006	Smoking	0.2	2.9(2.1,3.9)	<.0001	2.4(1.8,3.2)	<.0001
0.36	0.8	30	0.0006	CRP	0.21	1.8(1.4,2.4)	<.0001	1.8(1.4,2.4)	<.0001
0.27	0.86	11	0.0001	ACR	0.15	2.2(1.6,2.9)	<.0001	1.9(1.4,2.6)	<.0001
0.58	0.53		0.03	Sex	0.48	1.7(1.3,2.2)	0.0002	1.7(1.3,2.2)	<.0001
0.31	0.8	38	0.01	HDL	0.21	1.7(1.3,2.4)	0.0004	1.7(1.3,2.4)	<.0001
0.34	0.76	111	0.06	Creat	0.24	1.6(1.2,2.2)	0.002	1.6(1.2,2.2)	0.002
0.25	0.84	155	0.06	LDL	0.17	1.6(1.1,2.2)	0.006	1.6(1.1,2.2)	0.006
0.15	0.87		0.02	AA	12.00%	1.6(1.2,2.1)	0.002	1.8(1.3,2.3)	<.0001
0.15	0.89		0.27	White	0.84	0.7(0.5,0.9)	0.01	0.6(0.5,0.8)	<.0001
0.05	0.99		0.002	CVD	0.01	6.4(3.4,12)	<.0001	4.1(2.2,7.9)	<.0001
0.05	0.98		0.01	Diabetes	0.02	2.7(1.6,4.5)	0.0002	2(1.2,3.4)	0.01
0.03	0.96		0.57	Hispanic	0.05	0.6(0.3,1.4)	0.22	0.7(0.3,1.5)	0.32

ACR; albumin to creatinine ratio mg/g, eGFR; estimated glomerular filtration rate ml/min/1.73m2, SBP; systolic blood pressure mmHg, glucose; serum glucose g/dl, BMI; body mass index kg/m^2, HTN; self-reported hypertension, HDL; high density lipoprotein mg/dl, LDL; low density lipoprotein mg/dl, WHR; waist to hip ratio, CRP; C reactive protein, CVD; cardiovascular disease, White; white race; AA; African American race, Creat; serum creatinine, Diastolic; diastolic blood pressure.
National Health and Nutrition Examination Survey-recommended analytical procedures were followed and the sampling wrights implicit in this complex survey sample design were used; WTPFSD6, SDPPSU6, and SDPSTRA6 as weight, cluster, and stratum variables, respectively. Logistic regression was used to calculate odds ratios (ORs) for death.

Table 3 Mortality associations characterized by nodes derived from classification tree analysis.

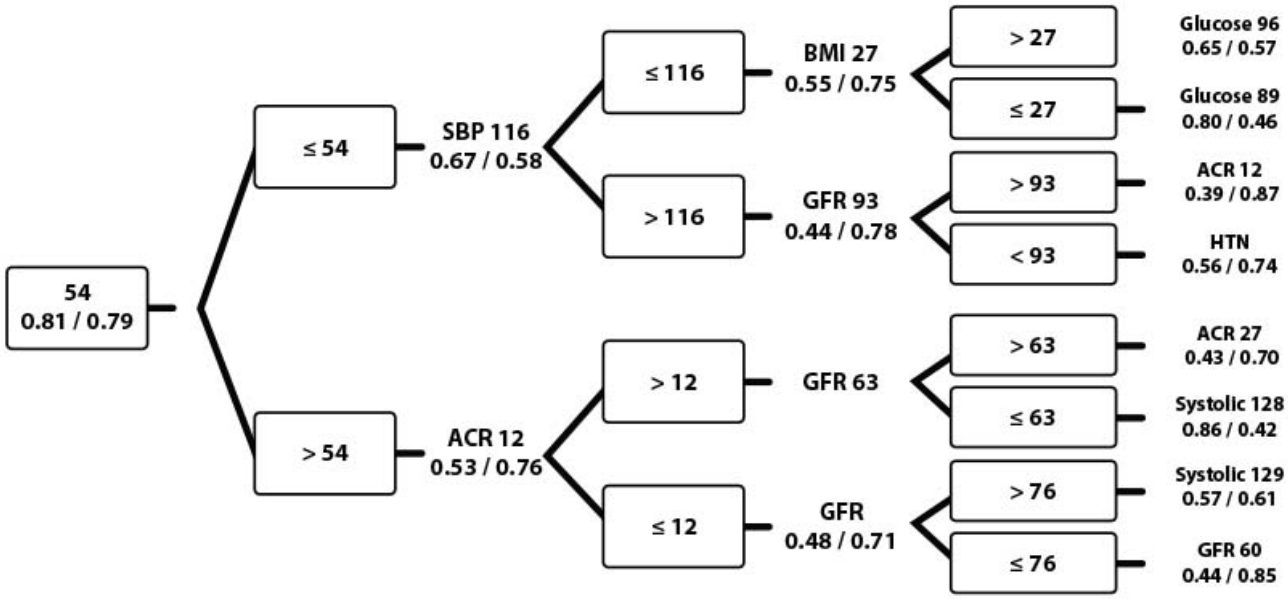
Group	C statistic	UOR 95% CI	Death prevalence	Age	St err
		Age excluded			
Reference group for comparison					
Age ≤ 54 SBP ≤ 116 BMI ≤ 27 Glucose ≤ 89	reference	reference			
Comparator groups					
Age > 54, ACR > 12, eGFR > 63	0.84	80.6(44.6,145.7)	0.57	67.99	0.59
Age > 54, ACR > 12, eGFR > 63, ACR > 27	0.9	86.5(46.5,160.8)	0.66	69.3	0.78
Age > 54, ACR > 12, eGFR > 63, ACR ≤ 27	0.88	76.7(41.8,140.5)	0.51	67	0.62
Age > 54, ACR > 12, eGFR ≤ 63	0.95	322.8(166.1,627.4)	0.84	76.1	0.74
Age > 54, ACR > 12, eGFR ≤ 63, SBP ≤ 128	0.86	172.5(70.9,419.8)	0.64	74	0.25
Age > 54, ACR > 12, eGFR ≤ 63, SBP > 128	0.95	381.9(190.5,765.5)	0.88	77	0.78
Age 54, ACR ≤ 12	0.73	44.3(24.8,79.1)	0.34	66	0.5
Age > 54, ACR ≤ 12, eGFR > 76	0.76	32.7(18.1,58.8)	0.27	63.2	0.33
Age > 54, ACR ≤ 12, eGFR > 76, SBP >129	0.84	44.2(24.2,80.7)	0.33	65.7	0.33
Age > 54, ACR ≤ 12, eGFR > 76, SBP ≤ 129	0.81	22.8(12.4,42)	0.2	61.3	0.33
Age > 54, ACR ≤ 12, GFR ≤ 76	0.86	71.5(39.4,129.8)	0.45	70.2	0.48
Age > 54, ACR ≤ 12, eGFR ≤ 60	0.93	192.2(97,381)	0.72	74.9	0.79
Age > 54, ACR ≤ 12, eGFR ≤ 76	0.86	49.8(27.2,91.4)	0.36	68.7	0.4
Age ≤ 54, SBP > 116	0.61	4.9(2.7,8.9)	0.07	38.2	0.36
Age ≤ 54, SBP > 116, eGFR > 93	0.61	4.2(2.3,7.8)	0.06	36.2	0.4
Age ≤ 54, SBP > 116, eGFR > 93, ACR > 12	0.75	8.7(4.5,16.9)	0.15	39.8	1.13
Age ≤ 54, SBP > 116, eGFR > 93, ACR ≤ 12	0.61	3.2(1.7,6)	0.04	35.6	0.46
Age ≤ 54, SBP > 116, eGFR ≤ 93	0.74	8(4.1,15.5)	0.14	44.5	0.54
Age ≤ 54, SBP > 116, eGFR ≤ 93, hypertension	0.77	13.5(6.5,28)	0.25	46.3	0.53
Age ≤ 54, SBP > 116, eGFR ≤ 93, No hypertension	0.69	5.2(2.4,11)	0.09	43.7	0.72
Age ≤ 54, SBP≤116, BMI > 27	0.62	3(1.5,5.7)	0.06	35.6	0.5
Age ≤ 54, SBP≤116, BMI > 27, Glucose > 96	0.67	4.1(2,8.5)	0.09	38.5	0.88
Age ≤ 54, SBP≤116, BMI > 27, Glucose ≤ 96	0.6	2.2(1,4.7)	0.04	33.4	0.57
Age ≤ 54, SBP≤116, BMI ≤ 27	0.6	2.3(1.1,4.5)	0.03	34.1	0.59
Age ≤ 54, SBP≤116, BMI ≤ 27, Glucose > 89	0.6	2.3(1.1,4.5)	0.03	34.1	0.59
Age ≤ 54, SBP ≤ 116, BMI ≤ 27, Glucose ≤ 89	reference group as above				
		Age included			
	C statistic	**UOR**			
Reference group for comparison					
Age ≤ 43, Glucose ≤ 96, BMI ≤ 27	reference	reference			
Comparator groups					

Age > 54	0.9	135(90,202.4)	0.68	74.9	0.35
Age > 54 - 67	0.79	22.6(15.1,33.9)	0.26	60.8	0.12
Age > 54 – 67, ACR > 12	0.86	38.9(25.1,60.1)	0.43	61.2	0.3
Age > 54 – 67, ACR > 12, CRP > 66	0.83	69.4(40.1,120.2)	0.58	61.6	0.31
Age > 54 – 67, ACR > 12, CRP ≤ 66	0.84	30.5(19.3,48.3)	0.39	61	0.38
Age > 54 – 67, ACR ≤ 12	0.79	16.8(11.1,25.5)	0.19	60.7	0.14
Age > 54 – 67, ACR ≤ 12, smoking	0.83	24.6(16,37.8)	0.26	60.7	0.21
Age > 54 – 67, ACR ≤ 12, no smoking	0.73	8.6(5.2,14.1)	0.1	60.6	0.27
Age > 67	0.89	73.2(48.4,110.7)	0.56	71.3	0.11
Age > 75	0.96	665.6(389.3,1138.2)	0.93	83.6	0.22
Age76 - 79	0.9	156.9(93.6,262.9)	0.67	77.4	0.08
Age76 – 79, HDL ≤ 57	0.88	203.8(113.2,366.8)	78.1	77.4	0.1
Age76 – 79, HDL > 57	0.77	94.4(47.4,188)	0.46	77.3	0.09
Age > 79	0.93	506.2(273.3,937.8)	0.9	90	0.05
Age > 82	0.94	926.5(452.5,1897.2)	0.95	86	0.18
Age ≤ 54	0.96	19.2(16-22.5)	0.05	35.7	0.25
Age 44 ≤ 54	0.69	4.7(2.9,7.6)	0.08	48	0.2
Age 44 ≤ 54, no hypertension	0.69	3.45(2.6-4.6)	0.08	48.3	0.2
Age 44 ≤ 54, no hypertension, WHR < 88	0.58	3.1(1.5,6.5)	0.02	47.7	0.26
Age 44 ≤ 54, no hypertension, WHR ≥ 88	0.69	5.4(3.3,8.8)	0.11	48.6	0.24
Age 44 ≤ 54, hypertension	0.77	13.8(8.5,22.5)	0.24	48.8	0.32
Age 44 ≤ 54, hypertension, HDL ≤ 37	0.71	37.3(18.9,73.5)	0.5	49	0.24
Age 44 ≤ 54, hypertension, HDL > 37	0.72	9.9(5.8,16.8)	0.15	48.7	0.4
Age ≤ 43	0.77	13.8(8.5,22.5)	0.24	48.8	0.32
Age ≤ 43, Glucose > 96	0.64	3(1.9,4.9)	0.05	34	0.34
Age ≤ 43, Glucose > 96, smoking	0.68	4.7(2.9,7.8)	0.07	34.6	0.41
Age ≤ 43, Glucose > 96, no smoking	0.56	1.6(0.9,3)	0.03	33.4	0.52
Age ≤ 43, Glucose ≤ 96		18(14-24)	30.5	0.24	0.02
Age ≤ 43, Glucose ≤ 96, BMI > 27		7.9(5.3-11.6)	32	0.41	0.04
	reference				
Age ≤ 43, Glucose ≤ 96, BMI ≤ 27	0.73	0.1(0.1,0.2)	0.01	0.3	0.28

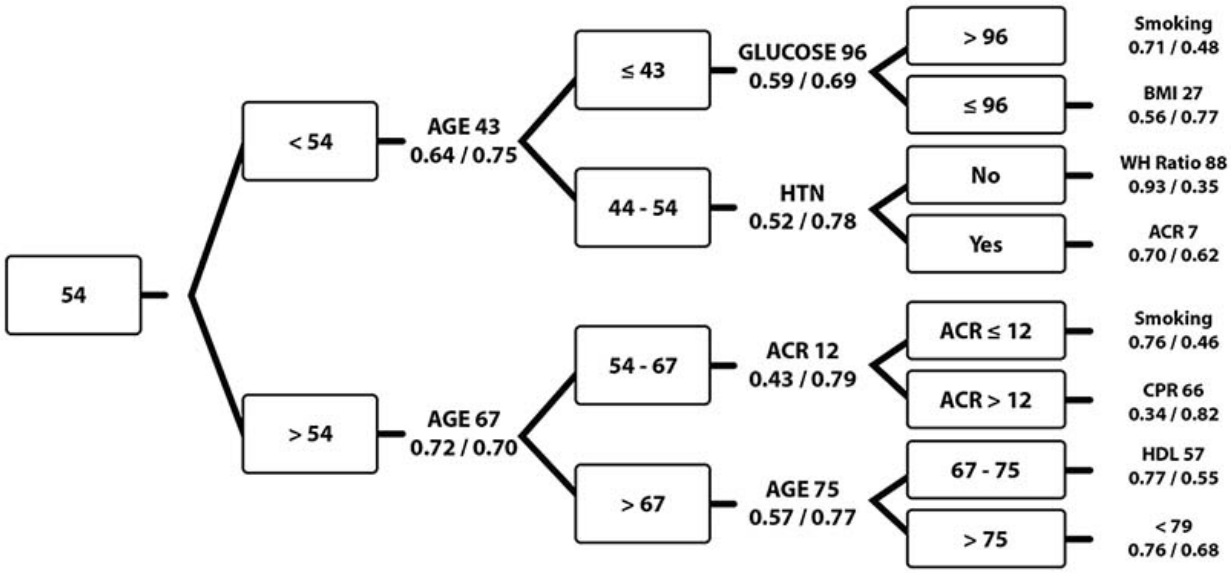
ACR; albumin to creatinine ratio, eGFR; estimated glomerular filtration rate, SBP; systolic blood pressure, glucose; serum glucose, BMI; body mass index, hypertension; self-reported hypertension, HDL; high density lipoprotein, WHR; waist to hip ratio, CRP; C reactive protein. Death prevalence; proportion of subgroup who had died by the end of follow up.

Appendix table 2 A

A Binary recursive partitioning for all-cause mortality discrimination with age excluded after appearing in parent nodes.



B Binary recursive partitioning for all-cause mortality discrimination with age included in subsequent nodes.



Appendix: Supplementary tables.

Age excluded: description of parent nodes and leaves of the recursive partitioning trees.

A. With age excluded.

Sn	Sp	Thresholds	P	Variable	UOR	P	AOR	P
				Overall				
80.88	79.07	53	<.0001	**Age**				
76.77	70.47	94	<.0001	**GFR**			1(0.8,1.2)	0.626
65.02	77.92	127	<.0001	**SBP**	2.3(1.8,3.1)	<0.001	1.5(1.3,1.8)	<0.001
61.09	72.23	8	<.0001	**ACR**	2.2(1.6,2.9)	<0.001	1.7(1.5,2)	<0.001
72.01	57	92	<.0001	**WHR**	2.6(2,3.5)	<0.001	1.5(1.3,1.8)	<0.001
68.41	59.13	96	<.0001	**Gluc**	2.1(1.6,2.8)	<0.001	1.3(1.1,1.5)	0.002
44.81	81.61	1	<.0001	**HTN**		.....	1.3(1.1,1.6)	<0.001
18.29	97.44	1	<.0001	**CVD**	6.4(3.4,12)	<0.001	2.6(2,3.3)	<0.001
41.66	74.05	111	<.0001	**Creat**	1.6(1.2,2.2)	0.002	1.3(1.1,1.6)	<0.001
40.15	75.49	22	<.0001	**CRP**	1.8(1.4,2.4)	<0.001	1.4(1.2,1.6)	<0.001
38.42	76.11	149	<.0001	**LDL**	1.6(1.1,2.2)	0.006	1(0.8,1.2)	0.848
63.71	47.94	1	<.0001	**Smoking**		.....	2.2(1.9,2.6)	<0.001
46.09	64.27	27	<.0001	**BMI**	0.7(0.4,1.3)	0.233	1.1(0.9,1.2)	0.523
9.7	97.25	1	<.0001	**DM**	2.7(1.6,4.5)	<0.001	1.6(1.2,2.1)	0.001
24.34	81.41	82	0.01	**DBP**	3.7(2.7,5)	<0.001	1.3(1.1,1.6)	0.001
30.28	74.66	40	0.009	**HDL**	1.5(1.2,2)	0.003	1.3(1.1,1.6)	0.001
49.92	53.7	1	0.141	**sex**	1.7(1.3,2.2)	<0.001	1.7(1.4,2)	<0.001
9.82	89.32	1	0.005	**White**	0.7(0.5,0.9)	0.011	0.7(0.6,0.9)	<0.001
9.82	89.32	1	0.23	**AA**	1.6(1.2,2.1)	0.002	1.5(1.2,1.8)	<0.001
1.7	95.55	1	0.01	**Hisp**	0.6(0.3,1.4)	0.221	0.6(0.4,1.1)	0.085
				Age ≤ 54				
Sn	**Sp**	**Threshold**	**P**	**Variable**	**UOR**	**P**	**AOR**	**P**
63.57	75.14	43	0.0001	**Age**				
66.72	57.87	116	0.0001	**SBP**	2.3(1.8,3.1)	<0.001	1.6(1.2,2.2)	0.001
37.72	85.77	1	0.0001	**HTN**	2.7(2,3.7)	<0.001	2(1.5,2.7)	<0.001
56.59	64.07	96	0.0001	**Gluc**	2.1(1.6,2.8)	<0.001	1.4(1.1,1.9)	0.013
29.39	90.89	86	0.0001	**DBP**	3.7(2.7,5)	<0.001	2.8(2,3.8)	<0.001
34.88	82.49	93	0.0009	**GFR**	1.9(1.4,2.7)	<0.001	1(0.7,1.5)	0.898
68.12	47.99	1	0.0006	**Smoking**	2.9(2.1,3.9)	<0.001	2.4(1.8,3.2)	<0.001
35.6	79.52	30	0.0006	**CRP**	1.8(1.4,2.4)	<0.001	1.5(1.2,2.1)	0.003
26.92	85.54	11	0.0001	**ACR**	2.2(1.6,2.9)	<0.001	1.9(1.4,2.6)	<0.001
58.38	52.85	1	0.03	**sex**	1.7(1.3,2.2)	<0.001	1.7(1.3,2.2)	<0.001
31.13	79.81	38	0.01	**HDL**	1.5(1.2,2)	0.003	1.6(1.1,2.1)	0.005
33.51	76.31	111	0.06	**Creat**	1.6(1.2,2.2)	0.002	1.5(1.1,2)	0.016
25.37	83.92	155	0.06	**LDL**	1.6(1.1,2.2)	0.006	1.1(0.8,1.6)	0.473

15.33	88.62	1	0.27	**White**	0.7(0.5,0.9)	0.011	0.6(0.5,0.8)	0.001
15.33	88.62	1	0.02	**AA**	1.6(1.2,2.1)	0.002	1.8(1.3,2.3)	<0.001
4.57	98.85	1	0.002	**CVD**	6.4(3.4,12)	<0.001	4.1(2.2,7.9)	<0.001
4.58	98.27	1	0.01	**DM**	2.7(1.6,4.5)	<0.001	2(1.2,3.4)	0.011
3.43	95.48	1	0.57	**Hisp**	0.6(0.3,1.4)	0.221	0.7(0.3,1.5)	0.32

Age ≤ 54, SBP > 116

Sn	**Sp**	**Threshold**	**P**	**Variable**	**UOR**	**P**	**AOR**	**P**
73.91	64.97	43	0.0001	**Age**				
43.81	77.62	93	0.0007	**GFR**	1.9(1.3,2.8)	0.001	1.1(0.7,1.7)	0.591
49.01	77.34	1	0.0001	**HTN**	2.4(1.7,3.4)	<0.001	1.9(1.3,2.7)	<0.001
36.27	87.44	89	0.0001	**DBP**	2.9(2,4.2)	<0.001	2.7(1.8,3.9)	<0.001
30.25	90.47	138	0.0001	**SBP**	3.8(2.6,5.6)	<0.001	2.8(1.9,4.1)	<0.001
34.38	84.68	11	0.0001	**ACR**	2.6(1.8,3.8)	<0.001	2.2(1.6,3.2)	<0.001
72.61	46.26	92	0.01	**WHR**	2.4(1.7,3.5)	<0.001	1.9(1.3,2.8)	0.001
61.26	55.66	27	0.02	**BMI**	0.7(0.5,1)	0.061	0.8(0.6,1.1)	0.228
40.2	75.74	30	0.02	**CRP**	1.8(1.3,2.5)	0.001	1.6(1.1,2.2)	0.014
37.72	75.7	38	0.01	**HDL**	1.8(1.3,2.6)	0.002	1.8(1.2,2.6)	0.003
15.21	96.85	190	0.001	**LDL**	2.2(1.1,4.1)	0.017	1.7(0.9,3.3)	0.106
68.06	43.21	1	0.071	**Smoking**	2.7(1.9,4)	<0.001	2.4(1.6,3.6)	<0.001
71.8	37.06	93	0.12	**Gluc**	1.2(0.9,1.8)	0.271	0.9(0.6,1.4)	0.704
40.89	66.9	111	0.26	**Creat**	1.4(0.9,1.9)	0.096	1.4(1,2.1)	0.051
5.51	98.52	1	0.004	**CVD**	5.3(2.6,11)	<0.001	3.5(1.7,7.4)	0.001
68.44	34.94	1	0.61	**sex**	1.5(1,2.1)	0.037	1.9(1.3,2.8)	0.001
5.11	97.67	1	0.12	**DM**	2.9(1.6,5.3)	<0.001	2.1(1.1,3.8)	0.019
13.73	87.07	1	0.31	**White**	0.9(0.6,1.2)	0.439	0.8(0.5,1.1)	0.116
13.73	87.07	1	0.75	**AA**	1.2(0.9,1.8)	0.219	1.4(1,2.1)	0.044
0.8	95.53	1	0.003	**Hisp**	0.5(0.2,1.7)	0.291	0.6(0.2,1.8)	0.324

Age ≤ 54 SBP > 116, eGFR > 93

Sn	Sp	Threshold	P	**Variable**	**UOR**	**P**	**AOR**	**P**
68.43	70.89	42	0.0001	**Age**				
38.94	86.72	12	0.0001	**ACR**	2.7(1.8,4.1)	<0.001	2.2(1.4,3.4)	<0.001
30.74	93.52	140	0.0001	**SBP**	4.6(2.9,7.2)	<0.001	3.2(2,5.2)	<0.001
80.9	42.05	1	0.003	**Smoking**	3.6(2.2,5.8)	<0.001	3.2(2,5.2)	<0.001
43.32	78.45	1	0.001	**HTN**	2.2(1.4,3.3)	<0.001	1.7(1.1,2.6)	0.013
82.04	38.36	93	0.001	**Gluc**	1.5(0.9,2.3)	0.099	1.1(0.7,1.7)	0.776
33.12	86.75	88	0.001	**DBP**	2.8(1.8,4.3)	<0.001	2.5(1.6,3.8)	<0.001
62.21	57.32	27	0.02	**BMI**	0.8(0.5,1.2)	0.301	0.9(0.6,1.4)	0.777
88.49	29.82	88	0.02	**WHR**	3.7(2,7)	<0.001	2.9(1.5,5.6)	0.001
36.34	76.04	30	0.05	**CRP**	1.7(1.1,2.5)	0.016	1.4(0.9,2.1)	0.106
68.12	42.97	49	0.12	**HDL**	1.2(0.8,1.8)	0.407	1.3(0.8,1.9)	0.249
72.24	36.09	115	0.19	**GFR**	1.2(0.8,1.9)	0.298	0.6(0.4,1)	0.042
70.3	36.25	114	0.38	**LDL**	1.1(0.7,1.6)	0.734	0.8(0.5,1.2)	0.296

20.5	85.88	1	0.60	**White**	0.7(0.5,1)	0.08	0.6(0.4,1)	0.035
20.5	85.88	1	0.16	**AA**	1.5(1,2.3)	0.039	1.7(1.1,2.5)	0.016
69.59	34.32	1	0.58	**sex**	1.6(1.1,2.5)	0.028	2.2(1.4,3.5)	<0.001
5.43	97.99	1	0.07	**DM**	2.6(1.3,5.3)	0.007	1.8(0.9,3.8)	0.104
99.58	2.65	72	0.009	**Creat**	2(0.5,8.5)	0.329	2.1(0.5,9)	0.301
3.18	98.38	1	0.37	**CVD**	2.8(0.9,8.3)	0.067	1.8(0.6,5.6)	0.282
1.43	94.86	1	0.03	**Hisp**	0.7(0.2,2.2)	0.52	0.7(0.2,2.3)	0.539

Age ≤ 54 SBP > 116, eGFR ≤ 93

Sn	Sp	Threshold	P	**Variable**	**UOR**	**P**	**AOR**	**P**
56.3	73.48	1	0.008	**HTN**	2.6(1.3,5.1)	0.005	2.5(1.3,4.9)	0.009
81.89	47.02	46	0.009	**Age**		.....		<0.001
53.8	73.42	86	0.01	**DM**	2.8(1.4,5.5)	0.003	3.2(1.6,6.5)	0.001
31.21	89.15	80	0.02	**CRP**	2.4(1,5.5)	0.039	2.1(0.9,4.9)	0.085
24.55	95.39	190	0.0004	**LDL**	3.2(1.2,8.2)	0.017	2.9(1.1,7.5)	0.031
25.51	91.49	74	0.024	**GFR**	1.8(0.7,4.5)	0.193	1.8(0.7,4.4)	0.221
33.93	82.66	101	0.08	**WHR**	2.7(1.3,5.7)	0.006	2.5(1.2,5.3)	0.012
72.93	41.9	124	0.23	**SBP**	1.8(0.9,3.9)	0.114	1.6(0.8,3.5)	0.202
44.91	69.54	38	0.14	**HDL**	3.1(1.6,6.1)	0.001	3.1(1.6,6.2)	0.001
36.71	76.95	32	0.13	**BMI**	0.4(0.2,0.9)	0.017	0.4(0.2,0.8)	0.013
28.58	84.14	10	0.18	**ACR**	2.8(1.4,5.6)	0.003	2.8(1.4,5.7)	0.003
79.26	31.74	111	0.21	**Creat**	1.3(0.6,2.8)	0.465	1.6(0.7,3.4)	0.242
8.49	99.01	1	0.0007	**CVD**	9.9(3.2,31.3)	<0.001	8.1(2.5,26.1)	<0.001
66.98	37.08	1	0.70	**sex**	1.1(0.6,2.3)	0.693	1.3(0.6,2.6)	0.461
4.68	96.57	1	0.76	**DM**	4(1.3,12.2)	0.017	3.1(1,9.9)	0.055
96.43	4.08	81	0.73	**Gluc**	1.6(0.2,12.4)	0.677	1.1(0.1,9.3)	0.907
51.59	47.21	1	0.91	**Smoking**	1.5(0.8,3)	0.242	1.3(0.6,2.6)	0.487
5.05	91.19	1	0.07	**White**	1.5(0.7,3.2)	0.307	1.2(0.6,2.7)	0.59

Age ≤ 54, SBP ≤ 116

Sn	**Sp**	**Threshold**	**P**	**Variable**	**UOR**	**P**	**AOR**	**P**
55.41	74.92	27	0.0001	**BMI**	0.6(0.4,0.9)	0.012	0.6(0.4,1)	0.046
55.21	73.63	92	0.0001	**WHR**	2(1.2,3.1)	0.004	1.5(1,2.5)	0.073
53.61	74.72	96	0.0001	**Gluc**	2.5(1.6,4)	<0.001	1.9(1.2,3.1)	0.007
42.84	82.55	43	0.0007	**Age**		.....		<0.001
68.24	51.48	1	0.01	**Smoking**	2.7(1.6,4.3)	<0.001	2.3(1.4,3.7)	0.001
73.11	41.63	68	0.02	**DBP**	1.6(1,2.6)	0.059	1.3(0.8,2.1)	0.367
48.78	63.76	110	0.09	**SBP**	1.2(0.8,1.9)	0.413	1.1(0.7,1.7)	0.807
19.45	90.34	50	0.009	**CRP**	1.5(0.8,2.6)	0.207	1.4(0.8,2.6)	0.221
18.52	89.74	1	0.003	**White**	0.5(0.3,0.8)	0.006	0.5(0.3,0.8)	0.002
18.52	89.74	1	0.003	**AA**	2(1.3,3.2)	0.002	2.2(1.4,3.6)	0.001
15.1	91.91	1	0.26	**HTN**	1.6(0.8,3.3)	0.194	1.4(0.7,2.9)	0.329
73.12	33.53	4	0.33	**ACR**	1.4(0.8,2.3)	0.192	1.4(0.9,2.3)	0.174
59.13	47.51	111	0.44	**GFR**	1.2(0.7,1.8)	0.52	0.6(0.3,1)	0.065

33.41	71.06	42	0.58	**HDL**	1.3(0.8,2.1)	0.249	1.2(0.7,2)	0.449
8.69	95.45	1	0.22	**Hisp**	0.8(0.2,2.5)	0.666	0.8(0.3,2.7)	0.755
38.19	65.89	1	0.63	**sex**	1.2(0.7,1.9)	0.471	1.1(0.7,1.8)	0.636
11.57	91.73	168	0.54	**LDL**	1.2(0.6,2.7)	0.599	0.9(0.4,2.1)	0.855
3.53	98.7	1	0.11	**DM**	1.5(0.4,4.8)	0.525	1.4(0.4,4.5)	0.605
18.7	83.16	111	0.77	**Creat**	1.4(0.8,2.5)	0.22	1.2(0.7,2.2)	0.452
2.69	99.08	1	0.20	**CVD**	6.1(1.7,21.7)	0.005	5.3(1.4,19.2)	0.012

Age ≤ 54, SBP ≤ 116, BMI ≤ 27

Sn	**Sp**	**Threshold**	**P**	**Variable**	**UOR**	**P**	**AOR**	**P**
79.81	46.36	89	0.002	**Gluc**	2.3(1.1,4.5)	0.019	1.9(1,3.9)	0.063
55.03	69.53	38	0.004	**Age**		.....		<0.001
32.3	88.58	94	0.003	**WHR**	2.5(1.2,5.1)	0.01	2(0.9,4.1)	0.072
28.69	91.61	1	0.0001	**White**	0.4(0.2,0.7)	0.004	0.4(0.2,0.7)	0.001
28.69	91.61	1	0.0001	**AA**	2.9(1.6,5.5)	0.001	3.3(1.7,6.2)	<0.001
66.48	52.94	1	0.08	**Smoking**	2.6(1.4,5)	0.004	2.3(1.2,4.4)	0.016
48.79	67.56	1	0.15	**sex**	2.1(1.1,3.9)	0.018	2(1.1,3.8)	0.026
54.81	52.81	69	0.43	**DBP**	1.7(0.9,3.2)	0.106	1.4(0.8,2.7)	0.268
23.94	83.39	111	0.27	**Creat**	2.1(1.1,4.2)	0.032	1.9(0.9,3.8)	0.072
14.35	90.85	36	0.36	**HDL**	2.1(0.9,4.9)	0.076	2(0.9,4.7)	0.1
11.54	93.31	1	0.49	**HTN**	1.2(0.4,4.1)	0.717	1.1(0.3,3.8)	0.821
5.54	99.26	1	0.02	**CVD**	10.4(2.1,51.7)	0.004	10.2(2,52)	0.005
66.31	38.45	102	0.66	**LDL**	1.2(0.6,2.2)	0.63	1(0.5,1.9)	0.918
10.81	93.59	50	0.43	**CRP**	1.5(0.6,3.9)	0.415	1.5(0.6,4)	0.391
83.87	18.97	100	0.78	**SBP**	1.7(0.6,4.3)	0.287	1.5(0.6,3.9)	0.41
69.79	32.18	4	0.81	**ACR**	1(0.5,1.9)	0.967	1(0.5,2)	0.902
1.47	99.2	1	0.59	**DM**	1.5(0.2,11.6)	0.683	1.3(0.2,10.1)	0.791
5.72	94.89	1	0.91	**Hisp**	0.5(0.1,3.4)	0.443	0.5(0.1,3.6)	0.474
2.52	94.22	84	0.26	**GFR**	1.2(0.3,5.1)	0.795	0.7(0.2,3)	0.611
3.05	91.19	26	0.09	**BMI**	1.5(0.5,4.8)	0.521	1.7(0.5,5.5)	0.395

Age ≤ 54, SBP ≤ 116, BMI > 27

Sn	**Sp**	**Threshold**	**P**		**UOR**	**P**	**AOR**	**P**
43.76	87.5	45	**0.0002**	**age**		.....		
65.04	56.93	96	**0.03**	**Gluc**	1.8(0.9,3.6)	0.075	1.4(0.7,2.8)	0.359
84.64	36.15	88	**0.05**	**WHR**	1.6(0.8,3.5)	0.212	1.4(0.7,3.1)	0.377
48.27	69.26	6	**0.09**	**ACR**	1.5(0.8,2.9)	0.245	1.6(0.8,3.1)	0.205
65.47	51.56	110	**0.13**	**SBP**	1.3(0.7,2.5)	0.448	1(0.5,2.1)	0.897
69.65	47.12	1	**0.08**	**Smoking**	2.7(1.3,5.5)	0.006	2.4(1.2,4.9)	0.016
87.38	25.17	68	**0.073**	**DBP**	1.5(0.7,3.2)	0.324	1.1(0.5,2.4)	0.836
59.38	51.98	109	**0.28**	**GFR**	1.4(0.7,2.8)	0.287	0.8(0.4,1.7)	0.528
11.07	97.1	1	**0.03**	**Hisp**	1.2(0.3,5.3)	0.787	1.3(0.3,5.9)	0.696
26.41	80.62	50	**0.38**	**CRP**	1.1(0.5,2.3)	0.821	1.1(0.5,2.4)	0.751
17.97	87.73	1	**0.54**	**HTN**	1.6(0.7,4)	0.302	1.5(0.6,3.7)	0.423

16.23	87.08	170	**0.74**	**LDL**	1.6(0.6,4.3)	0.331	1.4(0.5,3.7)	0.555
5.19	97.22	1	**0.39**	**DM**	1.1(0.3,5)	0.858	1.2(0.3,5.3)	0.803
12.16	89.55	30	**0.86**	**HDL**	0.9(0.2,3.8)	0.857	0.8(0.2,3.7)	0.825
6.5	94.05	121	**0.92**	**Creat**	1.1(0.2,4.7)	0.916	0.9(0.2,4)	0.908
0.4	98.55	1	**0.26**	**CVD**	2.8(0.3,23.6)	0.338	2.1(0.2,18.7)	0.49
37.44	61.36	31	**0.93**	**BMI**	1.2(0.6,2.3)	0.684	1.2(0.6,2.3)	0.68
10.33	84.17	1	**0.75**	**White**	0.8(0.4,1.6)	0.524	0.7(0.4,1.4)	0.35
10.33	84.17	1	**0.15**	**AA**	1.2(0.6,2.4)	0.592	1.3(0.7,2.7)	0.429
29.67	60.92	1	**0.47**	**Sex**	0.5(0.2,1.3)	0.174	0.5(0.2,1.2)	0.102

Age > 54

Sn	**Sp**	**Threshold**	**P**	**Variable**	**UOR**	**P**	**AOR**	**P**
72.2	69.52	67	0.0001	**Age**		.....		
52.7	76.15	12	0.0001	**ACR**	2.5(2.1,3)	<0.001	2(1.6,2.4)	<0.001
58.59	63.57	135	0.0001	**SBP**	2.1(1.7,2.4)	<0.001	1.4(1.1,1.7)	0.001
29.28	91.55	63	0.0001	**GFR**	4.3(3.4,5.4)	<0.001	1.8(1.4,2.3)	<0.001
46.85	68.41	104	0.0001	**Gluc**	1.5(1.2,1.7)	<0.001	1.6(1.3,1.9)	<0.001
22.22	91.16	1	0.0001	**CVD**	3.1(2.4,4)	<0.001	2.5(1.9,3.3)	<0.001
62.45	47.68	1	0.0008	**Smoking**	1.5(1.3,1.8)	<0.001	2.5(2,3.1)	<0.001
46.84	63.09	1	0.003	**HTN**	1.3(1.1,1.5)	0.003	1.2(1,1.5)	0.037
32.09	77.83	40	0.0002	**CRP**	1.4(1.2,1.7)	<0.001	1.8(1.4,2.2)	<0.001
28.76	80.18	121	0.0001	**Creat**	2(1.6,2.4)	<0.001	1.4(1.2,1.8)	0.001
60.19	48.75	95	0.0001	**WHR**	1.5(1.2,1.7)	<0.001	1.6(1.3,2)	<0.001
32.27	75.3	41	0.004	**HDL**	1.2(1,1.5)	0.02	1.4(1.1,1.7)	0.002
47.5	57.48	1	0.09	**sex**	1.6(1.3,1.8)	<0.001	1.8(1.4,2.1)	<0.001
11.17	92.71	1	0.06	**DM**	1.5(1.2,2)	0.002	1.6(1.2,2.1)	0.003
25.6	77.33	165	0.15	**LDL**	1(0.8,1.2)	0.809	1.1(0.9,1.4)	0.345
8.24	92.43	1	0.17	**White**	1.2(1,1.4)	0.095	0.8(0.6,1)	0.037
8.24	92.43	1	0.47	**AA**	0.9(0.7,1.1)	0.353	1.4(1.1,1.7)	0.009
0.39	99.79	105	0.48	**DM**	1.5(0.5,4.4)	0.515	3.2(1,10.2)	0.048
1.43	98.75	40	0.77	**BMI**	1.4(0.8,2.7)	0.265	1(0.5,1.9)	0.952
1.2	95.84	1	0.01	**Hisp**	0.5(0.3,0.9)	0.024	0.6(0.3,1.2)	0.16

Age > 54, ACR ≤ 12

Sn	**Sp**	**Threshold**	**P**	**Variable**	**UOR**	**P**	**AOR**	**P**
67.4	72.19	67	0.0001	**Age**				
47.67	71.17	76	0.0001	**GFR**	2.2(1.8,2.7)	<0.001	0.9(0.7,1.2)	0.359
58.27	60.26	130	0.0001	**SBP**	2.1(1.7,2.6)	<0.001	1.3(1,1.7)	0.025
48.3	68.81	103	0.0001	**Gluc**	1.5(1.2,1.9)	<0.001	1.8(1.4,2.3)	<0.001
66.86	46	101	0.0001	**Creat**	1.9(1.5,2.3)	<0.001	1.5(1.1,1.9)	0.003
19.8	91.61	1	0.0001	**CVD**	3.2(2.3,4.5)	<0.001	2.6(1.8,3.8)	<0.001
57.52	53.84	96	0.002	**WHR**	1.6(1.3,2)	<0.001	1.7(1.3,2.1)	<0.001
62.23	48.94	1	0.003	**Smoking**	1.5(1.2,1.9)	<0.001	2.3(1.8,3)	<0.001
40.31	70.61	1	0.009	**HTN**	1.4(1.1,1.8)	0.003	1.3(1,1.6)	0.066

54.22	55.23	6	0.01	**ACR**	1.5(1.2,1.9)	<0.001	1.2(1,1.6)	0.079
29.33	79.5	40	0.002	**CRP**	1.4(1.1,1.7)	0.011	1.6(1.2,2.1)	0.002
51.93	56.15	1	0.02	**sex**	1.7(1.4,2.1)	<0.001	2(1.5,2.5)	<0.001
37.88	68.15	43	0.04	**HDL**	1.2(1,1.5)	0.105	1.4(1.1,1.8)	0.013
23.71	81.41	171	0.03	**LDL**	1.2(0.9,1.5)	0.277	1.4(1,1.9)	0.03
8.91	93.9	1	0.87	**White**	0.9(0.7,1.2)	0.619	0.7(0.5,0.9)	0.009
8.91	93.9	1	0.02	**AA**	1.1(0.9,1.5)	0.349	1.6(1.1,2.1)	0.005
7.8	94.01	35	0.26	**BMI**	1.1(0.7,1.6)	0.797	0.7(0.4,1)	0.077
6.69	94.55	1	0.44	**DM**	1.1(0.8,1.7)	0.532	1(0.6,1.6)	0.893
0.15	99.97	103	0.13	**DM**	5.2(0.6,46.8)	0.14	12.3(1.2,122.5)	0.032
1.37	95.43	1	0.03	**Hisp**	0.6(0.3,1.4)	0.259	0.8(0.3,2.1)	0.726

Age > 54, ACR ≤ 12, eGFR > 76

Sn	**Sp**	**Threshold**	**P**	**Variable**	**UOR**	**P**	**AOR**	**P**
52.65	80.19	67	0.0001	**Age**		.....		
56.81	60.8	129	0.0002	**SBP**	1.9(1.5,2.6)	<0.001	1.3(0.9,1.8)	0.103
46.58	70.09	103	0.002	**Gluc**	1.7(1.3,2.3)	<0.001	1.9(1.4,2.6)	<0.001
67.5	49.08	1	0.0001	**Smoking**	1.9(1.4,2.5)	<0.001	2.6(1.9,3.7)	<0.001
83.37	29.65	95	0.02	**GFR**	2.1(1.5,3)	<0.001	0.9(0.6,1.3)	0.456
55.14	55.39	96	0.03	**WHR**	1.7(1.3,2.3)	<0.001	1.8(1.3,2.4)	0.001
54.24	55.36	1	0.04	**sex**	1.9(1.4,2.6)	<0.001	2.1(1.5,2.9)	<0.001
33.21	76.36	8	0.03	**ACR**	1.4(1,1.9)	0.025	1.1(0.8,1.6)	0.456
29.56	78.32	40	0.04	**CRP**	1.3(1,1.8)	0.078	1.5(1.1,2.1)	0.022
85.15	22.15	62	0.03	**HDL**	1.4(1,2)	0.051	1.6(1.1,2.4)	0.017
43.04	62.46	101	0.18	**Creat**	1.5(1.1,2)	0.006	1.8(1.3,2.4)	<0.001
13.39	91.99	1	0.11	**CVD**	3.3(2.1,5.1)	<0.001	2.7(1.6,4.4)	<0.001
33.22	72.05	1	0.24	**HTN**	1.1(0.8,1.4)	0.662	1(0.7,1.5)	0.789
29.27	74.88	29	0.32	**BMI**	1.2(0.9,1.7)	0.191	1.1(0.8,1.5)	0.62
8.67	94.18	1	0.68	**White**	0.9(0.7,1.3)	0.73	0.8(0.5,1.1)	0.145
8.67	94.18	1	0.05	**AA**	1.1(0.8,1.6)	0.473	1.4(0.9,2)	0.128
20.83	81.78	171	0.44	**LDL**	1.1(0.8,1.6)	0.502	1.4(0.9,2.1)	0.095
5.04	95.65	1	0.69	**DM**	1.2(0.7,2)	0.573	1.1(0.6,2)	0.817
0.1	99.95	103	0.51	**DM**	3.5(0.3,39.1)	0.303	8.6(0.7,101.5)	0.087
1.77	94.12	1	0.08	**Hisp**	0.7(0.3,1.7)	0.38	1(0.4,2.8)	0.995

Age > 54, ACR ≤ 12, eGFR ≤ 76

Sn	**Sp**	**Threshold**	**P**	**Variable**	**UOR**	**P**	**AOR**	**P**
54.35	89.77	75	0.0001	**Age**		.....		
43.78	84.5	60	0.0001	**GFR**	3.8(2.5,5.8)	<0.001	2.2(1.4,3.4)	0.001
45.03	75.13	43	0.0001	**HDL**	1.7(1.2,2.4)	0.007	2(1.3,3)	0.002
26.83	90.66	1	0.0001	**CVD**	2.7(1.6,4.4)	<0.001	2.5(1.4,4.5)	0.002
53.36	63.93	102	0.0001	**Gluc**	1.4(1,2)	0.062	1.8(1.2,2.6)	0.008
74.5	42.46	126	0.0007	**SBP**	2.4(1.6,3.5)	<0.001	1.6(1,2.4)	0.037
78.17	37.45	4	0.01	**ACR**	1.8(1.3,2.7)	0.001	1.7(1.1,2.7)	0.014

48.1	67.07	1	0.006	**HTN**	1.6(1.1,2.3)	0.007	1.8(1.2,2.7)	0.006
50.12	62.94	147	0.006	**LDL**	1.3(0.9,1.8)	0.15	1.5(1,2.3)	0.038
74.05	37.98	111	0.02	**Creat**	1.7(1.1,2.5)	0.01	2(1.3,3.2)	0.004
66.19	45.78	94	0.05	**WHR**	1.7(1.2,2.5)	0.003	1.6(1,2.4)	0.032
23.79	88.14	66	0.0004	**CRP**	1.6(1,2.6)	0.038	2(1.2,3.4)	0.012
49.4	58.09	1	0.22	**sex**	1.7(1.2,2.4)	0.003	1.7(1.1,2.6)	0.009
56.44	48.59	1	0.46	**Smoking**	1.3(0.9,1.8)	0.151	1.9(1.2,2.8)	0.003
18.86	84	31	0.46	**BMI**	1.1(0.7,1.7)	0.8	0.6(0.3,1)	0.049
9.17	93.21	1	0.40	**White**	0.9(0.6,1.4)	0.681	0.5(0.3,0.9)	0.013
9.17	93.21	1	0.25	**AA**	1.1(0.7,1.7)	0.603	2.1(1.2,3.4)	0.006
28.17	72.81	80	0.79	**DM**	1.1(0.7,1.6)	0.78	1.5(1,2.4)	0.08
8.52	91.83	1	0.91	**DM**	1(0.5,2)	0.921	1(0.5,2)	0.953
0.93	98.65	1	0.54	**Hisp**	0.8(0.2,3.2)	0.756	0.5(0.1,2.9)	0.436

Age > 54, ACR > 12

Sn	Sp	Threshold	P	**Variable**	**UOR**	**P**	**AOR**	**P**
62.81	76.41	71	0.0001	**Age**				
33.7	88.56	63	0.0001	**GFR**	4(2.8,5.8)	<0.001	2.1(1.4,3.2)	<0.001
68.26	47.55	135	0.002	**SBP**	1.5(1.1,2)	0.008	1.1(0.8,1.5)	0.542
47.38	66.76	27	0.005	**ACR**	1.3(1,1.7)	0.086	1.1(0.8,1.6)	0.401
24.38	89.71	1	0.0001	**CVD**	2.4(1.7,3.5)	<0.001	2.1(1.4,3.2)	<0.001
31.3	82.06	121	0.0001	**Creat**	2.1(1.5,2.8)	<0.001	1.6(1.1,2.3)	0.006
33.43	78.56	41	0.03	**HDL**	1.3(1,1.8)	0.065	1.6(1.1,2.2)	0.011
34.64	73.22	100	0.19	**WHR**	1.3(1,1.7)	0.076	1.6(1.1,2.2)	0.005
56.75	50.83	101	0.12	**Gluc**	1.1(0.8,1.5)	0.422	1.2(0.9,1.6)	0.295
34.57	72.47	40	0.12	**CRP**	1.3(1,1.7)	0.103	1.7(1.2,2.4)	0.001
62.66	43.67	1	0.26	**Smoking**	1.5(1.2,2)	0.003	2.8(2,3.9)	<0.001
43.53	61.74	1	0.22	**sex**	1.6(1.2,2.1)	0.001	1.7(1.2,2.3)	0.001
23.89	78.83	165	0.45	**LDL**	0.9(0.7,1.2)	0.549	1(0.7,1.4)	0.964
15.17	86.86	1	0.66	**DM**	1.4(0.9,2)	0.096	1.7(1.1,2.5)	0.017
0.7	99.13	105	0.82	**DM**	0.6(0.2,2)	0.429	1.4(0.4,4.9)	0.575
1.84	96.65	40	0.23	**BMI**	3.1(1.3,7.2)	0.009	2.2(0.9,5.4)	0.087
1.05	97.13	1	0.17	**Hisp**	0.3(0.1,1)	0.042	0.3(0.1,1.1)	0.071
7.64	87.74	1	0.01	**White**	1.8(1.3,2.4)	0.001	1.1(0.8,1.6)	0.625
7.64	87.74	1	0.03	**AA**	0.6(0.4,0.9)	0.004	1(0.7,1.5)	0.918
52.7	39.07	1	0.07	**HTN**	1.3(1,1.8)	0.065	0.9(0.6,1.2)	0.371

Age > 54, ACR > 12, eGFR > 63

Sn	Sp	Threshold	P	**Variable**	**UOR**	**P**	**AOR**	**P**
69.5	64.13	67	0.0001	**Age**		.....		
43.44	70.39	27	0.010	**ACR**	1.1(0.8,1.5)	0.454	1(0.7,1.4)	0.942
64	49.3	136	0.02	**SBP**	1.5(1.1,2)	0.02	1.1(0.8,1.6)	0.578
32.34	80.03	41	0.05	**HDL**	1.2(0.9,1.8)	0.217	1.5(1,2.2)	0.046
59.82	52.49	86	0.006	**GFR**	1.9(1.4,2.6)	<0.001	1(0.7,1.4)	0.829

19.33	91.22	1	0.002	**CVD**	1.8(1.2,2.8)	0.008	1.8(1.1,2.8)	0.02
50.17	59.46	104	0.08	**Gluc**	1.2(0.8,1.6)	0.35	1.3(0.9,1.8)	0.185
64.16	44.63	1	0.18	**Smoking**	1.6(1.2,2.2)	0.002	3.1(2.1,4.5)	<0.001
79.68	27.65	90	0.15	**WHR**	1.5(1,2.3)	0.042	1.6(1,2.5)	0.041
25.26	80.17	56	0.31	**CRP**	1.3(0.9,1.8)	0.207	1.7(1.1,2.5)	0.011
42.22	62.56	1	0.44	**sex**	1.4(1,2)	0.025	1.6(1.1,2.2)	0.011
16.46	85.53	1	0.70	**DM**	1.4(0.9,2.1)	0.149	1.5(0.9,2.3)	0.086
98.49	2.9	72	0.38	**Creat**	2.9(1.1,7.8)	0.036	2.4(0.8,7.1)	0.1
23.72	77.17	163	0.86	**LDL**	0.8(0.6,1.2)	0.319	0.9(0.6,1.4)	0.716
2.56	97.52	40	0.96	**BMI**	2.3(0.9,5.9)	0.097	1.9(0.7,5.1)	0.215
0.4	99.61	105	0.97	**DM**	0.9(0.2,3.3)	0.862	1.6(0.4,6.4)	0.488
0.8	96.91	1	0.19	**Hisp**	0.2(0,0.8)	0.028	0.2(0,0.9)	0.04
7.93	88.2	1	0.03	**White**	1.5(1.1,2.2)	0.023	1.1(0.7,1.6)	0.761
7.93	88.2	1	0.07	**AA**	0.7(0.5,1.1)	0.11	1.1(0.7,1.6)	0.7
48.59	41.58	1	0.07	**HTN**	0.7(0.5,0.9)	0.03	0.8(0.6,1.2)	0.344

Age > 54, ACR > 12, eGFR ≤ 63

Sn	**Sp**	**Threshold**	**P**	**Variable**	**UOR**	**P**	**AOR**	**P**
58.22	80.14	77	0.0001	**Age**		.....		
85.59	42.08	128	0.0001	**SBP**	2.2(1,4.9)	0.048	2.2(0.9,5)	0.074
32.39	91.94	46	0.001	**GFR**	1.9(0.8,4.4)	0.117	2.1(0.9,5.1)	0.086
42.25	76.05	98	0.02	**WHR**	2(1,4.1)	0.061	2.8(1.3,6)	0.011
44.15	72.81	150	0.05	**LDL**	1.2(0.6,2.3)	0.691	1.3(0.6,2.7)	0.504
21.05	92.3	171	0.03	**Creat**	1.3(0.5,3.1)	0.578	2.3(0.9,6)	0.1
34.32	77.99	1	0.23	**CVD**	3.3(1.3,8.2)	0.01	3(1.2,7.7)	0.021
74.65	37.47	96	0.15	**Gluc**	2.1(1.1,4.3)	0.033	2.1(1,4.4)	0.053
45.78	65.33	40	0.26	**ACR**	1(0.5,2)	0.997	1.4(0.7,3)	0.367
12.62	97.2	1	0.02	**DM**	3.5(0.8,15.3)	0.093	4.9(1.1,22.2)	0.041
26.66	81.34	38	0.45	**HDL**	2.5(0.9,6.7)	0.067	2.5(0.9,6.8)	0.078
20.98	85.56	82	0.40	**DM**	1.6(0.7,3.9)	0.262	3.3(1.2,9.1)	0.02
51.15	54.02	22	0.63	**CRP**	1.2(0.6,2.4)	0.602	1.3(0.6,2.7)	0.445
46.11	55.44	1	0.87	**sex**	1.4(0.7,2.8)	0.308	1.8(0.9,3.7)	0.125
1.54	98.79	1	0.84	**Hisp**	0.7(0.1,6.5)	0.759	0.9(0.1,9.2)	0.932
81.14	18.62	22	0.98	**BMI**	1.1(0.4,2.6)	0.857	0.8(0.3,2.1)	0.679
59.7	36.3	1	0.66	**Smoking**	1.2(0.6,2.5)	0.537	1.8(0.9,3.8)	0.124
7.06	84.16	1	0.10	**White**	3.1(1.5,6.4)	0.003	1.7(0.7,3.9)	0.206
7.06	84.16	1	0.04	**AA**	0.3(0.1,0.7)	0.003	0.6(0.2,1.3)	0.205
60.77	19.64	1	0.06	**HTN**	0.4(0.2,0.8)	0.02	0.5(0.2,1.1)	0.081

The analytical procedures recommended by the National Health and Nutrition Examination Survey were followed and the sampling weights designed for complex sample survey design were used; WTPFSD6, SDPPSU6, and SDPSTRA6 as weight, cluster and stratum variables. HDL; high density lipoprotein, LDL; low density lipoprotein, Gluc; glucose, Creat; creatinine, ACR; albumin to creatinine ratio, BMI; body mass index, CRP; C-reactive protein, CVD; cardiovascular disease, AA; African American, Hisp; Hispanic race, WHR; waist to hip ratio, SBP; systolic blood pressure, DBP; diastolic blood pressure

B. Age included:
Detailed description of the nodes and leaves of the recursive partitioning trees with age included.

Age included								
Age > 67 (after age > 54)								
Sn	Sp	Threshold	P	Variable	UOR	P	AOR	P
57.4	77	75	0.0001	Age	5.7(4.3,7.6)	<0.001		
66.21	57.68	9	0.0001	ACR	1.6(1.2,2.2)	0.001	1.6(1.2,2.2)	0.001
37.76	82.05	63	0.0001	GFR	1.5(1.1,2.1)	0.01	1.5(1.1,2.1)	0.012
47.88	69.77	103	0.0001	Gluc	1.6(1.2,2.1)	0.001	1.6(1.2,2.1)	0.001
41.34	73.63	44	0.0001	HDL	1.6(1.2,2.2)	0.001	1.6(1.2,2.2)	0.001
24.06	89.03	1	0.0001	CVD	2.4(1.6,3.6)	<0.001	2.4(1.6,3.6)	<0.001
61.57	51.11	95	0.003	WHR	1.7(1.3,2.3)	<0.001	1.7(1.3,2.3)	<0.001
50.01	61.56	111	0.001	Creat	1.5(1.1,2)	0.004	1.5(1.1,2)	0.004
47.47	63.98	1	0.005	Sex	2.3(1.7,3)	<0.001	2.3(1.7,3)	<0.001
46.25	65	143	0.01	SBP	1.2(0.9,1.7)	0.13	1.2(0.9,1.7)	0.13
31.12	79.17	40	0.02	CRP	1.6(1.2,2.3)	0.002	1.6(1.2,2.3)	0.002
55.18	54.65	1	0.02	Smoking	2.2(1.6,2.9)	<0.001	2.2(1.6,2.9)	<0.001
11.77	94.76	1	0.009	DM	1.9(1.2,3)	0.008	1.9(1.2,3)	0.008
40.9	65.55	149	0.13	LDL	1.1(0.8,1.4)	0.58	1.1(0.8,1.4)	0.58
46.02	58.9	1	0.20	HTN	1.1(0.8,1.5)	0.43	1.1(0.8,1.5)	0.43
18.84	83.25	82	0.56	DBP	1.5(1.1,2.2)	0.02	1.5(1.1,2.2)	0.02
74.59	27.14	23	0.61	BMI	1(0.7,1.4)	0.999	1(0.7,1.4)	0.99
6.62	93.82	1	0.67	White	0.9(0.6,1.2)	0.42	0.9(0.6,1.2)	0.42
6.62	93.82	1	0.70	AA	1.3(0.9,1.9)	0.14	1.3(0.9,1.9)	0.14
0.87	98.03	1	0.17	Hisp	0.3(0.1,0.9)	0.03	0.3(0.1,0.9)	0.03
Age > 75								
Sn	Sp	Threshold	P	Variable	UOR	P	AOR	P
76.44	67.75	79	0.0001	Age	4.1(2.5,6.9)	<0.001		
69.84	51.31	57	0.02	HDL	1.5(0.9,2.6)	0.099	1.5(0.9,2.6)	0.11
46.81	72.27	16	0.002	ACR	1.5(0.9,2.5)	0.122	1.3(0.8,2.3)	0.29
40.25	78.2	1	0.006	Sex	2.9(1.7,5.1)	<0.001	2.9(1.6,5)	<0.001
34.82	82.48	56	0.03	GFR	1.8(1,3.2)	0.07	1.4(0.8,2.6)	0.27
28.21	88.62	131	0.03	Creat	2.5(1.3,4.9)	0.007	2.3(1.2,4.6)	0.02
65.02	51.06	137	0.10	SBP	1.2(0.7,1.9)	0.57	1(0.6,1.8)	0.87
31.74	84.07	33	0.009	CRP	1.6(0.9,2.9)	0.12	1.5(0.8,2.8)	0.16
88.55	27.14	88	0.01	WHR	1.5(0.7,2.9)	0.287	1.6(0.8,3.4)	0.18
40.5	74.34	1	0.05	Smoking	1.7(1,2.9)	0.05	1.8(1,3.1)	0.04
58.43	56.1	99	0.03	Gluc	1.6(1,2.6)	0.08	1.6(1,2.7)	0.06
72.24	39.37	23	0.16	BMI	0.9(0.5,1.6)	0.84	0.9(0.5,1.6)	0.69
11.75	98.11	1	0.0001	DM	1.8(0.7,4.5)	0.25	2.4(0.9,6.3)	0.08
16.08	93.45	82	0.04	DBP	2(0.9,4.6)	0.09	2.1(0.9,4.9)	0.07

45.82	61.4	1	0.46	HTN	1(0.6,1.7)	0.94	1.1(0.7,1.8)	0.74
80.78	23.54	109	0.53	LDL	0.8(0.4,1.5)	0.53	0.9(0.5,1.7)	0.76
6	95.45	1	0.70	White	1.3(0.7,2.6)	0.39	1.1(0.5,2.2)	0.84
6	95.45	1	0.41	AA	0.8(0.4,1.7)	0.60	1.1(0.5,2.3)	0.85
24.86	76.46	1	0.85	CVD	1.4(0.8,2.6)	0.28	1.4(0.7,2.6)	0.31
1.31	98.25	1	0.69	Hisp	0.4(0.1,2.1)	0.29	0.4(0.1,2)	0.24
Age 76-79 (after > 54)								
Sn	Sp	Threshold	P	Variable	UOR	P	AOR	P
77.02	55.3	57	0.0001	HDL	2.2(1,4.5)	0.04	2.1(1,4.4)	0.046
50.3	78.65	1	0.001	Smoking	2(1,4.3)	0.06	2(0.9,4.2)	0.08
93.89	34.77	87	0.0001	WHR	4.1(1.5,11.4)	0.007	4.1(1.5,11.4)	0.008
70.82	53.78	98	0.001	Gluc	2.1(1,4.3)	0.04	2.1(1,4.3)	0.04
37.43	85.4	28	0.009	BMI	0.5(0.2,1.1)	0.08	0.5(0.2,1.1)	0.09
45.37	77.11	1	0.007	Sex	2.9(1.3,6.3)	0.007	2.9(1.3,6.2)	0.008
25.54	96.16	32	0.01	ACR	2.8(0.9,8.6)	0.07	2.8(0.9,8.6)	0.07
20.29	98.24	1	0.0003	DM	2.4(0.8,7.4)	0.12	2.4(0.8,7.3)	0.13
26.47	91.59	79	0.004	Age	1.7(0.7,4.1)	0.27		<0.001
21.78	95.96	60	0.002	CRP	5.9(1.3,25.7)	0.02	5.7(1.3,25.3)	0.02
51.13	66.48	1	0.17	HTN	1.4(0.7,2.9)	0.32	1.5(0.7,3)	0.31
26.36	86.91	56	0.18	GFR	1.7(0.6,4.4)	0.29	1.6(0.6,4.3)	0.32
23.64	88.86	131	0.16	Creat	2.8(1,7.7)	0.047	2.8(1,7.6)	0.049
12.51	98.99	163	0.007	SBP	7.6(1,58.4)	0.05	7.7(1,59.3)	0.05
57.14	54.27	135	0.23	LDL	0.9(0.5,1.9)	0.86	0.9(0.5,1.9)	0.83
8.43	95.68	1	0.35	White	0.7(0.3,1.9)	0.54	0.7(0.3,1.9)	0.52
8.43	95.68	1	0.11	AA	1.5(0.6,4)	0.39	1.5(0.6,4.1)	0.38
41.51	62.26	74	0.69	DBP	1.5(0.7,3)	0.28	1.6(0.8,3.2)	0.23
1.24	98.42	1	0.81	Hisp	0.3(0,5.3)	0.43	0.3(0,5.2)	0.42
22.93	76.31	1	0.93	CVD	1.3(0.5,3.1)	0.55	1.3(0.5,3.1)	0.55
Age > 79 (after > 54)								
Sn	Sp	Threshold	P	Variable	UOR	P	AOR	P
68.39	55.13	82	0.006	Age	2.1(1,4.6)	0.049		
55.33	65.22	111	0.04	Creat	2.4(1.1,5.2)	0.03	2.4(1.1,5.1)	0.03
73.12	47.19	135	0.05	SBP	1.3(0.6,2.7)	0.57	1.2(0.5,2.6)	0.7
62.24	56.93	69	0.06	GFR	1.8(0.9,3.9)	0.11	1.8(0.8,3.8)	0.14
37.83	81.32	1	0.01	Sex	2.8(1.2,6.5)	0.02	2.9(1.2,6.7)	0.01
85.95	29.99	69	0.04	HDL	2.6(1.1,6.2)	0.03	2.5(1.1,6)	0.04
47.53	66.46	17	0.11	ACR	1.2(0.6,2.7)	0.6	1.2(0.5,2.6)	0.68
35.92	76.74	30	0.15	CRP	1.4(0.6,3.3)	0.39	1.5(0.6,3.5)	0.35
52.69	56.63	95	0.27	WHR	1.5(0.7,3.3)	0.27	1.6(0.7,3.3)	0.26
21.8	86.9	80	0.13	DBP	1.4(0.5,3.9)	0.48	1.4(0.5,3.8)	0.51
7.72	97.74	1	0.17	DM	2.7(0.4,20.5)	0.34	3(0.4,22.8)	0.29
7.7	96.67	31	0.38	BMI	0.5(0.1,3.5)	0.45	0.4(0.1,3.2)	0.41

98.9	5.41	82	0.08	Gluc	9.2(1.5,57.4)	0.02	11.6(1.8,75.9)	0.01
25.77	76.9	1	0.71	CVD	1.4(0.5,3.5)	0.50	1.4(0.6,3.6)	0.48
86.52	16.07	100	0.59	LDL	1.1(0.4,3)	0.83	1.2(0.4,3.2)	0.74
4.85	94.78	1	0.72	White	1.8(0.6,5)	0.26	1.8(0.6,4.9)	0.28
4.85	94.78	1	0.90	AA	0.6(0.2,1.9)	0.41	0.6(0.2,1.9)	0.43
1.34	97.74	1	0.61	Hisp	0.4(0,3.3)	0.38	0.4(0,3.4)	0.38
35.88	62.12	1	0.84	Smoking	1.6(0.7,3.6)	0.26	1.7(0.7,3.8)	0.21
43.31	46.95	1	0.28	HTN	0.7(0.3,1.5)	0.38	0.7(0.3,1.6)	0.44
Age 54-67								
Sn	Sp	Threshold	P	Variable	UOR	P	AOR	P
43.12	79.07	12	0.0001	ACR	2.3(1.7,3)	<0.001	2.2(1.6,2.9)	<0.001
76.99	44.24	1	0.0001	Smoking	2.8(2.1,3.7)	<0.001	2.8(2.1,3.8)	<0.001
55.27	62.99	130	0.0001	SBP	1.9(1.5,2.5)	<0.001	1.7(1.3,2.3)	<0.001
55.27	62.99	130	0.0001	WHR	1.3(0.8,1.9)	0.26	1.1(1.1,1.1)	<0.001
49.1	67.88	104	0.0001	Gluc	1.7(1.3,2.3)	<0.001	1.7(1.3,2.2)	<0.001
68.62	45.82	59	0.002	Age	2.1(1.5,2.8)	<0.001		
34.48	76.91	40	0.006	CRP	1.8(1.4,2.4)	<0.001	1.9(1.4,2.5)	<0.001
46.53	64.83	1	0.03	HTN	1.5(1.1,1.9)	0.005	1.4(1,1.8)	0.02
18.17	92.33	1	0.0004	CVD	2.7(1.8,4)	<0.001	2.5(1.7,3.8)	<0.001
34.45	74	41	0.06	HDL	1.3(1,1.7)	0.06	1.3(1,1.8)	0.06
8.87	98.2	60	0.0001	GFR	5.1(2.8,9.3)	<0.001	4.3(2.3,8)	<0.001
49.28	56.07	1	0.24	Sex	1.5(1.2,2)	0.001	1.5(1.2,2)	0.002
26.43	77.63	31	0.33	BMI	0.9(0.7,1.2)	0.55	0.9(0.7,1.2)	0.49
11.9	91.65	1	0.84	White	0.8(0.6,1)	0.09	0.8(0.6,1)	0.07
11.9	91.65	1	0.03	AA	1.4(1,1.8)	0.04	1.4(1,1.9)	0.04
38.17	64.71	155	0.48	LDL	1(0.8,1.3)	0.92	1(0.7,1.3)	0.86
54.59	48.2	101	0.50	Creat	1.5(1.1,1.9)	0.004	1.4(1.1,1.9)	0.01
9.64	92.34	1	0.45	DM	1.5(1,2.2)	0.06	1.4(0.9,2.2)	0.09
26.87	74.66	83	0.74	DBP	1.1(0.8,1.5)	0.43	1.2(0.9,1.5)	0.35
1.23	94.72	1	0.05	Hisp	0.7(0.3,1.7)	0.44	0.8(0.3,1.9)	0.59
Age 54-67, ACR > 12								
Sn	Sp	Threshold	P	Variable	UOR	P	AOR	P
33.82	82.16	66	0.02	CRP	2.3(1.5,3.8)	<0.001	2.3(1.4,3.7)	0.001
22.35	91.87	1	0.007	CVD	2(1.1,3.7)	0.02	2(1.1,3.7)	0.02
78.36	35.83	58	0.02	Age	2.1(1.2,3.6)	0.007		
77.98	36	1	0.07	Smoking	2.9(1.8,4.8)	<0.001	2.9(1.8,4.8)	<0.001
46.47	64.34	24	0.16	ACR	1.2(0.8,1.9)	0.35	1.2(0.8,1.9)	0.34
13.35	97.33	60	0.0003	GFR	4.6(2,10.6)	<0.001	4.2(1.8,9.8)	0.001
36.74	73.43	41	0.19	HDL	1.1(0.7,1.7)	0.83	1.1(0.7,1.7)	0.76
36.36	72.22	100	0.20	WHR	1.7(1.1,2.7)	0.02	1.6(1,2.6)	0.03
53.09	53.92	134	0.38	SBP	1.3(0.8,2.1)	0.21	1.2(0.8,1.9)	0.46
76.48	30.46	121	0.42	LDL	0.8(0.5,1.2)	0.28	0.7(0.4,1.2)	0.17

20.42	85.11	121	0.17	Creat	**1.5(0.9,2.4)**	0.13	1.4(0.8,2.4)	0.192
50	55.3	104	0.47	Gluc	1(0.6,1.5)	1	1(0.6,1.5)	0.92
2.5	98.69	105	0.49	DBP	1.5(0.4,5.2)	0.55	1.5(0.4,5.3)	0.55
14.13	85.81	1	0.77	White	0.9(0.6,1.5)	0.81	1(0.6,1.5)	0.84
14.13	85.81	1	0.99	AA	1.1(0.7,1.7)	0.79	1.1(0.7,1.7)	0.79
15.01	84.01	1	0.86	DM	1.4(0.8,2.5)	0.24	1.3(0.8,2.4)	0.31
2.44	96.28	1	0.66	Hisp	1(0.3,3.5)	0.96	0.9(0.2,3.3)	0.89
40.8	57.64	1	0.86	Sex	1.3(0.8,2)	0.22	1.3(0.8,2)	0.28
1.06	96.51	40	0.04	BMI	1.6(0.5,5.2)	0.46	1.5(0.5,5.2)	0.49
55.75	35.09	1	0.23	HTN	0.8(0.5,1.3)	0.43	0.8(0.5,1.3)	0.44

Age 54-67, ACR ≤ 12

Sn	Sp	Threshold	P	Variable	UOR	P	AOR	P
76.24	46.42		0.0001	Smoking	2.6(1.8,3.8)	<0.001	2.6(1.8,3.8)	<0.001
54.87	66.25	102	0.0007	Gluc	2.1(1.5,2.9)	<0.001	2(1.4,2.9)	<0.001
48.9	68.84	130	0.003	SBP	1.9(1.3,2.6)	<0.001	1.7(1.2,2.3)	0.005
68.45	46.14	59	0.003	Age	2(1.4,3)	<0.001		
74.9	37.74	92	0.03	WHR	2.1(1.4,3.1)	0.001	2(1.3,3)	0.001
39.55	72.7		0.02	HTN	1.6(1.1,2.3)	0.008	1.5(1,2.1)	0.03
63.39	48.82	101	0.01	Creat	2(1.4,2.8)	<0.001	1.9(1.3,2.7)	0.001
55.72	55.66		0.01	Sex	1.8(1.3,2.6)	0.001	1.8(1.3,2.6)	0.001
36.22	72.25	29	0.10	BMI	1(0.7,1.4)	0.87	1(0.7,1.4)	0.87
29.04	79.05	40	0.11	CRP	1.4(0.9,2)	0.09	1.4(1,2.1)	0.06
36.08	71.79	42	0.09	HDL	1.6(1.1,2.2)	0.01	1.6(1.1,2.3)	0.01
15.01	92.46		0.04	CVD	2.9(1.7,4.9)	<0.001	2.6(1.5,4.4)	<0.001
76.62	30.14	95	0.31	GFR	1.4(0.9,2)	0.10	1.1(0.7,1.6)	0.68
26.62	79.43	171	0.13	LDL	1.4(0.9,2)	0.10	1.4(0.9,2.1)	0.10
45.42	58.06	6	0.45	ACR	1.3(0.9,1.8)	0.12	1.2(0.9,1.7)	0.26
10.22	93.2		0.04	AA	1.4(1,2.1)	0.08	1.5(1,2.2)	0.07
10.22	93.2		0.45	White	0.8(0.5,1.1)	0.19	0.7(0.5,1.1)	0.13
24.73	77.37	83	0.70	DBP	1(0.7,1.5)	0.99	1(0.7,1.5)	0.91
5.56	94.55		0.95	DM	1(0.5,2)	0.96	1(0.5,2)	0.97
0.31	94.3		0.0001	Hisp	0.5(0.2,1.9)	0.33	0.7(0.2,2.3)	0.50

Age ≤ 54 (age included)

Sn	Sp	Threshold	P	Variable	UOR	P	AOR	P
63.57	75.14	43	0.0001	Age	3.8(2.9,5)	<0.001		
66.82	62.1	92	0.0001	WHR	2.6(2,3.5)	<0.001	2.6(2,3.5)	<0.001
59.32	66.8	27	0.0001	BMI	0.6(0.4,0.7)	<0.001	0.6(0.4,0.7)	<0.001
66.72	57.87	116	0.0001	SBP	2.3(1.8,3.1)	<0.001	1.6(1.2,2.2)	0.001
37.72	85.77		0.0001	HTN	2.7(2,3.7)	<0.001	2(1.5,2.7)	<0.001
56.59	64.07	96	0.0001	Gluc	2.1(1.6,2.8)	<0.001	1.4(1.1,1.9)	0.01
29.39	90.89	86	0.0001	DBP	3.7(2.7,5)	<0.001	3.7(2.7,5)	<0.001
34.88	82.49	93	0.0009	GFR	1.9(1.4,2.7)	<0.001	1(0.7,1.5)	0.90

68.12	47.99		0.0006	Smoking	2.9(2.1,3.9)	<0.001	2.4(1.8,3.2)	<0.001
35.6	79.52	30	0.0006	CRP	1.8(1.4,2.4)	<0.001	1.8(1.4,2.4)	<0.001
26.92	85.54	11	0.0001	ACR	2.2(1.6,2.9)	<0.001	1.9(1.4,2.6)	<0.001
58.38	52.85		0.03	Sex	1.7(1.3,2.2)	<0.001	1.7(1.3,2.2)	<0.001
31.13	79.81	38	0.010	HDL	1.7(1.3,2.4)	<0.001	1.7(1.3,2.4)	<0.001
33.51	76.31	111	0.06	Creat	1.6(1.2,2.2)	0.002	1.6(1.2,2.2)	0.002
25.37	83.92	155	0.06	LDL	1.6(1.1,2.2)	0.006	1.6(1.1,2.2)	0.006
15.33	88.62		0.02	AA	1.6(1.2,2.1)	0.002	1.8(1.3,2.3)	<0.001
15.33	88.62		0.27	White	0.7(0.5,0.9)	0.011	0.6(0.5,0.8)	0.001
4.57	98.85		0.002	CVD	6.4(3.4,12)	<0.001	4.1(2.2,7.9)	<0.001
4.58	98.27		0.01	DM	2.7(1.6,4.5)	<0.001	2(1.2,3.4)	0.011
3.43	95.48		0.57	Hisp	0.6(0.3,1.4)	0.22	0.7(0.3,1.5)	0.32

Age ≤ 43 (after ≤ 54)

Sn	Sp	Threshold	P	Variable	UOR	P	AOR	P
59.08	69.31	96	0.0001	Gluc	2.2(1.5,3.3)	<0.001	1.9(1.3,2.8)	0.001
72.74	50.11		0.002	Smoking	3.6(2.3,5.5)	<0.001	3.3(2.1,5)	<0.001
54.51	68.12	27	0.0001	BMI	0.7(0.5,1)	0.04	0.7(0.5,1)	0.04
55.23	66.97	92	0.0003	WHR	2.4(1.6,3.5)	<0.001	2(1.4,3)	<0.001
87.96	27.63	27	0.0007	Age	2.3(1.4,3.8)	0.002		
51.01	63.35	116	0.03	SBP	1.8(1.2,2.6)	0.003	1.6(1.1,2.3)	0.02
22.58	88.06	12	0.02	ACR	2.2(1.4,3.4)	<0.001	2.1(1.4,3.2)	0.001
14.47	95.53	89	0.0003	DBP	3.2(1.9,5.3)	<0.001	3.2(1.9,5.3)	<0.001
22.05	87.76		0.002	AA	2.1(1.4,3)	<0.001	2(1.4,3)	<0.001
22.05	87.76		0.008	White	0.5(0.4,0.7)	0.001	0.5(0.4,0.8)	0.001
15.06	91	121	0.21	Creat	1.5(0.8,2.6)	0.18	1.5(0.8,2.6)	0.18
53.15	52.67		0.48	Sex	1.7(1.2,2.5)	0.006	1.7(1.2,2.5)	0.006
17.58	88.08		0.22	HTN	1.4(0.8,2.3)	0.20	1.2(0.7,2)	0.43
23.72	80.98	147	0.42	LDL	1.5(0.9,2.3)	0.09	1.5(0.9,2.3)	0.09
8.91	95.24	99	0.06	CRP	1.5(0.8,2.8)	0.24	1.5(0.8,2.8)	0.24
13.16	90.8	92	0.42	GFR	1.3(0.7,2.5)	0.49	1(0.5,1.9)	0.98
7.58	95.4		0.34	Hisp	0.7(0.3,2)	0.56	0.8(0.3,2.1)	0.61
3.07	98.71		0.11	DM	1.7(0.7,4.3)	0.27	1.5(0.6,3.9)	0.37
2.56	99.2		0.18	CVD	2.4(0.6,10.2)	0.25	2(0.5,8.6)	0.36
10.42	89.89	34	0.95	HDL	1.1(0.6,2)	0.83	1.1(0.6,2)	0.83

Age ≤ 43, Glucose ≤ 96

Sn	Sp	Threshold	P	Variable	UOR	P	AOR	P
56.2	76.88	27	0.0001	BMI	0.5(0.3,0.8)	0.006	0.5(0.3,0.8)	0.006
74.55	50.95		0.04	Smoking	4.3(2.3,8.1)	<0.001	4.1(2.2,7.6)	<0.001
61.75	59.87	88	0.007	WHR	2.4(1.4,4.2)	0.002	2.2(1.2,3.8)	0.007
32.27	87.47		0.002	AA	2.7(1.6,4.7)	<0.001	2.7(1.5,4.6)	0.001
32.27	87.47		0.004	White	0.4(0.2,0.7)	0.002	0.4(0.2,0.7)	0.002
43.2	73.76	117	0.04	SBP	2.1(1.2,3.6)	0.009	1.9(1.1,3.3)	0.02

71.7	41.83	88	0.14	Gluc	1.2(0.7,2.1)	0.47	1.2(0.7,2)	0.59
79.6	32.57	27	0.11	Age	1.9(1,3.6)	0.05		
20.12	90.55		0.06	HTN	1.7(0.8,3.4)	0.17	1.5(0.7,3.2)	0.26
18.61	90.59	82	0.12	DBP	2.6(1.4,4.9)	0.002	2.6(1.4,4.9)	0.002
21.46	87.25	12	0.24	ACR	1.7(0.9,3.3)	0.11	1.7(0.9,3.3)	0.11
67.47	40.08	53	0.32	HDL	1(0.6,1.8)	0.86	1(0.6,1.8)	0.86
5.45	99.34		0.004	DM	2.8(0.6,11.9)	0.17	2.9(0.7,12.3)	0.16
5.17	99.23		0.05	CVD	4.8(0.6,39)	0.14	3.8(0.5,31.6)	0.21
7.67	96.08	99	0.39	CRP	1.2(0.4,3.2)	0.78	1.2(0.4,3.2)	0.78
6.47	96.75	85	0.35	GFR				
10.54	92.53	121	0.49	Creat	2(0.9,4.3)	0.08	2(0.9,4.3)	0.08
71.22	31.13	98	0.73	LDL	0.9(0.5,1.5)	0.63	0.9(0.5,1.5)	0.63
5.02	95.72		0.86	Hisp	0.4(0.1,3)	0.38	0.4(0.1,3.2)	0.41
32.01	60.48		0.47	Sex	1.4(0.8,2.4)	0.26	1.4(0.8,2.4)	0.24

Age ≤ 43 Glucose > 96

Sn	**Sp**	**Threshold**	**P**	Variable	**UOR**	**P**	**AOR**	**P**
71.48	48.22		0.06	Smoking	2.9(1.6,5.2)	<0.001	2.7(1.5,4.8)	0.001
84.9	32.47	32	0.02	Age	2.6(1.3,5)	0.005		
46.94	68.33	6	0.04	ACR	2.6(1.5,4.5)	<0.001	2.5(1.5,4.3)	0.001
67.88	46.99	92	0.07	WHR	2.4(1.3,4.3)	0.004	2.1(1.2,3.9)	0.01
26.05	86.98	110	0.04	Gluc	2.1(1.2,3.7)	0.02	1.8(1,3.3)	0.046
16.8	92.96	89	0.06	DBP	2.5(1.3,5)	0.006	2.5(1.3,5)	0.006
31.04	77.14	149	0.40	LDL	1.7(1,3.1)	0.066	1.7(1,3.1)	0.07
31.95	74.5	31	0.46	BMI	1.1(0.6,2)	0.71	1.1(0.6,2)	0.71
18.19	87.53	121	0.49	Creat	1(0.4,2.2)	0.91	1(0.4,2.2)	0.91
13.74	91.7	134	0.09	SBP	2.8(1.5,5.4)	0.002	2.5(1.3,4.9)	0.006
17.8	86.74	92	0.58	GFR	1.1(0.5,2.7)	0.81	0.9(0.4,2.2)	0.86
9.02	95.26	100	0.09	CRP	1.6(0.7,3.8)	0.32	1.6(0.7,3.8)	0.32
9.35	94.67		0.35	Hisp	0.9(0.3,3)	0.89	1(0.3,3.2)	0.94
14.98	88.4		0.29	AA	1.8(1.1,3.1)	0.03	1.7(1,3)	0.04
14.98	88.4		0.22	White	0.6(0.3,1)	0.048	0.6(0.3,1)	0.06
67.78	35.02		0.79	Sex	1.5(0.9,2.7)	0.15	1.7(0.9,3)	0.08
0.75	99.15		0.92	CVD	1.1(0.1,8.7)	0.91	1.1(0.1,8.4)	0.94
1.42	97.29		0.39	DM	1(0.3,3.1)	0.94	0.9(0.3,2.9)	0.84
15.82	82.5		0.83	HTN	1(0.5,2.1)	0.96	0.9(0.5,1.9)	0.83
11.49	84.62	34	0.55	HDL	0.8(0.3,1.8)	0.52	0.8(0.3,1.8)	0.52

Age 44-54 (after ≤ 54)

Sn	**Sp**	**Threshold**	**P**	Variable	**UOR**	**P**	**AOR**	**P**
51.87	77.81		0.0001	HTN	2.9(1.9,4.4)	<0.001	2.8(1.9,4.3)	<0.001
38.01	87.08	86	0.0001	DBP	3.2(2.1,5)	<0.001	3.2(2.1,5)	<0.001
62.69	62.27	27	0.0005	BMI	0.6(0.4,0.8)	0.006	0.6(0.4,0.8)	0.006
59.26	62.3	124	0.007	SBP	1.9(1.3,2.9)	0.002	1.8(1.2,2.8)	0.004

45.83	75.12	33	0.003	CRP	1.8(1.2,2.8)	0.004	1.8(1.2,2.8)	0.004
74.95	45.28	92	0.02	WHR	1.7(1.1,2.7)	0.01	1.7(1.1,2.6)	0.02
42.28	75.69	38	0.008	HDL	2.1(1.4,3.3)	<0.001	2.1(1.4,3.3)	<0.001
80.52	35.67	4	0.01	ACR	2(1.2,3.2)	0.005	1.9(1.2,3.1)	0.008
62.05	53.48		0.04	Sex	1.6(1.1,2.4)	0.02	1.6(1.1,2.4)	0.02
18.42	95.53	190	0.0005	LDL	1.9(0.9,3.7)	0.08	1.9(0.9,3.7)	0.08
56.95	55.48	49	0.10	Age	1.6(1.1,2.5)	0.02		
39.79	71.33	111	0.13	Creat	1.4(0.9,2.2)	0.11	1.4(0.9,2.2)	0.11
14.95	95.87	74	0.004	GFR	1.7(0.7,3.9)	0.23	1.6(0.7,3.7)	0.3
80.31	28.68	91	0.15	Gluc	1.1(0.7,1.9)	0.63	1.1(0.7,1.8)	0.74
64.87	40.69		0.40	Smoking	1.7(1.1,2.6)	0.02	1.6(1.1,2.5)	0.03
5.98	97.61		0.05	CVD	5.7(2.6,12.2)	<0.001	5.4(2.5,11.7)	<0.001
5.64	96.75		0.31	DM	2.5(1.3,4.8)	0.007	2.3(1.2,4.5)	0.02
10.6	91.59		0.27	AA	1.4(0.9,2.2)	0.12	1.5(1,2.3)	0.07
10.6	91.59		0.53	White	0.8(0.5,1.2)	0.24	0.7(0.5,1.1)	0.17
0.51	95.77		0.0002	Hisp	0.5(0.1,2.3)	0.39	0.5(0.1,2.1)	0.35

Age 44-54 Hypertension? No

Sn	Sp	Threshold	P	Variable	UOR	P	AOR	P
93.45	34.9	88	0.0001	WHR	1.8(0.9,3.6)	0.122	1.7(0.8,3.5)	0.14
73.45	52.13		0.004	Sex	1.6(0.9,2.9)	0.09	1.7(0.9,2.9)	0.09
26.53	95.95	89	0.0001	DBP	4.8(2.2,10.2)	<0.001	4.8(2.2,10.2)	<0.001
33.57	83.97	167	0.08	LDL	1.6(0.8,3.1)	0.16	1.6(0.8,3.1)	0.16
48.42	69.02	123	0.12	SBP	1.6(0.9,2.8)	0.1	1.5(0.9,2.7)	0.14
46.23	70.8	111	0.08	Creat	1.5(0.8,2.7)	0.21	1.5(0.8,2.7)	0.21
42.03	72.32	51	0.21	Age	1.7(0.9,2.9)	0.08		
91.71	21.33	61	0.04	HDL	1.4(0.7,3)	0.34	1.4(0.7,3)	0.34
58.86	53.06	98	0.27	GFR	1.4(0.8,2.5)	0.22	1.4(0.8,2.4)	0.29
97.23	13.62	87	0.0008	Gluc	1.1(0.4,2.9)	0.86	1(0.4,2.6)	0.99
72.04	37.06	4	0.31	ACR	1.4(0.7,2.5)	0.33	1.3(0.7,2.4)	0.38
27.13	78.31	33	0.54	CRP	1.5(0.8,2.7)	0.2	1.5(0.8,2.7)	0.2
37.9	67.16	27	0.55	BMI	0.8(0.4,1.4)	0.41	0.8(0.4,1.4)	0.41
64.02	40.76		0.59	Smoking	1.9(1,3.5)	0.048	1.8(1,3.4)	0.05
4.31	98.38		0.19	CVD	5.2(1.5,17.3)	0.008	4.8(1.4,16.4)	0.01
8.88	93.03		0.45	AA	1.2(0.6,2.3)	0.61	1.3(0.7,2.5)	0.48
8.88	93.03		0.50	White	0.9(0.5,1.8)	0.86	0.9(0.5,1.7)	0.73
2.04	97.47		0.73	DM	2.3(0.8,6.3)	0.11	2.1(0.8,5.9)	0.14
0.45	95.6		0.0005	Hisp	0.5(0.1,3.7)	0.48	0.5(0.1,3.6)	0.47

Age 44-54, Hypertension? Yes

Sn	Sp	Threshold	P	Variable	UOR	P	AOR	P
69.56	62.09	7	0.0009	ACR	2.5(1.3,4.7)	0.004	2.4(1.3,4.6)	0.007
51.21	84.33	37	0.0001	HDL	3.8(1.9,7.4)	<0.001	3.8(1.9,7.4)	<0.001
62.26	69.19	31	0.0003	BMI	0.4(0.2,0.7)	0.002	0.4(0.2,0.7)	0.002

66.5	61.85	30	0.0005	CRP	1.5(0.8,2.7)	0.23	1.5(0.8,2.7)	0.23
47.31	79.54	101	0.003	WHR	2.8(1.5,5.4)	0.002	2.8(1.4,5.3)	0.002
33.67	91.86	152	0.0001	SBP	5.2(2.6,10.5)	<0.001	5(2.4,10.4)	<0.001
20.97	97.45	186	0.0001	LDL	3.6(1.2,10.4)	0.02	3.6(1.2,10.4)	0.02
29.55	88.73	93	0.02	DBP	2.7(1.3,5.6)	0.007	2.7(1.3,5.6)	0.007
19.44	97.88	69	0.0001	GFR	3.1(0.8,12.1)	0.10	3.1(0.8,11.9)	0.11
59.84	53.46	49	0.20	Age	1.5(0.8,2.8)	0.18		
51.47	58.21		0.41	Sex	1.9(1,3.4)	0.04	1.9(1,3.4)	0.04
71.19	37.29	96	0.36	Gluc	1(0.5,1.9)	1	1(0.5,1.8)	0.90
33.82	73.18	111	0.45	Creat	1.5(0.8,2.8)	0.26	1.5(0.8,2.8)	0.26
65.66	40.43		0.49	Smoking	1.5(0.8,2.9)	0.19	1.5(0.8,2.8)	0.21
8.99	94.23		0.51	DM	2(0.8,5)	0.13	1.9(0.8,4.7)	0.18
7.53	94.95		0.56	CVD	4.2(1.5,11.8)	0.006	4.1(1.5,11.6)	0.007
12.19	86.51		0.71	AA	1.2(0.6,2.1)	0.65	1.2(0.6,2.2)	0.56
12.19	86.51		0.27	White	0.9(0.5,1.6)	0.71	0.9(0.5,1.6)	0.66
0.57	96.35		0.04	Hisp	0.7(0.1,6.5)	0.79	0.6(0.1,5.6)	0.68

The analytical procedures recommended by the National Health and Nutrition Examination Survey were followed and the sampling weights designed for complex sample survey design were used; WTPFSD6, SDPPSU6, and SDPSTRA6 as weight, cluster and stratum variables. HDL; high density lipoprotein, LDL; low density lipoprotein, Gluc; glucose, Creat; creatinine, ACR; albumin to creatinine ratio, BMI; body mass index, CRP; C-reactive protein, CVD; cardiovascular disease, AA; African American, Hisp; Hispanic race, WHR; waist to hip ratio, SBP; systolic blood pressure, DBP; diastolic blood pressure.

Chapter 4

End Stage Renal Disease from HIV Nephropathy in the United States.

Given the advances in the treatment of HIV infection, what is happening to the incidence of End Stage Renal Disease from HIV nephropathy?

Reference:

End-stage renal disease from human immunodeficiency virus–associated nephropathy in the United States, 2001 through 2010.
Sexton DJ, Reule S, Solid C, Collins AJ, Foley RN.
JAMA Intern Med. 2014 May;174(5):809-11.

End-Stage Renal Disease due to HIV-Associated Nephropathy in the United States, 2001-2010

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This study was performed as a deliverable under Contract No. HHSN267200715002C (National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland). The authors have no conflicts of interest with its subject matter.

Word count: 1905

Abstract

Importance: The clinical landscape of human immunodeficiency virus (HIV) in the US has changed considerably in the last decade. Highly active anti-retroviral treatment has been associated with a reduced incidence of HIV-associated nephropathy and improvement in renal function, but temporal trends in the clinical epidemiology of end-stage renal disease due to HIV-associated nephropathy in the United States have not been systematically defined.

Objective: We aimed to determine whether incidence rates and outcomes of end-stage renal disease due to HIV-associated nephropathy have improved in parallel with the changed outlook for HIV-infected individuals.

Design: Retrospective cohort study.

Setting: United States Renal Data System data.

Participants: Patients with HIV-associated nephropathy who initiated maintenance renal replacement therapy between 2001 and 2010 (n = 1,072,161).

Main Outcomes and Measures: Death, wait-listing for renal transplant, and renal transplant. National census data were used as denominators for calculating incidence rates, and biennial incidence ratios were standardized against rates seen in 2001 and 2002.

Results: During the study period, 7990 patients initiated renal replacement therapy due to HIV-associated nephropathy. Relative to 2001-2002, standardized incidence ratios remained stable until 2005-2006, and then declined stepwise to 0.74 (95% confidence interval 0.70-0.78, $P <$ 0.001) in 2009-2010. Patients with HIV-associated nephropathy were more likely to be young, male, black, and Hispanic; after matching for these characteristics, compared to matched controls mortality rates were higher with HIV-associated nephropathy (23.1 vs. 9.0 per 100 patient-years,

$P < 0.001$), and rates of wait-listing for renal transplant (2.4 vs. 10.6 per 100 patient-years, $P < 0.001$) and renal transplant (0.7 vs. 4.5 per 100 patient-years, $P < 0.001$) were lower.

Conclusions and Relevance: While HIV-associated nephropathy has declined as a cause of end-stage renal disease in the US, comparative outcomes on renal replacement therapy remain poor and exhibit racial variation. Our findings suggest causes for optimism (such as declining incidence) and concern (such as racial disparities, emergence in older populations, stagnation of survival rates in the current millennium, and low rates of renal transplant).

Introduction

Human immunodeficiency virus (HIV) infection is a condition with worldwide public health importance and protean clinical features. Before the advent of effective antiviral therapy, acquired immunodeficiency syndrome (AIDS) invariably resulted in profound immunosuppression and opportunistic infection. Mortality rates were extremely high; in 1984, fewer than half of patients survived for a year after their first AIDS-defining opportunistic illness.[1;2] It was soon apparent that renal sequelae were both prominent and ominous. HIV-associated nephropathy (HIVAN) emerged as a common cause of progressive chronic kidney disease in inadequately treated HIV infection in patients predominantly of African descent, characterized phenotypically by focal glomerulosclerosis and an increasingly evident genetic predisposition.[3-12]

With access to optimal care, the outlook for HIV-infected individuals has changed substantially in the past two decades.[13-16] Regarding renal function, observational evidence suggests that highly active anti-retroviral (HAART) treatment has been associated with a reduced incidence of HIVAN and improvement in renal function, particularly when commenced prior to the onset of AIDS.[17-19]

Surprisingly, temporal trends in the clinical epidemiology of end-stage renal disease (ESRD) due to HIVAN in the United States have not been systematically defined. The current study is an attempt to address this public health need.

Methods

Objectives

The main objectives of this study were to enumerate trends in incidence ratios, standardized to 2001-2002, of ESRD due to HIVAN treated with renal replacement therapy (RRT) in the US for 2001 to 2010. Regarding clinical outcomes after inception of RRT (wait-listing for renal transplant, renal transplant, and death), we set out to compare rates in matched patients with and without HIVAN, and to estimate hazards ratios for these outcomes among patients with HIVAN.

Subjects

In this retrospective study, we used United States Renal Data System (USRDS) standard analysis files to study US patients who initiated maintenance RRT between 2001 and 2010 (n = 1,072,161). Patient characteristics at dialysis initiation were determined from the Centers for Medicare & Medicaid (CMS) Medical Evidence Report (form CMS-2728), a federal requirement for all new maintenance RRT patients in the US, with corresponding data available in the USRDS Medevid95 and Medevid05 files. These files contain data pertaining to patient characteristics at dialysis initiation, such as age, sex, serum albumin, cause of kidney failure among other factors, which are taken from the information gathered by the completion of form CMS-2728. Form CMS-2728 changed twice in the past two decades, in 1995 and 2005. Additions to the 2005 version include information about predialysis nephrologist care and vascular access at hemodialysis initiation. In both the 1995 and the 2005 versions, one of 82 causes is entered as the primary cause of ESRD, and the options available are identical. For this study, cases of ESRD due to HIVAN were those with the primary cause of ESRD listed as "AIDS nephropathy" on form CMS-2728. Dates of death and first renal transplant were obtained from the Patients file, and first listing for transplant was determined from the Waitlist_ki and Waitlist_kp files.

Analysis

US census data were used to determine population denominators for each of the years examined, with age in 5-year increments and race/ethnicity classified as non-Hispanic white, non-Hispanic black, Hispanic, and other.[20] The Poisson distribution was used to calculate incidence rates of RRT-requiring ESRD due to HIVAN. For standardized incidence ratios, expected incidence rates were calculated by applying incidence rates in 2000 for each of the 168 (21 x 2 x 4) possible combinations of age (21 subgroups), sex (2 subgroups), and race-ethnicity (4 subgroups) to the corresponding subgroup of the US population for each year 2001 to 2010. Chi-square analysis and logistic regression, respectively, were used for unadjusted and adjusted comparisons of patients with and without ESRD due to HIVAN at initiation of RRT. In order to compare clinical outcomes between patients with and without HIVAN, patients were matched according to year of initiation of RRT (in two-year intervals), age (in 1-year increments), sex, race, Hispanic ethnicity, and geographic region (northeastern, mid-western, southern, and western states of the US). Poisson regression was used to calculate incidence rates and adjusted hazards ratios (AHRs) for events occurring after initiation of RRT. Follow-up ended on June 30, 2011; as outcomes were similar when follow-up was censored at transplant, only uncensored findings are reported here. SAS, v9.1.3 (Cary, North Carolina) was used for data analysis.

Results

In 2001-2002, 1669 cases of RRT due to HIVAN occurred in the US, a rate of 2.9 cases per million per year (Table 1). Rates exceeded this value for non-Hispanic black patients (21.2) and for patients aged 45-64 years (4.5). Standardized incidence ratios for the overall population declined between the 2001-2002 and 2009-2010 (2009-2010, ratio 0.74 vs. 2001-2002), with a

stepwise decline from 2005-2006. Standardized incidence ratios fell in most groups studied, with the lowest ratio in 2009-2010 in the group aged 0-44 years (ratio 0.59), followed by groups characterized by Hispanic ethnicity (0.67), non-Hispanic black race/ethnicity (0.69), male sex (0.73), and female sex (0.76). Ratios increased in two groups, age ≥ 65 years (1.99) and non-Hispanic white race/ethnicity (1.86).

Table 2 shows characteristics at the time of RRT initiation in patients with and without HIVAN. When adjustment was made for demographic variables, characteristics associated with HIVAN included younger age; male sex; black race; Hispanic ethnicity; alcohol abuse; drug abuse; hemodialysis for RRT; catheters for hemodialysis; short duration of nephrology care; higher estimated glomerular filtration rate; lower body mass index, serum albumin level, and hemoglobin level; and absence of ischemic heart disease and diabetes. Regarding numerical size, adjusted odds ratios (AORs) for HIVAN exceeded 2.0 for black race (AOR 15.53), drug abuse (AOR 4.47), serum albumin level < 3.5 g/dL (AOR 3.38), and nephrology care ≤ 12 months (AOR 2.51); AORs were < 0.5 for age 40-64 years and ≥ 65 years (AOR 0.42 and 0.02), ischemic heart disease (AOR 0.30), diabetes (AOR 0.13), peritoneal dialysis for RRT (AOR 0.42), preemptive transplant (AOR 0.02), and body mass index ≥ 30 kg/m^2 (AOR 0.25).

Over a mean follow up of 4.1 years, 62.7% of patients with HIVAN died, while 6.5% were listed for renal transplant and 2% underwent renal transplant. Figure 1 shows rates for these outcomes in subgroups of patients with HIVAN and in a matched cohort of patients without HIVAN (see eTable 1 in the Supplement for rates and 95% confidence intervals). In the overall matched population, mortality rates were higher with HIVAN (23.1 vs. 9.0 per 100 person-years, a ratio of 2.6), a pattern seen in all groups studied. Among patients with HIVAN, unadjusted associations of higher mortality rates included older age, non-Hispanic black race/ethnicity, and

female sex. Patients with HIVAN were 4.4 times less likely to be wait-listed for transplant. Among patients with HIVAN, factors associated with higher rates of listing included age younger than 40 years, non-Hispanic white race/ethnicity, and other race/ethnicity. Patients with HIVAN were 6.4 times less likely to undergo transplant; associations of higher transplant rates in patients with HIVAN included age younger than 40 years, non-Hispanic white race/ethnicity, and other race/ethnicity.

Table 3 shows AHRs for death, wait-listing for transplant, and transplant in the HIVAN ESRD population. Factors associated with higher hazards of death and lower hazards of listing and transplant included older age, drug abuse, hemodialysis for RRT, catheters for hemodialysis, shorter duration of nephrology care, and lower serum albumin level. Factors associated with lower mortality were body mass index ≥ 30 kg/m^2, serum hemoglobin level > 9.0 g/dL, initiation of RRT in 2005-2006, and peritoneal dialysis for RRT. Mortality hazards ratios exceeded 1.5 for serum albumin level < 3.5 g/dL (AHR 2.07), nephrology care $\leq$ 12 months (AHR 1.77), catheters (AHR 1.62) and grafts (AHR 1.60) for hemodialysis, and age $\geq$ 65 years (AHR 1.57). Corresponding characteristics for wait-listing for transplant included peritoneal dialysis for RRT (AHR 2.68), and RRT initiation in 2009-2010 (AHR 1.75) and 2007-2008 (AHR 1.56). Peritoneal dialysis for RRT was also associated with an increased likelihood of undergoing transplant (AHR 4.25).

Discussion

We found that overall rates of RRT-requiring ESRD from HIVAN declined in the United States between 2001 and 2010. While declines occurred in most subgroups examined, standardized incidence ratios rose for patients aged older than 64 years. End-stage HIVAN

patient outcomes on dialysis were inferior to outcomes for non-HIVAN patients, differed by race and ethnicity, and, apart from wait-listing for renal transplant, did not change appreciably throughout the decade.

Few studies have systematically addressed ESRD from HIVAN as a public health issue in the United States. For example, a PubMed search performed on October 28, 2013, with the search terms "hiv or aids or human immune deficiency virus," "nephropathy or kidney disease or glomerulonephritis," "dialysis," "renal replacement therapy," "United States," and "trends or incidence or epidemiology" yielded no studies of new RRT patients after 2004. Based on USRDS data, Eggers and Kimmel found that although the prevalence of HIV infection in the US ESRD population appeared to be increasing between 1995 and 2000, counts for incident HIV infection appeared to be stable.[21] Before this time, encouraging survival trends had been apparent in the US. For example, Ahuja and colleagues showed that annual death rates were almost halved, from 45.8 to 24.0 deaths per 100 patient-years, between 1990 and 1999.[22] Survival trends were similar among 115 patients initiating maintenance dialysis at San Francisco General Hospital between 1985 and 2002.[23]

We found that wait-listing for potential renal transplant was more likely for HIVAN patients initiating RRT more recently. Renal transplant in HIV-positive patients is an emerging field. In one notable prospective study from 2010, Stock and colleagues reported findings from 150 patients with CD4+ T-cell counts of at least 200 per cubic millimeter and undetectable plasma HIV type 1 (HIV-1) RNA levels who underwent transplant between 2003 and 2009 in the US. Survival rates at 1 and 3 years were 94.6% and 88.2%, and corresponding graft survival percentages were 90.4% and 73.7%, respectively.[24] The reasons for low rates of transplant in HIVAN is likely multifactorial, including practical issues related to HIV medication interaction,

access to medical care and socioeconomic factors, as well as the law around transplant in HIV. Moving legislature in the United States could change the landscape for patients with organ failure and HIV, such as the sanctioning of organ transplantation between HIV-positive donors to HIV-positive recipients in some US states. Access to medical care has previously been reported to partially explain the higher mortality and lower transplant rates in African Americans. In the case of HIVAN it is possible that factors related to socioeconomic factors and race contribute to the likelihood of receiving HARRT which may therefore impact on morbidity and mortality. 16

Several limitations of our study should be highlighted. This was a non-experimental study of associations; causes and effects cannot be separated with assurance, and the hypothesis that the decline in end-stage HIVAN seen in the US during this period reflects therapeutic advances such as HAART remains unproven. The study is retrospective and registry-based and lacks desirable data elements that a prospective design could provide. While a true tissue diagnosis in all patients would be desirable, this aspiration is likely utopian.[25] Information about hepatitis B and hepatitis C was not available. Questions about HIV positivity and AIDS as a comorbid illness at dialysis initiation were removed from the 2005 Medical Evidence Report. Thus, it is not possible to refute with certainty the hypothesis that the apparently salutary trends for HIVAN reflect changing fashions in labelling cause of renal disease in patients living with HIV, and not a change in the incidence of HIVAN. If death rates from causes other than ESRD have declined, competing risk considerations might suggest that incidence rates of HIVAN might increase, because potential time at risk for HIVAN would increase. In this scenario, a decline in HIVAN rates would be more impressive considered in the light of survival rates having improved during the timeframe studied. The availability of aggregated census data (as opposed

to longitudinal data for individuals) precludes accurate quantification of the true size of a competing death effect.

Despite its limitations, this study may provide some worthwhile information about two important domains of public health, chronic kidney disease and living with HIV. It suggests causes for optimism (such as declining incidence) and concern (such as racial disparities, emergence in older populations, stagnation of survival rates in the current millennium, and low rates of renal transplant). If our findings are valid, they suggest both meaningful progress and challenges for the future.

Acknowledgments

This study was performed as a deliverable under Contract No. HHSN267200715002C (National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland). The authors have no conflicts of interest with its subject matter. Dr. Foley had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors conducted and are responsible for the data analysis. The authors thank USRDS colleagues Delaney Berrini, BS, for manuscript preparation, and Nan Booth, MSW, MPH, ELS, for manuscript editing.

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Table 1. Standardized incidence ratios of RRT-requiring ESRD due to HIV-associated nephropathy, 2001-2010.

Subgroup	Rate	Standardized Incidence Ratio, vs. 2001-2002			
Biennium	2001-2002	2003-2004	2005-2006	2007-2008	2009-2010
Cases/million population	1669/286	1680/291	1709/297	1573/303	1359/308
All	2.9	0.98 (0.93-1.03)	0.97 (0.92-1.02)	0.87 (0.83-0.91)[b]	0.74 (0.70-0.78)[c]
Age, years					
0-44	2.9	0.91 (0.85-0.97)	0.91 (0.86-0.97)	0.71 (0.66-0.76)[c]	0.59 (0.55-0.64)[c]
45-64	4.5	1.08 (1.00-1.16)	1.02 (0.94-1.09)	1.06 (0.99-1.14)	0.89 (0.82-0.95)
≥ 65	0.4	1.41 (0.95-1.88)	1.85 (1.33-2.36)	1.84 (1.34-2.34)	1.99 (1.49-2.49)[a]
Sex					
Male	4	0.96 (0.90-1.01)	0.93 (0.87-0.98)	0.85 (0.80-0.90)[b]	0.73 (0.68-0.78)[c]
Female	1.8	1.03 (0.94-1.11)	1.06 (0.98-1.15)	0.92 (0.84-1.00)	0.76 (0.69-0.83)[b]
Race/ethnicity					
Non-Hispanic white	0.2	1.29 (1.03-1.56)	1.37 (1.10-1.63)	1.49 (1.21-1.77)	1.86 (1.54-2.18)[b]
Non-Hispanic black	21.2	0.96 (0.91-1.01)	0.96 (0.91-1.01)	0.85 (0.80-0.89)[b]	0.69 (0.65-0.73)[c]
Hispanic	1.4	1.02 (0.84-1.21)	0.87 (0.70-1.03)	0.78 (0.63-0.93)	0.67 (0.54-0.81)[a]
Other	0.3	1.15 (0.41-1.89)	1.18 (0.46-1.90)	1.11 (0.43-1.79)	1.06 (0.41-1.70)

Note: Parameter estimates are either rates per million per year or standardized incidence ratios (standardized to 2001-2002) with 95% confidence intervals in parentheses. With PE denoting Point Estimate, CL Confidence Limit, Obs Observed Incidence Rate, Exp Expected Incidence Rate from rates seen in 2001-2002, standardized incidence ratios were calculated and reported as [PE_{Obs}/PE_{Exp}] ([5% CL_{Obs}/PE_{Exp}]- [95% CL_{Obs}/PE_{Exp}]). *P* values refer to comparisons of observed rates and rates expected when those seen in 2001-2002 were applied to the years under consideration. $P \geq 0.05$ unless otherwise indicated.

ESRD, end-stage renal disease; HIV, human immunodeficiency virus; RRT, renal replacement therapy. [a] $0.01 \leq P$ (vs. 2000) < 0.05; [b] $0.001 \leq P$ (vs. 2000) < 0.01; [c] P (vs. 2000) ≤ 0.001.

Table 2. Baseline characteristics at initiation of renal replacement therapy (*n* = 7990)

Characteristics	Percentage With Event		
	HIVAN	No HIVAN	AOR HIVAN
n	7990	1,064,171	
Year of first RRT			
2001-2002	20.9	18.3	1 (Reference)
2003-2004	21	19.2	0.96 (0.90-1.03)
2005-2006	21.4	20.2	0.92 (0.85-0.98)
2007-2008	19.7	20.7	0.82 (0.76-0.88)
2009-2010	17	21.5	0.71 (0.66-0.76)
Age, years			
< 40	34.2	9	1 (Reference)
40-64	62.9	41.7	0.42 (0.40-0.44)
≥ 65	2.9	49.3	0.02 (0.02-0.03)
Sex			
Male	66.6	55.5	1 (Reference)
Female	33.4	44.5	0.61 (0.58-0.64)
Race			
White	11.2	65.9	1 (Reference)
Black	87.3	27.9	15.53 (14.37-16.79)
Other	1.5	6.2	1.12 (0.92-1.36)
Ethnicity			
Non-Hispanic	93.3	86.5	1 (Reference)
Hispanic	6.7	13.5	1.63 (1.48-1.80)
Ischemic heart disease			
No	96.4	76.3	1 (Reference)
Yes	3.6	23.7	0.30 (0.27-0.34)
Diabetes			
No	89.3	47.8	1 (Reference)
Yes	10.7	52.2	0.13 (0.12-0.14)
Alcohol abuse			
No	95.3	98.5	1 (Reference)
Yes	4.7	1.5	2.00 (1.80-2.23)
Drug abuse			
No	86.4	98.9	1 (Reference)
Yes	13.6	1.1	4.47 (4.18-4.79)
Mode of RRT			
Hemodialysis	96.8	91.2	1 (Reference)
Peritoneal dialysis	3.2	6.6	0.42 (0.37-0.48)
Preemptive transplant	0	2.2	0.02 (0-0.06)
Initial hemodialysis access			
Fistula	6.7	13.9	1 (Reference)
Graft	2.4	3.6	1.19 (0.94-1.49)

Catheter	90.9	82.5	1.99 (1.76-2.25)
Prior nephrology care, months			
> 12	9.1	24.3	1 (Reference)
≤ 12	90.9	75.7	2.51 (2.26-2.78)
GFR, mL/min/1.73 m^2			
≤ 15	88.7	80.4	1 (Reference)
> 15	11.3	19.6	0.63 (0.59-0.68)
BMI, kg/m^2			
< 30	85.8	66.3	1 (Reference)
≥ 30	14.2	33.7	0.25(0.23-0.26)
Albumin, g/dL			
≥ 3.5	13.3	35	1 (Reference)
< 3.5	86.7	65	3.38 (3.14-3.64)
Hemoglobin, g/dL			
< 9	46.1	25.6	1 (Reference)
≥ 9	53.9	74.4	0.62 (0.59-0.65)

Note: Parameter estimates are presented as column percentages or odds ratios with 95% confidence intervals in parentheses. As data fields for predialysis vascular access for hemodialysis and predialysis nephrology care were available only in the 2005 version of the Medical Evidence Report, the denominators for these variables consisted 58.6% of the study population in whom the 2005 version of the form was completed. Missing data: GFR, 0.6%; BMI, 1.4%; albumin, 24.9%; hemoglobin, 8.4%. *P* values < 0.001 throughout.

AOR, adjusted (for age, sex, race, ethnicity) odds ratio; BMI, body mass index; GFR, glomerular filtration rate; HIVAN, human immune deficiency-associated nephropathy; RRT, renal replacement therapy.

Table 3. Adjusted hazards ratios for outcomes on RRT, patients with HIVAN (n = 7990)

Subgroups	Outcomes					
	Death	*P*	Wait-Listing for Transplant	*P*	Transplant	*P*
Percentage	62.7	-	6.5	-	2.0	-
Year of first RRT						
2001-2002	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
2003-2004	1.02 (0.94-1.10)	0.639	1.26 (0.97-1.63)	0.082	1.30 (0.87-1.95)	0.202
2005-2006	0.90 (0.83-0.97)	0.007	1.31 (1.01-1.69)	0.045	0.88 (0.56-1.39)	0.584
2007-2008	0.96 (0.88-1.05)	0.396	1.56 (1.19-2.05)	0.001	0.71 (0.41-1.24)	0.23
2009-2010	1.05 (0.94-1.18)	0.35	1.75 (1.25-2.43)	0.001	0.94 (0.49-1.83)	0.862
Age, years						
< 40	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
40-64	1.14 (1.08-1.21)	< 0.001	0.75 (0.63-0.90)	0.002	0.67 (0.49-0.92)	0.012
≥ 65	1.57 (1.33-1.85)	< 0.001	0.14 (0.04-0.58)	0.006	0 (0-.)	0.999
Sex						
Male	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
Female	1.17 (1.11-1.24)	< 0.001	0.79 (0.65-0.97)	0.022	0.87 (0.62-1.23)	0.427
Race						
White	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
Black	1.01 (0.91-1.13)	0.84	0.63 (0.49-0.81)	0.003	0.40 (0.27-0.60)	< 0.001
Other	1.10 (0.86-1.4)	0.448	1.31 (0.73-2.35)	0.441	1.73 (0.81-3.71)	0.159
Hispanic ethnicity						
No	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
Yes	0.96 (0.86-1.07)	0.462	0.93 (0.65-1.35)	0.717	1.56 (0.91-2.65)	0.103
Ischemic heart disease						
No	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
Yes	1.10 (0.95-1.27)	0.211	0.88 (0.51-1.54)	0.663	0.45 (0.11-1.84)	0.268
Diabetes						
No	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-

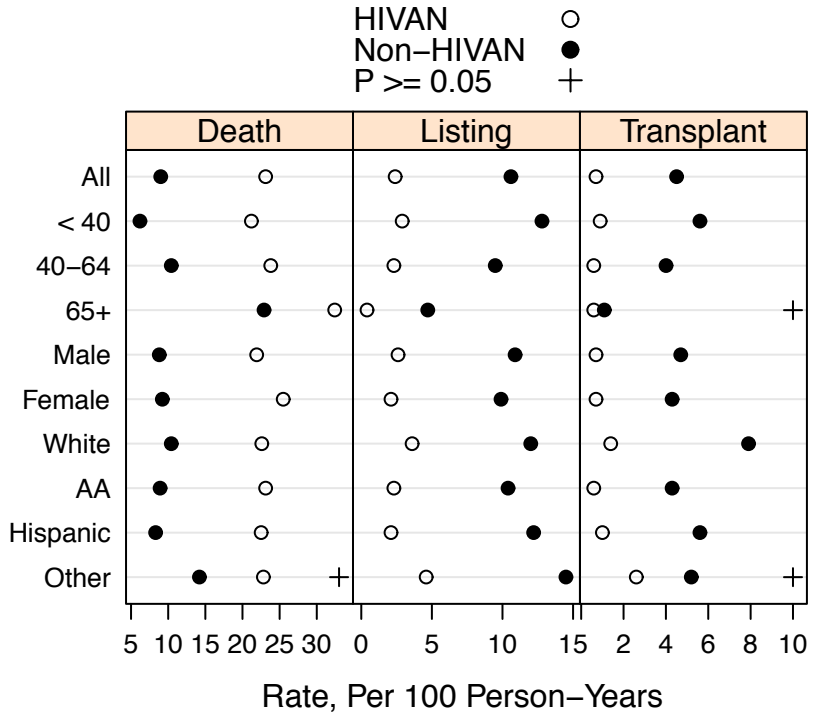
Yes	1.02 (0.93-1.12)	0.695	1.25 (0.94-1.65)	0.128	0.84 (0.47-1.53)	0.577
Alcohol abuse						
No	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
Yes	1.32 (1.16-1.5)	< 0.001	0.51 (0.27-0.95)	0.033	0.52 (0.17-1.65)	0.269
Drug abuse						
No	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
Yes	1.40 (1.3-1.51)	< 0.001	0.25 (0.15-0.42)	< 0.001	0.10 (0.03-0.42)	0.001
Mode of RRT						
Hemodialysis	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
Peritoneal dialysis	0.63 (0.53-0.74)	< 0.001	2.68 (1.99-3.63)	< 0.001	4.25 (2.74-6.58)	< 0.001
Preemptive transplant	0 (0-.)	0.998	0 (0-.)	0.999	0 (0-.)	1
Hemodialysis access						
Fistula	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
Graft	1.60 (1.15-2.24)	0.005	0.58 (0.24-1.40)	0.227	0 (0-.)	1
Catheter	1.62 (1.33-1.97)	< 0.001	0.45 (0.30-0.66)	< 0.001	0.27 (0.13-0.54)	< 0.001
Prior nephrology care, months						
> 12	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
≤ 12	1.77 (1.49-2.10)	< 0.001	0.31 (0.23-0.41)	< 0.001	0.19 (0.11-0.33)	< 0.001
GFR, mL/min/1.73 m^2						
< 15	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
≥ 15	1.4 (1.26-1.56)	< 0.001	0.76 (0.49-1.18)	0.219	1.33 (0.72-2.46)	0.36
BMI, kg/m^2						
< 30	1 (Reference)		1 (Reference)		1 (Reference)	
≥ 30	0.64 (0.59-0.70)	< 0.001	1.43 (1.15-1.78)	0.001	1.23 (0.82-1.84)	0.317
Serum albumin, g/dL						
≥ 3.5	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
< 3.5	2.07 (1.86-2.31)	< 0.001	0.48 (0.39-0.59)	< 0.001	0.41 (0.28-0.60)	< 0.001
Hemoglobin, g/dL						
< 9.0	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
> 9.0	0.91 (0.85-0.96)	0.001	1.2 (1-1.45)	0.052	1.33 (0.95-1.86)	0.098

Note: Parameter estimates are presented with either standard errors or 95% confidence intervals in parentheses.

AHR, adjusted (for age, sex, race, ethnicity) hazards ratio; BMI, body mass index; GFR, glomerular filtration rate; HIVAN, human immune deficiency-associated nephropathy; RRT, renal replacement therapy.

Figure Legend

Figure 1. Rates of death, wait-listing for transplant, and transplant in patients with HIVAN (*n* = 7786, 98.7%) and an equal number of matched control patients without HIVAN. Factors used for matching were: biennium of dialysis initiation (2001-2002, 2003-2004, 2005-2006, 2007-2008, 2009-2010); age (in 1-year increments); sex; race/ethnicity (non-Hispanic black, non-Hispanic white, Hispanic, other), and geographic region (northeastern, mid-western, southern, and western states of the US). $P < 0.05$ for rate comparisons of patients with and without HIVAN, unless otherwise indicated. See eTable 1 in the Supplement for rates and 95% confidence intervals.



Supplement

eTable 1 for Figure 1. Rates (per 100 person-years, with 95% confidence intervals in parentheses) of death, wait-listing for transplant, and renal transplant in patients with HIVAN (*n* = 7786, 98.7 %) and an equal number of matched control patients without HIVAN

	Death (Figure 1)		Transplant List (Figure 2)		Transplant (Figure 3)	
	HIVAN+	HIVAN-	HIVAN+	HIVAN-	HIVAN+	HIVAN-
All	23.1 (22.4-23.7)	9 (8.6-9.3)	2.4 (2.2-2.7)	10.6 (10.2-11)	0.7 (0.6-0.8)	4.5 (4.3-4.8)
2001-2002	23.3 (22-24.5)	9.5 (8.9-10.1)	2 (1.6-2.4)	8.7 (8-9.5)	0.8 (0.6-1)	5.1 (4.6-5.6)
2003-2004	24.1 (22.8-25.4)	9 (8.4-9.6)	2.4 (2-2.8)	9.8 (9-10.7)	0.9 (0.7-1.2)	5 (4.5-5.6)
2005-2006	21.1 (19.9-22.4)	8.7 (8-9.4)	2.5 (2-2.9)	10.9 (10-11.9)	0.7 (0.5-0.9)	4.6 (4.1-5.1)
2007-2008	23 (21.5-24.7)	8.3 (7.5-9.1)	2.9 (2.4-3.5)	12.6 (11.4-13.8)	0.5 (0.3-0.7)	3.8 (3.3-4.5)
2009-2010	25.3 (22.9-27.8)	8.9 (7.7-10.4)	3.2 (2.4-4.2)	15.4 (13.6-17.5)	0.7 (0.4-1.2)	2.1 (1.5-2.8)
< 40	21.2 (20.2-22.3)	6.2 (5.8-6.6)	2.9 (2.5-3.3)	12.8 (12-13.6)	0.9 (0.7-1.1)	5.6 (5.1-6)
40-64	23.8 (23-24.6)	10.4 (9.9-10.8)	2.3 (2-2.5)	9.5 (9-10.1)	0.6 (0.5-0.8)	4 (3.7-4.4)
65+	32.4 (27.6-38)	22.9 (19.4-27.1)	0.4 (0.1-1.7)	4.7 (3.2-7.1)	0.6 (0.5-0.8)	1.1 (0.5-2.4)
Male	21.9 (21.2-22.7)	8.8 (8.5-9.2)	2.6 (2.3-2.9)	10.9 (10.4-11.5)	0.7 (0.6-0.9)	4.7 (4.4-5)
Female	25.5 (24.3-26.7)	9.2 (8.6-9.8)	2.1 (1.8-2.5)	9.9 (9.2-10.7)	0.7 (0.5-0.9)	4.3 (3.9-4.7)
White	22.6 (20.2-25.3)	10.4 (9-11.9)	3.6 (2.7-4.9)	12 (10.2-14.2)	1.4 (0.9-2.3)	7.9 (6.6-9.6)
AA	23.1 (22.4-23.8)	8.9 (8.5-9.2)	2.3 (2.1-2.6)	10.4 (9.9-10.8)	0.6 (0.5-0.8)	4.3 (4-4.5)
Hispanic	22.9 (20.4-25.7)	9.1 (7.8-10.6)	2.2 (1.5-3.2)	12.2 (10.4-14.4)	1.1 (0.6-1.8)	5.6 (4.5-6.9)
Other	16.5 (9.8-27.9)	10.8 (6-19.5)	7.2 (3-17.2)	19 (10.5-34.3)	3.7 (1.2-11.5)	5.9 (2.4-14.1)
Northeast	21.9 (20.7-23)	9.1 (8.5-9.7)	2.8 (2.4-3.3)	13.6 (12.6-14.5)	0.9 (0.7-1.2)	4.9 (4.4-5.4)
Midwest	20.6 (18.8-22.5)	8.2 (7.3-9.2)	2.9 (2.2-3.7)	9.8 (8.6-11.2)	1 (0.6-1.5)	5.3 (4.5-6.2)
South	24.3 (23.4-25.2)	8.9 (8.5-9.4)	2 (1.7-2.3)	9.4 (8.8-9.9)	0.6 (0.4-0.7)	4.3 (4-4.6)
West	17 (14.7-19.7)	9 (7.6-10.8)	5.4 (4.1-7.2)	13.5 (11.2-16.2)	1.1 (0.6-2)	4.7 (3.6-6.1)

Chapter 5

End Stage Renal Disease from Lupus Nephritis

In parallel with developments in immunosuppressive treatments for glomerulonephritis, has the incidence of ESRD from Lupus Nephritis changed over time?

Reference:

ESRD from lupus nephritis in the United States, 1995-2010. Sexton DJ, Reule S, Solid C, Chen SC, Collins AJ, Foley RN. Clin J Am Soc Nephrol. 2015 Feb 6;10(2):251-9. doi: 10.2215/CJN.02350314. Epub 2014 Dec 22.

End-Stage Renal Disease From Lupus Nephritis in the United States, 1995 to 2010

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Running title: ESRD From Lupus Nephritis

Key words: End-stage renal disease, epidemiology, lupus nephritis,

Word count: abstract, 250; text, 2073.

This study was supported by the United States Renal Data System, Minneapolis Medical Research Foundation, Minneapolis, Minnesota, USA. The authors report no conflicts of interest with the subject matter of this manuscript.

Abstract

Background and objectives: While the burden of end-stage renal disease (ESRD) from lupus nephritis in the US increased between the mid-1990s and mid-2000s and therapeutic approaches continue to evolve, current trends are unknown. We aimed to enumerate national trends in ESRD due to lupus nephritis, 2001-2010.

Design, setting, participants, and measurements: In this retrospective cohort study, we examined United States Renal Data System data (n = 1,069,343), 2001-2010, to calculate incidence rates and outcomes of ESRD from lupus nephritis treated with renal replacement therapy (n = 10,968).

Results: ESRD rates from lupus nephritis in 2001-2002 were 3.7 per million per year in the overall population, and higher among blacks (14.1), women (5.9), Hispanics (4.8), and patients aged 20-29 (4.2), 30-45 (5.6), and 45-64 (5.0) years. Standardized incidence ratios declined between 2001-2002 and 2009-2010 in the overall population (ratio 0.88), and among patients aged 45-64 and ≥ 65 years, women, whites, and Hispanics. Over 4.1 years of follow-up, overall mortality rates were equivalent in lupus nephritis patients and matched controls (8.1 vs. 8.1 per 100 person-years, P = 0.91). Adjusted hazards ratios for mortality were highest for ages 45-64 (2.04 vs. age 20-39 years) and ≥ 65 (4.7) years, and drug (2.36) and alcohol (2.05) abuse. Mortality declined over time, but rates of renal transplant also declined, and outcomes exhibited racial heterogeneity.

Conclusions: ESRD from lupus nephritis declined in the US in the past decade. While mortality rates on renal replacement therapy are high, several modifiable risk associations were apparent.

Introduction

Glomerulonephritis, which can be expected in 40% to 75% of patients with systemic lupus erythematosus (SLE), has ominous implications.[1;2] In this regard, therapeutic approaches to lupus nephritis have evolved substantially in the last three decades, and experimental evidence supports the use of many agents in both the induction and maintenance of remission.[3] While a wide array of agents (including cyclophosphamide,[3-6] systemic corticosteroids,[3;4] mycophenolate mofetil,[7-9] azathioprine,[10;11] and calcineurin inhibitors[12]) have been assessed, trial designs have generally relied on changes in urinary protein and glomerular filtration rates (GFRs) as primary outcomes, as opposed to end-stage renal disease (ESRD).[13] As management of lupus nephritis has continued to evolve throughout the past decade, and a previous study showed that the burden of ESRD from lupus nephritis increased between the mid-1990s and mid-2000s in several important subsets of the US population,[14] up-to-date information appears warranted. Hence, we set out to enumerate national trends in ESRD due to lupus nephritis between 2001 and 2010.

Materials and Methods

Objectives

The principal objectives of this study were to evaluate trends in standardized incidence ratios, relative to rates in 2001-2002, of ESRD due to SLE necessitating renal replacement therapy (RRT), in the US between 2001 and 2010. Regarding clinical outcomes after inception of RRT, we set out to compare rates of wait-listing for renal transplant, renal transplant, and death in matched patients with and without SLE, and to calculate hazards ratios for these outcomes among patients with SLE.

Subjects

In this retrospective study, we used United States Renal Data System (USRDS) standard analytical files to study US patients who initiated maintenance RRT between 2001 and 2010 (n = 1,069,343). Baseline characteristics at initiation of RRT were determined from the Centers for Medicare & Medicaid (CMS) Medical Evidence Report (form CMS-2728). By federal requirement, this form must be submitted for all new maintenance RRT patients in the US, and resultant data are housed in the USRDS Medevid95 and Medevid05 files. The Medical Evidence Report has changed twice in the past two decades, in 1995 and 2005. Unlike previous iterations, the 2005 version includes information about predialysis nephrologist care and vascular access at initiation of hemodialysis. In both versions, one of 82 causes is entered as the primary cause of ESRD, with identical options in the 1995 and 2005 versions. For this study, cases of ESRD due to SLE were those with the primary cause of ESRD listed as "Lupus erythematosus, (SLE nephritis)" in the Medical Evidence Report. Dates of death and first renal transplant were obtained from the Patients file, and first wait-listing for transplant was determined from the Waitlist_ki and Waitlist_kp files.

Analysis

US census data were used for population denominators for the years examined, with age in 5-year increments and race/ethnicity classified as non-Hispanic white, non-Hispanic black, Hispanic, and other.[15;16] The Poisson distribution was used to compute incidence rates of RRT-requiring ESRD due to SLE. For computation of standardized incidence ratios, expected incidence rates were calculated by applying incidence rates in 2001-2002 for each individual permutation of age, sex, and race/ethnicity to the corresponding subgroup of the US population

in subsequent 2-year periods. Chi-square analysis was used for unadjusted comparisons of patients with and without ESRD due to SLE, and logistic regression was used for adjusted comparisons. For comparisons of clinical outcomes of patients with and without SLE, patients were matched according to age (in 1-year intervals), sex, race, and ethnicity. Poisson regression was used to compute incidence rates and adjusted hazards ratios (AHRs) for events occurring after initiation of RRT, with follow-up ending on June 30, 2011. SAS, v9.1.3 (Cary, North Carolina) was used for data analysis. Since Hispanic ethnicity is an important demographic in the US, and was included on form CMS-2728 only in 2000, we restricted our analysis to 2001-2010. However, for the purposes of validation, we extended our analysis back to 1995 and found similar trends; these results are not presented.[17]

Results

In 2001-2002, 2101 patients began RRT because of lupus nephritis, a rate of 3.7 cases per million per year (Table 1); rates were higher for non-Hispanic black race/ethnicity (14.1); female sex (5.9); ages 20-29 (4.2), 30-44 (5.6), and 45-64 (5.0) years, and Hispanic ethnicity (4.8). Overall standardized incidence ratios declined between 2001-2002 and 2009-2010 (ratio 0.88), with a statistically significant decline apparent after 2008. Standardized incidence ratios fell between the first and last biennium in groups with the following characteristics: age 45-64 years (ratio 0.82), age ≥ 65 years (0.67), female sex (0.88), non-Hispanic white race/ethnicity (0.80), and Hispanic ethnicity (0.80).

After adjustment for age, sex, race, and ethnicity, associations of ESRD from SLE at baseline (Table 2) included initiation of RTT in 2001-2005; age 20-29 years; female sex; black race; other race; Hispanic ethnicity; absence of ischemic heart disease, diabetes, alcohol abuse,

and drug abuse; catheters for hemodialysis; longer duration of nephrologist care; higher estimated GFR; lower body mass index; and lower serum albumin and hemoglobin levels. Ranked by magnitude, adjusted odds ratios (AORs) for SLE were highest for female sex (6.09), black race (2.03 vs. white), and Hispanic ethnicity (1.48). AORs were lowest for age ≥ 65 years (0.02 vs. 20-29 years), diabetes (0.12), and drug abuse (0.41).

Over a mean follow-up of 4.1 years, 44% of lupus nephritis patients were listed for transplant, 23.8% underwent transplant, and 33.1% died. Figure 1 and supplemental Table S1 show rates for each of these outcomes in patients with SLE and in a matched cohort of patients without SLE. Rates of wait-listing were higher in the SLE cohort, overall (17.5 vs. 12.8 per 100 person-years, $P < 0.001$), and in most subgroups studied, with the exception of race/ethnicity classified as Hispanic (18.5 vs. 17.3 per 100 person-years, $P = 0.16$) and other (23 vs. 25.4 per 100 person-years, $P = 0.2$). Table 3 shows AHRs for listing for the SLE population; factors associated with listing included age 30-44 (1.13), other race (1.17), and peritoneal dialysis (1.6). Factors associated with a lower likelihood of listing included age ≥ 65 years (AHR 0.19 vs. 20-29 years), drug abuse (0.2), and alcohol abuse (AHR 0.32).

Rates of renal transplant were slightly higher in the SLE cohort, overall (7.8 vs. 7 per 100 person-years, $P < 0.001$), and in all subgroups studied, with the exception of race/ethnicity classified as Hispanic (7.7 vs. 8.1 $P = 0.49$) and other (9.1 vs. 10.3 per 100 person-years, $P = 0.21$) (Figure 1). In the first year after RRT initiation, renal transplant rates were equivalent in SLE and matched controls without SLE (6.7 vs. 6.7 per 100 person-years, $P = 0.96$). Table 3 shows AHRs for renal transplant for the SLE population; factors associated with a lower likelihood of renal transplant included initiation of RRT in 2006-2010; age < 20, 45-64, or ≥ 65 years; female sex, black or other race; Hispanic ethnicity; ischemic heart disease; diabetes; drug

abuse, arteriovenous graft or venous catheter for hemodialysis access; nephrology care for ≤ 12 months, GFR > 15 mL/min/1.73 m^2, body mass index ≥ 30 kg/m^2, and serum albumin < 3.5 g/dL. Regarding absolute size, AHRs were lowest for drug abuse (0.11), age ≥ 65 years (0.21 vs. 20-39 years), and GFR > 15 mL/min/1.73 m^2 (0.51).

Mortality rates were similar overall (8.1 vs. 8.1 per 100 person-years, $P = 0.91$) and within most predefined subgroups except age < 20 (5 vs. 2.6 per 100 person-years, $P < 0.001$) and 20-29 (5.3 vs. 4.2, per 100 person-years, $P < 0.001$) years, which were higher than matched controls, and white race (9.6 vs. 11.1 per 100 person-years, $P < 0.001$) which was lower than matched controls. In the first year after RRT initiation, mortality rates were higher in SLE patients than in non-SLE matched controls overall (12.5 vs. 10.9 per 100 person-years, $P = 0.001$) and in subgroups characterized by age < 20 (6.6 vs. 3.5 per 100 person-years, $P = 0.01$), 20-29 (7.9 vs. 6.2 per 100 person-years, $P = 0.03$), and ≥ 65 (41.9 vs. 34.1 per 100 person-years, $P = 0.02$) years; female sex (12.6 vs. 10.7 per 100 person-years, $P = 0.001$); non-Hispanic black race/ethnicity (12.9 vs. 10.9 per 100 person-years, $P = 0.004$); and Hispanic ethnicity (8.3 vs. 5.9 per 100 person-years, $P = 0.008$). This pattern of higher mortality in SLE patients in the first year after RRT initiation dissipated by the second year. Table 3 shows AHRs for death for patients with ESRD from SLE; factors associated with death included RRT initiation in 2001-2005, older age, black race, non-Hispanic ethnicity, ischemic heart disease, diabetes, alcohol abuse, drug abuse, hemodialysis as mode of RRT, catheters for hemodialysis, higher estimated GFR, and lower serum albumin and hemoglobin levels. Regarding absolute size, factors associated with the highest AHRs for death were age ≥ 65 years (4.7 vs. 20-29 years), drug abuse (2.36), and alcohol abuse (2.05). Factors associated with the lowest risk included pre-emptive transplant (AHR 0.11 vs. hemodialysis), other race/ethnicity (0.76), and Hispanic ethnicity (0.78).

Discussion

We found that standardized incidence ratios of ESRD from lupus nephritis in the US remained static throughout most of the last decade, with an apparent decline in 2009-2010. Groups for whom incidence declined included middle and older age groups, women, and Hispanic and non-Hispanic white race/ethnicity; incidence was stagnant for black race. Costenbader and colleagues examined similar issues in the US from 1995 to 2006.[14] However, this study showed increasing standardized incidence rates for age < 40 years, both sexes, and African American race, and statistically similar ratios for age ≥ 40 years, white race, and Hispanic ethnicity.[14] Although Hispanic ethnicity represented 16.7% of the US total population as of 2011, it was included on form CMS-2728 only in 2000.[17] Since Hispanic ethnicity is associated with higher prevalence of lupus nephritis, and higher and more rapid progression to ESRD, we considered it imperative to include this demographic and to report a uniform race/ethnicity comparison.[17-19]

While it is tempting to hypothesize that the salutary trends in lupus nephritis-related RRT may reflect more widespread use of treatments with proven efficacy for proximate outcomes, the non-experimental design of our study precludes a definitive answer. Attempting to ascribe these temporal trends to a particular intervention is difficult; however, outlining the chronology of major developments in treatment may be helpful.

Controlled trials of intravenous cyclophosphamide, corticosteroids, and azathioprine in lupus nephritis patients began in the 1970s and continued through the 1980s.[3] While efforts to refine these regimes continued in the 1990s and 2000s, cyclophosphamide-related toxicity prompted study of alternative agents.[4-6] Mycophenolate was granted US Food and Drug Administration approval for the prevention of renal allograft rejection in 1995, after which

studies in lupus nephritis began to emerge.[20;21] The first notable study comparing mycophenolate to cyclophosphamide and azathioprine in lupus nephritis patients was reported in 2000, and further studies followed suggesting superiority in remission induction with an improved safety profile.[7;9;22] In 2004, Contreras et al found that oral mycophenolate or azathioprine was more effective and safer than long-term intravenous cyclophosphamide in maintaining remission.[11] Use of these oral therapies may have become more widespread following this study.[22;23,25] Although randomized trials of calcineurin inhibitors have reported some success in lupus nephritis beginning in 1998, their main role appears to be as part of a multi-target therapy.[12;24;25]

In theory, declines in the population-level burden of SLE, the risk of lupus nephritis among patients with SLE, and the risk of ESRD among patients with lupus nephritis, could all lead to the apparently salutary trends seen in this study. Unfortunately there is no SLE-specific population denominator in the US over the same period.[14] Difficulties in defining this denominator include inability to identify milder cases or account for sampling disparities in race/ethnicity and access to medical care.[26] Furthermore, improved detection of SLE over time confounds comparisons of recent incidence rates to earlier studies.[27-29] There is an analogous lack of data from large representative lupus nephritis cohorts on trends in progression to ESRD over the study period.

Our study has several limitations, including a retrospective registry-based design and lack of information on renal pathology, severity of disease, and medication in the general population.

Despite its limitations, our study provides some useful information. While research efforts to develop alternative efficacious treatments with fewer side effects[13;30] are clearly needed, it is encouraging that rates of RRT from lupus nephritis are no longer accelerating, and may be declining. Configuration of nephrology care may also be important, with length of

predialysis nephrology care, smoking, substance abuse, body mass index, and mode of RRT representing potentially modifiable determinants of poorer outcomes.

Disclosures

The authors report no competing financial interests with the subject matter of this manuscript.

Acknowledgments

This study was supported by the United States Renal Data System (USRDS), Minneapolis Medical Research Foundation, Minneapolis, Minnesota, USA. The data reported here have been supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US government. The Irish Nephrology Society research bursary funded Dr. Donal Sexton. The authors thank Chronic Disease Research Group colleagues Beth Forrest for regulatory assistance, Delaney Berrini, BS, for manuscript preparation, and Nan Booth, MSW, MPH, ELS, for manuscript editing.

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Table 1. Standardized Incidence Ratios of RRT-Requiring ESRD Due to Systemic Lupus Erythematosus, 2001-2010

Biennium	2001-2002	2003-2004		2005-2006		2007-2008		2009-2010	
US population/biennium	286,000,000	291,000,000		297,000,000		303,000,000		308,000,000	
ESRD cases	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected	Observed
All	2101	2170	2249	2242	2246	2312	2268	2380	2103
Age, years									
< 20	343	356	390	367	401	377	413	389	370
20-29	143	148	173	156	166	162	154	164	142
30-44	950	956	1032	965	988	976	1030	984	968
45-64	772	816	808	858	790	883	796	904	744
≥ 65	261	271	259	282	246	302	251	325	218
Sex									
Men	369	381	445	395	420	407	413	419	384
Women	1732	1789	1804	1847	1826	1905	1855	1961	1719
Race/ethnicity									
Non-Hispanic white	628	633	622	637	566	642	558	646	519
Non-Hispanic black	989	1015	1124	1042	1073	1067	1107	1092	1027
Hispanic	360	389	361	419	417	450	445	481	383
Other	124	133	142	143	190	153	158	161	174

	Rate	Standardized Incidence ratios, vs 2001-2002			
All	3.7 (0.1)	1.04 (0.02)	1 (0.02)	0.98 (0.02)	0.88 (0.02)[b]
Age, years					
< 20	0.2 (0)	1.34 (0.23)	1.24 (0.22)	1.14 (0.21)	1.07 (0.21)
20-29	4.2 (0.2)	1.09 (0.06)	1.09 (0.05)	1.09 (0.05)	0.95 (0.05)
30-44	5.6 (0.2)	1.08 (0.03)	1.02 (0.03)	1.06 (0.03)	0.98 (0.03)
45-64	5 (0.2)	0.99 (0.03)	0.92 (0.03)	0.9 (0.03)	0.82 (0.03)[b]
≥ 65	2.8 (0.2)	0.95 (0.06)	0.87 (0.06)	0.83 (0.05)	0.67 (0.05)[b]
Sex					
Men	1.3 (0.1)	1.17 (0.06)	1.06 (0.05)	1.01 (0.05)	0.92 (0.05)
Women	5.9 (0.1)	1.01 (0.02)	0.99 (0.02)	0.97 (0.02)	0.88 (0.02)[b]
Race/ethnicity					
Non-Hispanic white	1.6 (0.1)	0.98 (0.04)	0.89 (0.04)	0.87 (0.04)	0.8 (0.04)[b]

Non-Hispanic black	14.1 (0.5)	1.11 (0.03)	1.03 (0.03)	1.04 (0.03)	0.94 (0.03)
Hispanic	4.8 (0.3)	0.93 (0.05)	0.99 (0.05)	0.99 (0.05)	0.8 (0.04)[a]
Other	3.6 (0.3)	1.07 (0.09)	1.33 (0.1)	1.03 (0.08)	1.08 (0.08)

Note: Parameter estimates are either rates per million per year or standardized incidence ratios (standardized to 2001-2002) with 95% confidence intervals in parentheses. With PE denoting Point Estimate, CL Confidence Limit, Obs Observed Incidence Rate, Exp Expected Incidence Rate from rates seen in 2001-2002, standardized incidence ratios were calculated and reported as [PE_{Obs}/PE_{Exp}] ([5% CL_{Obs}/PE_{Exp}]- [95% CL_{Obs}/PE_{Exp}]). *P* values refer to comparisons of observed rates and expected rates when rates seen in 2001-2002 were applied to the years under consideration. *P* ≥ 0.05 unless otherwise indicated. [a] $0.01 \leq P$ value < 0.05, [b] $0.001 \leq P$ value < 0.01 and [c] P value ≤ 0.001.

ESRD, end-stage renal disease; RRT, renal replacement therapy.

Table 2. Baseline Characteristics at RRT Initiation (*n* = 1,069,343)

Characteristic	SLE	No SLE	
n	10,968	1,058,375	AOR SLE
Year of first RRT			
2001-2005	49.9	47.5	1 (Reference)[c]
2006-2010	50.1	52.5	0.94 (0.9-0.98)
Age, years			
< 20	7.1	1.1	0.7 (0.64-0.76)
20-29	23.2	2.3	1 (Reference)
30-44	33.9	9.8	0.35 (0.34-0.37)
45-64	28.7	37.3	0.08 (0.07-0.08)
≥ 65	7.1	49.5	0.02 (0.01-0.02)
Sex			
Male	18.5	55.9	1 (Reference)
Female	81.5	44.1	6.09 (5.8-6.39)
Race			
White	42.3	65.8	1 (Reference)
Black	49.3	28.2	2.03 (1.94-2.12)
Other	8.4	6.1	1.52 (1.41-1.64)
Hispanic ethnicity			
No	82.1	86.6	1 (Reference)
Yes	17.9	13.4	1.48 (1.4-1.56)
Ischemic heart disease			
No	93.8	76.3	1 (Reference)
Yes	6.2	23.7	0.59 (0.55-0.64)
Cerebrovascular disease			
No	94.8	90.6	1 (Reference)[a]
Yes	5.2	9.4	1 (0.89-1.13)
Peripheral vascular disease			
No	96.7	86	1 (Reference)
Yes	3.3	14	0.48 (0.43-0.54)
Smoking			
No	95.7	93.8	1 (Reference)
Yes	4.3	6.2	0.64 (0.57-0.73)
Diabetes			
No	90.4	47.6	1 (Reference)
Yes	9.6	52.4	0.12 (0.11-0.12)
Alcohol abuse			
No	99.4	98.5	1 (Reference)
Yes	0.6	1.5	0.45 (0.35-0.58)
Drug abuse			
No	99.1	98.8[c]	1 (Reference)
Yes	0.9	1.2	0.41 (0.33-0.5)
Mode of RRT			
Hemodialysis	86.7	91.5	1 (Reference)[a]
Peritoneal dialysis	10.1	6.6	1.02 (0.95-1.09)
Preemptive transplant	3.2	1.9	0.89 (0.79-0.99)

Initial hemodialysis access			
Fistula	7.8	13.9	1 (Reference)
Graft	2.8	3.6	1.02 (0.84-1.23)
Catheter	89.4	82.5	1.34 (1.21-1.48)
Prior nephrology care, mo.			
> 12	31.5	24.1	1 (Reference)
≤ 12	68.5	75.9	0.6 (0.57-0.64)
GFR, mL/min/1.73 m^2			
≤ 15	86.8	87.5[b]	1 (Reference)
> 15	13.2	12.5	1.32 (1.24-1.4)
Body mass index, kg/m^2			
< 30	75.5	66.4	1 (Reference)
≥ 30	24.5	33.6	0.5 (0.48-0.52)
Albumin, g/dL			
≥ 3.5	26.9	35	1 (Reference)
< 3.5	73.1	65	1.43 (1.37-1.51)
Hemoglobin, g/dL			
< 9	38.9	25.6	1 (Reference)
≥ 9	61.1	74.4	0.83 (0.79-0.86)

Note: Parameter estimates are presented as column percentages or odds ratios with 95% confidence intervals in parentheses. As data fields for predialysis vascular access for hemodialysis and predialysis nephrology care were only available in the 2005 version of the Medical Evidence Report, the denominators for these variables consisted of 53.4% of the study population for whom the 2005 version of the form was completed. Missing data: GFR, 0.6%; BMI, 1.4%; albumin, 24.5%; prior nephrology care, mths. 40.9%, hemoglobin, 8.3%. AOR, adjusted (for age, sex, race, ethnicity) odds ratio; GFR, glomerular filtration rate; RRT, renal replacement therapy; SLE, systemic lupus erythematosus. *P* Values < 0.001 throughout for comparisons of presence or absence of SLE unless otherwise stated;

a P value ≥ 0.05.

b 0.01 ≤ P value < 0.05.

c 0.001 = P value < 0.01.

Table 3. Adjusted Hazards Ratios for Outcomes on RRT, Patients with Systemic Lupus Erythematosus (*n* = 10,968)

Variable	Reference	Outcomes		
		AHR Death	AHR Listing	AHR Transplant
	%/Yrs. Follow-up	33.1 %/4.1 years	44 %/2.3 years	23.8 %/3.2 years
Initial RRT 2006-2010	2001-2005	0.83 (0.77-0.89)	0.97 (0.91-1.03)[a]	0.88 (0.81-0.96)[c]
Age < 20 yrs.	Age 20-29 yrs.	1.11 (1-1.23)[b]	0.94 (0.87-1.01)[a]	0.84 (0.76-0.93)
Age 30-44 yrs.	Age 20-29 yrs.	0.96 (0.81-1.13)[a]	1.13 (1.02-1.27)[b]	1.21 (1.05-1.39)[c]
Age 45-64 yrs.	Age 20-29 yrs.	2.04 (1.85-2.25)	0.65 (0.59-0.71)	0.66 (0.6-0.74)
Age ≥ 65 yrs.	Age 20-29 yrs.	4.7 (4.16-5.3)	0.19 (0.15-0.24)	0.21 (0.15-0.28)
Female sex	Male	0.97 (0.89-1.05)[a]	0.99 (0.92-1.07)[a]	0.91 (0.82-1)[b]
Black race	White	1.18 (1.1-1.28)	1.05 (0.97-1.13)[a]	0.55 (0.5-0.6)
Other race	White	0.76 (0.66-0.88)	1.17 (1.05-1.31)[c]	0.77 (0.67-0.88)
Hispanic ethnicity	Non-Hispanic	0.78 (0.7-0.87)	1.03 (0.95-1.13)[a]	0.66 (0.59-0.74)
Ischemic heart disease	Absent	1.52 (1.37-1.7)	0.76 (0.64-0.9)[c]	0.73 (0.58-0.91)[c]
Cerebrovascular disease	Absent	1.26 (1.04-1.52)[b]	0.65 (0.51-0.82)	0.55 (0.39-0.79)[c]
Peripheral vascular disease	Absent	1.85 (1.61-2.13)	0.72 (0.57-0.9)[c]	0.66 (0.48-0.91)[c]
Smoking	Absent	1.53 (1.25-1.87)	0.64 (0.5-0.83)	0.59 (0.41-0.86)[c]
Diabetes mellitus	Absent	1.41 (1.28-1.56)	0.73 (0.64-0.82)	0.6 (0.5-0.72)
Alcohol abuse	Absent	2.05 (1.48-2.84)	0.32 (0.15-0.68)[c]	0.55 (0.25-1.24)[a]
Drug abuse	Absent	2.36 (1.79-3.1)	0.2 (0.11-0.39)	0.11 (0.03-0.43)[c]
Peritoneal dialysis	Hemodialysis	0.71 (0.63-0.79)	1.6 (1.46-1.75)	1.67 (1.51-1.86)
Preemptive transplant	Hemodialysis	0.11 (0.07-0.18)	-	-
Graft	Fistula	1.16 (0.87-1.54)[a]	0.82 (0.61-1.12)[a]	0.53 (0.32-0.88)[b]
Catheter	Fistula	1.09 (1.01-1.17)[b]	0.94 (0.88-1)[a]	0.8 (0.73-0.87)
Nephrology care ≤ 12 mo.	> 12	1.06 (0.98-1.14)[a]	0.88 (0.83-0.94)	0.72 (0.66-0.79)
GFR > 15 mL/min/1.73 m^2	≤ 15	1.39 (1.26-1.53)	0.61 (0.55-0.68)	0.51 (0.44-0.59)
Body mass index ≥ 30 kg/m^2	< 30	0.94 (0.87-1.01)[a]	0.86 (0.8-0.92)	0.74 (0.67-0.82)
Albumin < 3.5 g/dL	≥ 3.5	1.34 (1.26-1.44)	0.95 (0.89-1.01)[a]	0.87 (0.8-0.94)
Hemoglobin ≥ 9 g/dL	< 9.0	0.93 (0.87-0.99)[b]	0.96 (0.91-1.02)[a]	1.07 (0.99-1.16)[a]

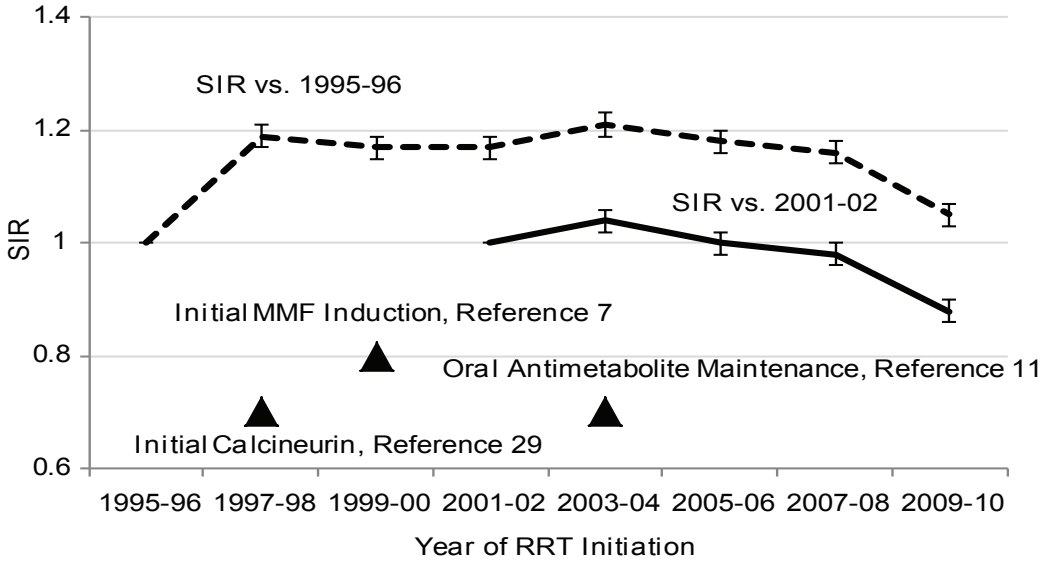
Hazards ratios are adjusted for age, sex, race, and ethnicity, and are presented with 95% confidence intervals in parentheses.

AHR, adjusted hazards ratio; GFR, glomerular filtration rate; RRT, renal replacement therapy.

Figure Legend

Figure 1. Trends in the burden of end-stage lupus nephritis in the United States, with incidence ratios standardized (by age, sex, and race) against the 1995–1996 biennium. Dark triangles indicate the chronology of notable randomized intervention studies. Error bars refer to 95% confidence intervals around the standardized incidence ratios (SIRs). MMF, mycophenolate mofetil.

Figure 1.


1.4
1.2
1
0.8
0.6
SIR
SIR vs. 1995-96
SIR vs. 2001-02
Initial MMF Induction, Reference 7
Oral Antimetabolite Maintenance, Reference 11
Initial Calcineurin, Reference 29
1995-96
1997-98
1999-00
2001-02
2003-04
2005-06
2007-08
2009-10
Year of RRT Initiation

Chapter 6

ESRD from HUS in the US

Eculizumab was approved by the FDA in 2012. What are the trends in ESRD from Hemolytic uremic syndrome prior to the introduction of this disease modifying drug?

Reference:

End-stage renal disease from hemolytic uremic syndrome in the United States, 1995-2010. Sexton DJ, Reule S, Solid CA, Chen SC, Collins AJ, Foley RN.
Hemodial Int. 2015 Oct;19(4):521-30. doi: 10.1111/hdi.12281. Epub 2015 Feb 17.

End-Stage Renal Disease from Hemolytic Uremic Syndrome in the United States, 1995 to 2010

Running head: ESRD from Hemolytic Uremic Syndrome

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Abstract

Background: Management of hemolytic uremic syndrome (HUS) has evolved rapidly, and optimal treatment strategies are controversial. However, it is unknown whether the burden of end-stage renal disease (ESRD) from HUS has changed, and outcomes on dialysis in the US are not well described.

Methods: We retrospectively examined data for patients initiating maintenance renal replacement therapy (RRT) (n = 1,557,117), 1995-2010, to define standardized incidence ratios (SIRs) and outcomes of ESRD from HUS) (n = 2241).

Results: Overall ESRD rates from HUS in 2001-2002 were 0.5 cases/million per year; and were higher for patients characterized by age 40-64 years (0.6), ≥ 65 years (0.7), female sex (0.6), and non-Hispanic African American race (0.7). SIRs remained unchanged ($P \geq 0.05$) between 2001-2002 and 2009-2010 in the overall population. Compared with patients with ESRD from other causes, patients with HUS were more likely to be younger, female, white, and non-Hispanic. Over 5.4 years of follow-up, HUS patients differed from matched controls with ESRD from other causes by lower rates of death (8.3 per 100 person-years in cases vs. 10.4 in controls, $P < 0.001$), listing for renal transplant (7.6 vs. 8.6 per 100 person-years, $P = 0.04$), and undergoing transplant (6.9 vs. 9 per 100 person-years, $P < 0.001$).

Conclusions: The incidence of ESRD from HUS appears not to have risen substantially in the last decade. However, given that HUS subtypes could not be determined in this study, these findings should be interpreted with caution.

Keywords: Dialysis outcomes, hemolytic uremic syndrome, incidence.

Introduction

Hemolytic uremic syndrome (HUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal dysfunction.[1;2] Shiga-toxin-producing Escherichia coli are thought to be responsible for 90% of cases, particularly in children, with the remaining cases attributable to a variety of disorders including among others; genetic defects in complement proteins, pneumococcal or other systemic infections, disseminated intravascular coagulation, hematopoietic stem cell therapy, certain medications and underlying autoimmune conditions.[1-8] This heterogeneity should be noted when considering trends in ESRD from HUS.

The term atypical HUS (aHUS) generally refers to cases not caused by Shiga toxin.[2] Estimated annual incidence of HUS due to genetic defects in regulatory complement proteins is approximately 2 per million in the general population, and progression to ESRD is thought to occur in up to 50% of patients. [3,8] In contrast, risk of subsequent ESRD development due to Shiga-toxin-associated HUS is thought to be low. [9] Renal pathology in HUS usually demonstrates thrombotic microangiopathy consisting of widening of the sub-endothelial space and microvascular thrombosis.

The mainstay of therapy for HUS varies with cause; it consists of a combination of plasma exchange, plasma infusion, immunosuppression, liver-kidney transplant, and novel therapies such as Eculizumab. [10-12]

For clinicians confronted with a management issue as thorny as that related to ESRD from HUS, information about the prognosis following institution of renal replacement therapy (RRT) could be informative. In addition, from a public health perspective, information about national trends in disease burden might also be relevant, not least because some treatment options are costly. Surprisingly, few if any current clinical epidemiological studies of ESRD

from HUS in the United States are available. Hence, we primarily set out to describe the incidence and outcomes of ESRD from HUS between 2001 and 2010 and secondarily between 1995 and 2010.

Materials and Methods

Objectives

The principal objectives of this study were to evaluate trends in standardized incidence ratios, relative to rates in 2001-2002, of ESRD from HUS necessitating RRT in the US between 2001 and 2010. We were secondarily interested in studying standardized incidence ratios relative to rates in 1995-1996. Regarding clinical outcomes after RRT initiation, we set out to quantify rates of death, listing for renal transplant, and renal transplant.

Subjects

In this retrospective study, we examined data for patients initiating maintenance RRT (n = 1,557,117) between 1995 and 2010. Baseline characteristics at RRT initiation were determined from the Centers for Medicare & Medicaid (CMS) Medical Evidence Report (form CMS-2728). By federal requirement, this form must be submitted for all new patients starting RRT in the US, and resultant data are housed in the United States Renal Data System Medevid95 and Medevid05 files. The Medical Evidence Report form changed twice in the past two decades, in 1995 and 2005. Unlike previous iterations, the 2005 version includes information about predialysis nephrologist care and vascular access for hemodialysis. On both versions, one of 82 causes is entered as the primary cause of ESRD, with identical options on the 1995 and 2005 versions. For this study, cases of ESRD from HUS were those with the primary cause of ESRD listed as "hemolytic uremic syndrome" in the Medical Evidence Report. Dates of death and first renal

transplant were obtained from the Patients file, and first listing for transplant was determined from the Waitlist_ki and Waitlist_kp files.

Analysis

US census data were used for population denominators for the years examined, with age in 5-year increments. Hispanic ethnicity has been routinely incorporated in US census documentation only since 2000; therefore, we performed two separate race/ethnicity analyses. Using rates in the 2001-2002 biennium for standardization, we accounted for Hispanic ethnicity and designated four race/ethnicity categories: non-Hispanic white, non-Hispanic African American, Hispanic, and other. For the analysis standardized against rates in the 1995-1996 biennium, we included three race categories: white, African American, and other. [13,14] The Poisson distribution was used to compute incidence rates of RRT-requiring ESRD from HUS. For computation of standardized incidence ratios, expected incidence rates were calculated by applying incidence rates in 2001-2002 and 1995-1996 separately for each individual permutation of age, sex, and race/ethnicity to the corresponding subgroup of the US population in subsequent 2-year periods. Chi-square analysis was used for unadjusted comparisons of patients with and without ESRD from HUS, and logistic regression was used for adjusted comparisons. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to estimate glomerular filtration rate at RRT initiation. For comparisons of clinical outcomes of patients with and without HUS, patients were matched according to year of RRT initiation (in 1-year intervals), age (in 1-year intervals), sex, race, and ethnicity. Poisson regression was used to compute incidence rates and proportional hazards regression to compute adjusted hazards ratios (AHRs) for events occurring after inception of RRT, with follow-up ending on June 30, 2011. SAS, v9.1.3 (SAS Institute, Inc., Cary, North Carolina) was used for data analysis.

Results

In 2001 and 2002, 287 patients began RRT because of ESRD from HUS, a rate of 0.5 cases per million per year (Table 1); similar or higher rates were seen with age younger than 5 years (0.5 per million per year), 40-64 years (0.6 per million per year), and 65 years or older (0.7 per million per year); female sex (0.6 per million per year); and non-Hispanic African American race (0.7 per million per year). Standardized incidence ratios remained unchanged ($P \geq 0.05$) between 2001-2002 and 2009-2010 in the overall population and in each subgroup studied (Table 1 and Figure 1).

In 1995 and 1996, 254 patients began RRT because of ESRD from HUS, a rate of 0.5 cases per million per year (Table 1); similar or higher rates were seen with age 40-64 years (0.5 per million per year) and 65 years or older (0.9 per million per year), female sex (0.6 per million per year), white race (0.5 per million per year), and African American race (0.6 per million per year). Standardized incidence ratios remained unchanged ($P \geq 0.05$) between 1995-1996 and 2009-2010 in the overall population (Table 1) and in each subgroup studied except female sex, for whom ratios fell to 0.74 by the 2009-2010 biennium.

In comparison to patients with ESRD from other causes, patients with ESRD from HUS were more likely to be characterized by (Table 2) age younger than 5 years (7.5% vs. 0.2% of patients with ESRD from other causes) and 5-19 years (10.2% vs. 1%), female sex (64.3% vs. 45.1%), white race (78.5% vs. 65.2%), and catheter use for hemodialysis (95.9% vs. 82.6%). After adjustment for age, sex, race, and ethnicity, associations of ESRD from HUS at baseline included RRT initiation in 1995-2000, younger age, female sex, white race, non-Hispanic ethnicity, hemodialysis as initial mode of RRT, venous catheters for hemodialysis vascular

access, shorter predialysis nephrology care, lower body mass index, lower serum albumin, lower serum hemoglobin, and absence of vascular disease. Ranked by magnitude, adjusted odds ratios (AORs) for HUS were 2.0 or higher for age younger than 5 years (AOR 12.85 vs. 20-39 years) and 5-19 years (AOR 3.45 vs. 20-39 years), female sex (AOR 2.45), venous catheter for hemodialysis vascular access (AOR 4.3 vs. fistula), and prior nephrology care for 12 months or less (AOR 3.56). AORs were 0.5 or less for age 40-64 years (AOR 0.32 vs. 20-39 years) and 65 years or older (AOR 0.11 vs. 20-39 years), African American race (AOR 0.35 vs. white race), other race (AOR 0.35), Hispanic ethnicity (AOR 0.27), ischemic heart disease (AOR 0.34), peripheral vascular disease (AOR 0.25), diabetes (AOR 0.11), and body mass index 30 kg/m^2 or higher (AOR 0.47).

Over a mean observation period of 5.4 years, 44.8% of patients with ESRD from HUS died, compared with 51.3 % of matched patients without HUS over 4.95 years. Figure 2 shows mortality rates for ESRD patients with HUS and a matched cohort of ESRD patients without HUS. Overall mortality rates were lower in HUS patients than in controls (8.3 vs. 10.4 per 100 person-years, $P < 0.001$). Among demographic subgroups examined, mortality rates were comparable to rates for controls in many subgroups. However rates were lower for patients with ESRD from HUS who initiated RRT in 1995-2000 (7.5 vs. 10.1 per 100-person years, $P < 0.001$), and for those characterized by age younger than 5 years (1.2 vs. 3.2 per 100-person years, $P = 0.003$), 20-39 years (3.9 vs. 5.4 per 100-person years, $P = 0.005$), 40-64 years (10.7 vs. 12.7 per 100-person years, $P = 0.008$), and 65 years or older (27.1 vs. 37.4 per 100-person years, $P < 0.001$); female sex (8.1 vs. 11.2 per 100-person years, $P < 0.001$); and non-Hispanic white race/ethnicity (8.9 vs. 11.3 per 100-person years, $P < 0.001$). When the comparison was isolated to the first year after RRT initiation, mortality rates were higher in HUS patients than in controls

overall (21.1 vs. 17.9 per 100 person-years, $P = 0.02$), and in patients characterized by RRT initiation between 2001-2005 (21.4 vs. 16.2 per 100-person years, $P = 0.03$), age 40-64 years (25 vs. 17.6 per 100-person years, $P = 0.002$), and female sex (22.2 vs. 18.1 per 100-person years, $P = 0.02$). By year 2 after RRT initiation, mortality rates in HUS patients were comparable overall to controls, and by year 3 were lower (Supplementary Table S1).

Table 3 shows AHRs for death in patients with ESRD from HUS. Regarding absolute size, mortality hazards ratios were 1.5 or greater for age 40-64 years (AHR 2.61 vs. 20-39 years) and age 65 years or older (AHR 5.58 vs. 20-39 years), and 0.67 or less for age younger than 5 years (AHR 0.37 vs. 20-39 years) and 5-19 years (0.39 vs. 20-39 years), peritoneal dialysis (AHR 0.65 vs. hemodialysis), pre-emptive transplant (AHR 0.12 vs. hemodialysis).

Figure 2 shows rates of listing for transplant in patients with ESRD from HUS and in matched controls. Overall listing rates were lower for HUS patients than for controls (7.6 vs. 8.6 per 100 person-years, $P = 0.04$); however, rates were comparable for all subgroups examined except age 5-19 years (10.6 vs. 14.9 per 100-person years, $P = 0.01$) and 20-39 years (8.9 vs. 11.6 per 100-person years, $P = 0.01$). Table 3 shows AHRs for listing for patients with ESRD from HUS. Regarding absolute size, AHRs were 0.67 or less for age 65 years or older (AHR 0.14 vs.< 20-39 years) and diabetes (AHR 0.62).

Overall transplant rates were lower in HUS patients than in controls (6.9 vs. 9 per 100 person-years, $P < 0.001$, Figure 2). Differences in rates were seen for all subgroups except patients characterized by RRT initiation in 2006-2010 (7.7 vs. 9.3 per 100-person years, $P = 0.17$), age 40-64 years (4.9 vs. 5.4 per 100-person years, $P = 0.39$), age 65 years or older (0.9 vs. 1.0 per 100-person years, $P = 0.82$), Hispanic ethnicity (6.5 vs. 9.4 per 100-person years, $P = 0.12$), and other race (8.4 vs. 6.7 per 100-person years, $P = 0.60$). A similar pattern was observed

for the first year after dialysis initiation; however, by year 2, transplant rates for HUS patients were comparable to rates for matched controls overall and in all subgroups studied (Supplementary Table S1). Table 3 shows AHRs for transplant for patients with ESRD from HUS. Regarding absolute size, AHRs were 1.5 or greater for age younger than 5 years (AHR 2.55 vs. 20-39 yrs) and age 5-19 years (AHR 1.59 vs. 20-39 years), and 0.67 or less for age 40-64 years (AHR 0.63 vs. 20-39 years), age 65 years or older (AHR 0.11 vs. 20-39 years), and African American race (AHR 0.51).

Discussion

We found that the incidence of ESRD from HUS remained largely unchanged over the past decade and indeed over the past 15 years of observation. While it is tempting to hypothesize that the discouraging trends in HUS-related RRT may reflect lack of effective treatments for HUS over the study period, the non-experimental design of our study precludes a definitive answer. There are many other plausible explanations for the smooth incidence of ESRD from HUS, such as a stable incidence of HUS in the population, a lack of change in progression to ESRD among patients with HUS, an increase in HUS balanced by a slower rate of progression to ESRD, or a decline in HUS in association with a quicker rate of progression to ESRD. Our study cannot determine this because of lack of information on true incident cases in the general population. The implication of the isolated apparent decline in ESRD incidence in females by the 2009-2010 biennium standardized against rates in 1995-1996 is unclear, with lack of a synchronous decline over the past decade. Multiple plausible explanations include improved diagnostic and disease labeling practices over the time frame, a treatment effect despite the lack of specific therapies, or a chance observation.

Novel mechanistic-based therapies for HUS are now emerging. In 2011, the US Food and Drug Administration granted accelerated approval for the use of Eculizumab in the treatment of aHUS based on promising non-randomized evidence and despite high cost. [12, 15-19] Therefore, our study is perhaps timely, since it defines outcomes such as survival on RRT for patients with ESRD from HUS, which is surprisingly good, before widespread use of Eculizumab.

Apprehension regarding recurrent aHUS after renal transplant may partially explain why rates of listing and transplant were lower in patients with ESRD from HUS than in matched controls.[2, 20-22] The likelihood of transplant was lower in African American patients over the study period; while the design of the our study precludes a definitive explanation, the racial disparity in transplant rates in the United States has been observed for most other causes of ESRD.[23,24]

The retrospective registry-based design and lack of information about treatments given prior to the onset of ESRD are potential limitations to our study. In addition, we were unable to discern case-specific causes of HUS such as Shiga-toxin-associated-HUS and atypical forms, or identify which particular genetic complement defect was responsible. In interpreting our findings, it is important to note that a diagnosis of HUS may encompass cases associated with underlying systemic infections, autoimmune diseases, and certain medications among other causes.[1-8] It is also therefore possible that changing trends in the incidence of individual specific causes of HUS may not have been appreciated where present.

However, despite its limitations, we believe that our study provides some useful information. The incidence of ESRD from HUS remained unchanged over the past decade. Although mortality of patients with ESRD from HUS in year 1 following RRT initiation exceeded mortality of patients with ESRD from other causes, overall and in certain subgroups,

and despite a lower likelihood of renal transplant, long-term survival was superior for patients with HUS. Given the cost of novel therapies, cognizance of the incidence and prognosis of ESRD from HUS may aid in nephrology care planning, particularly where resource are finite.

Acknowledgments

The authors have no conflicts of interest with the study's subject matter. The authors thank Chronic Disease Research Group colleagues Beth Forrest for regulatory assistance, Delaney Berrini, BS, for manuscript preparation, and Nan Booth, MSW, MPH, ELS, for manuscript editing.

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Table 1. Standardized incidence ratios of end-stage renal disease from hemolytic uremic syndrome requiring renal replacement therapy, 1995-2010 and 2001-2010

Subgroup	Rate	Standardized Incidence Ratio, vs. 1995-1996						
Biennium	1995-1996	1997-1998	1999-2000	2001-2002	2003-2004	2005-2006	2007-2008	2009-2010
Cases/million population	254/268	294/274	301/281	287/286	297/291	284/297	277/303	247/308
All	0.5 (0)	1.12 (0.07)	1.12 (0.06)	1.04 (0.06)	1.04 (0.06)	0.97 (0.06)	0.92 (0.06)	0.8 (0.05)
Age, years								
< 5	0.4 (0.1)	1.52 (0.35)	1.6 (0.35)	1.51 (0.34)	1.27 (0.31)	1.46 (0.33)	1.78 (0.36)	1.71 (0.35)
5-19	0.3 (0)	1.05 (0.16)	1.19 (0.17)	1.16 (0.16)	0.91 (0.15)	1.21 (0.17)	1.27 (0.17)	1.05 (0.15)
20-40	0.3 (0)	1.12 (0.14)	1.29 (0.15)	1.24 (0.15)	1.25 (0.15)	1.23 (0.15)	1.14 (0.15)	1.06 (0.14)
40-64	0.5 (0.1)	1.19 (0.11)	0.91 (0.09)	1.02 (0.1)	1.15 (0.1)	0.96 (0.09)	0.82 (0.08)	0.75 (0.08)
≥ 65	0.9 (0.1)	1.15 (0.12)	1.26 (0.13)	0.86 (0.1)	0.91 (0.11)	0.78 (0.1)	0.83 (0.1)	0.69 (0.08)
Sex								
Male	0.3 (0)	1.11 (0.11)	1.15 (0.11)	1.05 (0.11)	1.17 (0.11)	1.1 (0.11)	1.02 (0.1)	0.91 (0.1)
Female	0.6 (0)	1.13 (0.08)	1.1 (0.08)	1.03 (0.08)	0.98 (0.07)	0.91 (0.07)	0.87 (0.07)	0.74 (0.06)[a]
Race/ethnicity								
White	0.5 (0)	1.08 (0.07)	1.06 (0.07)	0.99 (0.07)	0.98 (0.07)	0.91 (0.06)	0.9 (0.06)	0.83 (0.06)
African American	0.6 (0.1)	1.39 (0.19)	1.27 (0.17)	1.16 (0.16)	1.29 (0.17)	1.23 (0.16)	0.95 (0.14)	0.62 (0.11)
Other	0.2 (0.1)	0.89 (0.47)	2.05 (0.61)	1.85 (0.55)	1.31 (0.45)	1.21 (0.42)	1.34 (0.42)	1.05 (0.36)

	Rate	Standardized Incidence Ratio, vs. 2001-2002			
Biennium	2001-2002	2003-2004	2005-2006	2007-2008	2009-2010
Cases/million population	287/286	297/291	284/297	277/303	247/308
All					
Age, years	0.5 (0)	1.02 (0.06)	0.96 (0.06)	0.92 (0.06)	0.8 (0.05)
< 5	0.5 (0.1)	0.86 (0.21)	1.01 (0.23)	1.25 (0.25)	1.21 (0.25)
5-19	0.3 (0)	0.79 (0.13)	1.06 (0.15)	1.12 (0.15)	0.93 (0.14)
20-40	0.4 (0.1)	1.01 (0.12)	1.01 (0.12)	0.95 (0.12)	0.88 (0.12)
40-64	0.6 (0.1)	1.13 (0.1)	0.95 (0.09)	0.81 (0.08)	0.75 (0.08)
≥ 65	0.7 (0.1)	1.08 (0.12)	0.94 (0.12)	1.01 (0.12)	0.84 (0.1)
Sex					
Male	0.3 (0)	1.11 (0.11)	1.05 (0.1)	0.98 (0.1)	0.88 (0.09)

Female	0.6 (0)	0.97 (0.07)	0.91 (0.07)	0.89 (0.07)	0.76 (0.06)
Race/ethnicity					
Non-Hispanic white	0.5 (0)	0.97 (0.07)	0.93 (0.07)	0.93 (0.07)	0.88 (0.06)
Non-Hispanic African American	0.7 (0.1)	1.11 (0.15)	1.1 (0.15)	0.83 (0.12)	0.56 (0.1)
Hispanic	0.2 (0.1)	1.49 (0.3)	0.95 (0.23)	0.96 (0.23)	0.67 (0.18)
Other	0.3 (0.1)	0.62 (0.29)	0.88 (0.32)	1.1 (0.34)	0.78 (0.28)

Note: Parameter estimates are rates per million per year or standardized incidence ratios (standardized to 2001-2002) with standard deviation in parentheses. With PE denoting Point Estimate, CL Confidence Limit, Obs Observed Incidence Rate, Exp Expected Incidence Rate from rates seen in 2001-2002, standardized incidence ratios were estimated and reported as [PEObs/PEExp] ([5% CLObs/PEExp]-[95% CLObs/PEExp]). *P* values refer to comparisons of observed rates and rates expected when those seen in 2001-2002 were applied to the years under consideration. $P \geq 0.05$ (vs. 2001-2002) for all comparisons unless otherwise stated, [a] $0.01 \leq P$ value < 0.05. Since Hispanic ethnicity has been routinely tabulated in US census documents only from 2000 onward, we performed a separate analysis from 2001 to consider Hispanic ethnicity, using the 2001-2002 biennium for standardization. Four race/ethnicity categories were used for this analysis, non-Hispanic white, non-Hispanic African American, Hispanic, and other race/ethnicity. For standardized incidence ratios standardized against the 1995-1996 biennium, we used three race categories: white, African American, and other.

Table 2. Baseline characteristics at initiation of renal replacement therapy (*n* = 1,557,117)

	Hemolytic Uremic Syndrome		
Variable	Yes, %	No, %	AOR (95%CI)
n	2241	1,554,876	
Year			
1995-2000	37.9	31.3	1.12 (1.01-1.23)
2001-2005	32.4	32.6	1 (Reference)
2006-2010	29.8	36.1	0.85 (0.76-0.94)
Age, years			
< 5	7.5	0.2	12.85 (10.72-15.39)
5-19	10.2	1	3.45 (2.95-4.04)
20-39	22.9	8.6	1 (Reference)
40-64	39	41.3	0.32 (0.29-0.35)
≥ 65	20.4	48.9	0.11 (0.1-0.13)
Sex			
Male	35.7	54.9	1 (Reference)
Female	64.3	45.1	2.45 (2.25-2.67)
Race			
White	78.5	65.2	1 (Reference)
African American	18	28.7	0.35 (0.31-0.39)
Other	3.5	6.1	0.35 (0.28-0.43)
Hispanic ethnicity			
Non-Hispanic	93.6	87.1	1 (Reference)
Hispanic	6.4	12.9	0.27 (0.23-0.32)
Ischemic heart disease			
No	93.4	75.9	1 (Reference)
Yes	6.6	24.1	0.34 (0.29-0.41)
Diabetes			
No	91.9	50.2	1 (Reference)
Yes	8.1	49.8	0.11 (0.1-0.13)
Alcohol abuse			
No	98.7	98.5a	1 (Reference)[a]
Yes	1.3	1.5	1.08 (0.75-1.57)
Drug abuse			
No	98.9	98.9a	1 (Reference)[a]
Yes	1.1	1.1	0.95 (0.64-1.41)
Mode of RRT			
Hemodialysis	84.3	90.5	1 (Reference)
Peritoneal dialysis	12.4	7.8	0.61 (0.53-0.7)
Preemptive transplant	3.3	1.7	0.52 (0.41-0.66)
Initial hemodialysis access			
Fistula	3.3	13.8	1 (Reference)
Graft	0.8	3.6	0.94 (0.35-2.49)
Catheter	95.9	82.6	4.3 (2.78-6.65)
Prior nephrology care, months			
> 12	9.4	24.2	1 (Reference)
≤ 12	90.6	75.8	3.56 (2.79-4.55)
eGFR, mL/min/1.73 m^2			

≤ 15	85.7	89.7	1 (Reference)[a]
> 15	14.3	10.3	0.93 (0.81-1.06)
Body mass index, kg/m^2			
< 30	82.4	69.6	1 (Reference)
≥ 30	17.6	30.4	0.47 (0.42-0.53)
Albumin, g/dL			
≥ 3.5	28.6	35.2	1 (Reference)
< 3.5	71.4	64.8	1.55 (1.4-1.72)
Hemoglobin, g/dL			
< 9	40.9	28.8	1 (Reference)
≥ 9	59.1	71.2	0.63 (0.58-0.69)
Cerebrovascular disease			
No	96.3	90.6	1 (Reference)[c]
Yes	3.7	9.4	0.57 (0.39-0.83)
Peripheral vascular disease			
No	97.3	86	1 (Reference)
Yes	2.7	14	0.25 (0.2-0.33)
Smoking			
No	93.1	93.8a	1 (Reference)[a]
Yes	6.9	6.2	1.07 (0.81-1.42)

Note: Parameter estimates are presented as column percentages or odds ratios, with 95% confidence intervals in parentheses. As data fields for predialysis vascular access for hemodialysis and nephrology care before RRT were not available before the 2005 version of the Medical Evidence Report, the denominators for these variables consisted of 36.7% of the study population for whom the 2005 version of the form was completed. Missing data: initial hemodialysis access (63.3 %); prior nephrology care, months (59.4 %); eGFR, mL/min/1.73 m^2 (1.5 %); body mass index, kg/m^2 (4.7 %); albumin, g/dL (25.2 %); hemoglobin, g/dL (11.1 %).

AOR, adjusted (by logistics regression, with age, sex, race, ethnicity as adjusters) odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy.

[a] P value ≥ 0.05.

[b] 0.01 ≤ P value < 0.05.

[c] 0.001 = P value < 0.01.

Table 3. Adjusted hazards ratios for outcomes on dialysis therapy, patients with HUS (*n* = 2241)

Variable	Reference	Outcomes		
		AHR Death	AHR Listing	AHR Transplant
Group	%/yrs. follow-up	44.8/5.4	28.9/3.7	24.8/3.8
Initial RRT 1995-2000	2001-2005	1.02 (0.88-1.18)[a]	0.99 (0.82-1.19)[a]	1.21 (1-1.46)[a]
Initial RRT 2006-2010	2001-2005	0.84 (0.7-1.01)[a]	1.07 (0.86-1.32)[a]	0.9 (0.71-1.15)[a]
Age < 5 yrs	Age 20-39 yrs.	0.37 (0.22-0.61)	1.53 (1.19-1.98)	2.55 (1.99-3.26)
Age 5-19 yrs	Age 20-39 yrs.	0.39 (0.26-0.59)	1.17 (0.91-1.5)[a]	1.59 (1.24-2.03)
Age 40-64 yrs.	Age 20-39 yrs.	2.61 (2.15-3.16)	0.78 (0.64-0.95)[b]	0.63 (0.51-0.79)
Age ≥ 65 yrs.	Age 20-39 yrs.	5.58 (4.56-6.83)	0.14 (0.09-0.23)	0.11 (0.06-0.2)
Female sex	Male	0.85 (0.74-0.96)[b]	0.99 (0.83-1.17)[a]	0.88 (0.74-1.04)[a]
African American race	White	1.01 (0.85-1.19)[a]	0.87 (0.71-1.08)[a]	0.51 (0.4-0.65)
Other race	White	0.77 (0.49-1.22)[a]	0.98 (0.66-1.46)[a]	0.73 (0.48-1.11)[a]
Hispanic ethnicity	Non-Hispanic	0.85 (0.63-1.13)[a]	0.94 (0.7-1.27)[a]	0.73 (0.53-1.01)[a]
Ischemic heart disease	Absent	1.42 (1.16-1.74)	0.64 (0.35-1.18)[a]	0.7 (0.36-1.38)[a]
Diabetes	Absent	1.18 (0.96-1.44)[a]	0.62 (0.4-0.97)[b]	1.25 (0.83-1.9)[a]
Alcohol abuse	Absent	1.07 (0.66-1.71)[a]	0.72 (0.3-1.76)[a]	0.68 (0.22-2.12)[a]
Drug abuse	Absent	0.93 (0.5-1.75)[a]	0.41 (0.15-1.09)[a]	0.27 (0.07-1.1)[a]
Peritoneal dialysis	Hemodialysis	0.65 (0.46-0.93)[b]	1.21 (0.92-1.6)[a]	1.11 (0.85-1.45)[a]
Preemptive transplant	Hemodialysis	0.12 (0.04-0.38)	.	.
Vascular access [d]				
Graft	Fistula	4.44 (0.89-22.2)[a]	0 (0-.)[a]	1.2 (0.14-10)[a]
Catheter	Fistula	2.22 (0.7-6.97)[a]	1.35 (0.33-5.5)[a]	0.51 (0.23-1.11)[a]
Nephrology care ≤ 12 mth.	≥ 12	1.47 (0.79-2.71)[a]	1.3 (0.77-2.18)[a]	0.73 (0.45-1.18)[a]
eGFR > 15 mL/min/1.73 m2	≤ 15	1.04 (0.82-1.31)[a]	0.78 (0.6-1.01)[a]	0.81 (0.63-1.05)[a]
Body mass index ≥ 30 kg/m2	< 30	0.82 (0.69-0.98)[b]	0.93 (0.74-1.18)[a]	0.8 (0.61-1.04)[a]
Albumin < 3.5 g/dL	≥ 3.5	1.27 (1.07-1.5)[c]	1.02 (0.84-1.23)[a]	0.93 (0.76-1.14)[a]
Hemoglobin ≥ 9 g/dL	< 9.0	0.91 (0.79-1.04)[a]	0.93 (0.78-1.1)[a]	0.96 (0.8-1.15)[a]
Cerebrovascular disease	Absent	0.49 (0.22-1.11)[a]	0.71 (0.29-1.74)[a]	0.43 (0.11-1.78)[a]
Peripheral vascular disease	Absent	1.26 (0.92-1.71)[a]	1.29 (0.69-2.42)[a]	1.25 (0.62-2.52)[a]
Smoking	Absent	0.79 (0.45-1.39)[a]	1.01 (0.57-1.76)[a]	0.95 (0.46-2)[a]

Hazards ratios are adjusted for age, sex, race, and ethnicity and are presented with 95% confidence intervals in parentheses. $P < 0.001$ unless otherwise indicated. AHR, adjusted hazards ratio; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy.

[a] P value ≥ 0.05. [b] 0.01 = P value < 0.05. [c] 0.001 = P value < 0.01

[d] For hemodialysis.

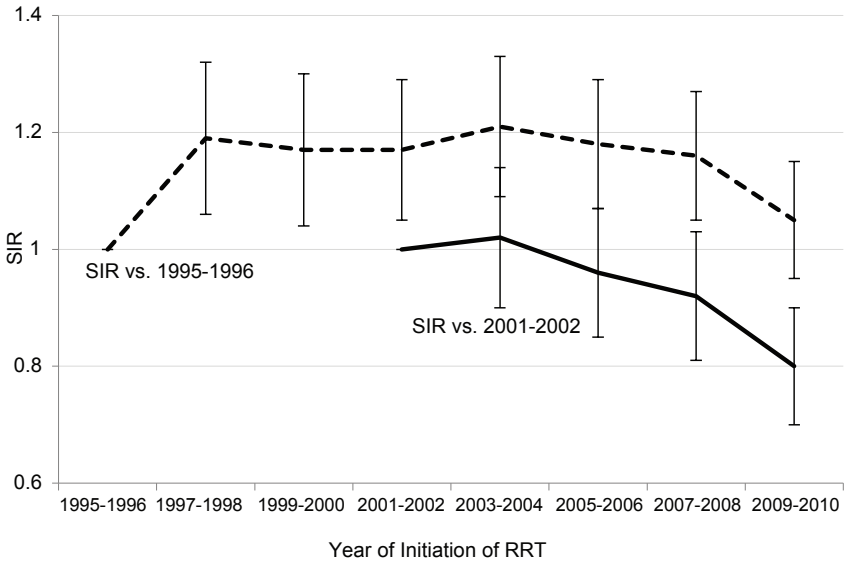
Figure Legends

Figure 1. Trends in the burden of end-stage renal disease from hemolytic uremic syndrome in the US, with incidence ratios standardized against both the 1995-1996 and the 2001-2002 biennia separately. Standardization factors against 1995-1996 were age, sex and race, while those against 2001-2002 were age, sex and race/ethnicity. Error bars show 95% confidence intervals. RRT, renal replacement therapy; SIR, standardized incidence ratio.

Figure 2. Outcome rates of patients with ESRD from HUS (*n* = 2202 [98.3%]) and a control group without HUS, matched according to year of RRT initiation (in 1-year intervals), age (in 1-year intervals), sex, race, and ethnicity at RRT initiation. Parameters shown are rates per 100 person-years, with error bars showing 95% confidence intervals. A formal tabulation of numerical estimates is available in Supplementary Table S1. AA, African American; ESRD, end-stage renal disease; HUS, hemolytic uremic syndrome; RRT renal replacement therapy.

Figure 1. Trends in the burden of end-stage renal disease from hemolytic uremic syndrome in the US, with incidence ratios standardized against both the 1995-1996 and the 2001-2002 biennia separately. Standardization factors against 1995-1996 were age, sex and race, while those against 2001-2002 were age, sex and race/ethnicity. Error bars show 95% confidence intervals. RRT, renal replacement therapy; SIR, standardized incidence ratio.

Figure 1.


1.4
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SIR
SIR vs. 1995-1996
SIR vs. 2001-2002
1995-1996
1997-1998
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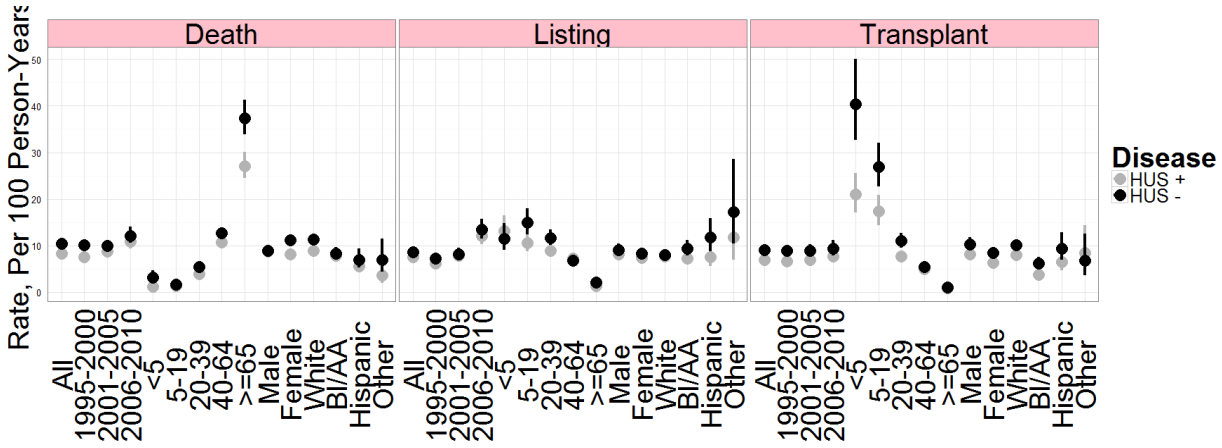
2005-2006
2007-2008
2009-2010
Year of Initiation of RRT

Figure 2. Outcome rates of patients with ESRD from HUS (*n* = 2202 [98.3%]) and a control group without HUS, matched according to year of RRT initiation (in 1-year intervals), age (in 1-year intervals), sex, race, and ethnicity at RRT initiation. Parameters shown are rates per 100 person-years, with error bars showing 95% confidence intervals. A formal tabulation of numerical estimates is available in Supplementary Table S1. AA, African American; ESRD, end-stage renal disease; HUS, hemolytic uremic syndrome; RRT renal replacement therapy.



Supplementary Table S1. Rates (per 100 person-years, with 95% confidence intervals in parentheses) of death, listing for renal transplant, and renal transplant in patients with ESRD from HUS (*n* = 2202, [98.3 %]) and an equal number of matched control patients without HUS. Participants were matched according to year of RRT initiation (in 1-year intervals), age (in 1-year intervals), sex, race, and ethnicity at RRT initiation.

	Outcome	HUS Overall	Controls Overall	Year 1 HUS	Year 1 Controls	Year 2 HUS	Year 2 Controls	Year 3 HUS	Year 3 Controls
All	Death	8.3 (7.8-8.9)	10.4 (9.8-11)	21.1 (19.2-23.3)	17.9 (16.2-19.9)[b]	10.2 (8.7-11.9)	12.4 (10.8-14.2)[a]	7 (5.7-8.5)	12.3 (10.6-14.4)
1995-2000	Death	7.5 (6.8-8.2)	10.1 (9.3-11)	22.8 (19.6-26.5)	20.1 (17.2-23.6)[a]	11 (8.7-13.9)	14.6 (11.9-17.9)[a]	7.1 (5.2-9.7)	15.8 (12.8-19.5)
2001-2005	Death	8.7 (7.8-9.7)	9.9 (9-11)[a]	21.4 (18.1-25.3)	16.2 (13.4-19.6)[b]	10.3 (7.9-13.4)	11.6 (9.1-14.7)[a]	8.7 (6.5-11.8)	10 (7.6-13.2)[a]
2006-2010	Death	10.9 (9.4-12.6)	12.1 (10.6-14)[a]	18.7 (15.5-22.6)	17 (14-20.7)[a]	8.9 (6.5-12.1)	10.3 (7.7-13.8)[a]	4.1 (2.4-7)	10 (7-14.3)[c]
< 5	Death	1.2 (0.7-2.1)	3.2 (2.3-4.6)[c]	3.6 (1.5-8.6)	5.8 (2.9-11.5)[a]	1.5 (0.4-6.1)	6.4 (3.2-12.9)[a]	0.8 (0.1-6)	5.5 (2.5-12.3)[a]
5-19	Death	1.4 (1-2.1)	1.6 (1.1-2.3)[a]	4.7 (2.5-8.7)	2.7 (1.2-6.1)[a]	1.5 (0.5-4.7)	2.5 (1-5.9)[a]	1.1 (0.3-4.3)	1.1 (0.3-4.3)[a]
20-39	Death	3.9 (3.3-4.6)	5.4 (4.6-6.2)[c]	5.7 (3.9-8.2)	8 (5.8-10.9)[a]	5.6 (3.8-8.3)	7.4 (5.2-10.5)[a]	3.6 (2.1-6)	6.8 (4.6-10)[a]
40-64	Death	10.7 (9.8-11.7)	12.7 (11.7-13.9)[c]	25 (21.7-28.9)	17.6 (14.9-20.7)[c]	12.8 (10.3-16)	13.3 (10.7-16.4)[a]	8.1 (6-10.9)	13.9 (11.1-17.5)[c]
≥ 65	Death	27.1 (24.5-30.1)	37.4 (33.8-41.3)	52.1 (45-60.3)	46.8 (40.2-54.5)[a]	24.4 (18.8-31.7)	30.8 (24.5-38.8)[a]	22.3 (16.2-30.6)	38.5 (29.9-49.6)[c]
Male	Death	8.8 (8-9.8)	8.9 (8.1-9.9)[a]	19.1 (16.2-22.7)	17.5 (14.7-20.9)[a]	12 (9.5-15.1)	10.4 (8.1-13.4)[a]	8.6 (6.4-11.7)	11.4 (8.7-14.8)[a]
Female	Death	8.1 (7.5-8.8)	11.2 (10.4-12)	22.2 (19.8-25)	18.1 (16-20.6)[b]	9.2 (7.5-11.2)	13.5 (11.5-15.9)[c]	6.1 (4.7-8)	12.9 (10.7-15.5)
White	Death	8.9 (8.3-9.5)	11.3 (10.6-12.1)	23.7 (21.3-26.4)	20.5 (18.3-22.9)[a]	10.3 (8.6-12.3)	12.8 (10.9-15)[a]	8.1 (6.5-10)	13.7 (11.6-16.3)
AA	Death	7.8 (6.7-9)	8.3 (7.1-9.6)[a]	16 (12.3-20.7)	12.1 (9-16.2)[a]	11.8 (8.5-16.4)	11.7 (8.5-16.2)[a]	4.9 (2.8-8.4)	8.5 (5.6-12.8)[a]
Hispanic	Death	5.6 (4.2-7.6)	7 (5.2-9.3)[a]	9.3 (5.2-16.9)	6.7 (3.3-13.3)[a]	6.7 (3.2-14.1)	11.5 (6.5-20.3)[a]	3.2 (1-9.9)	10.3 (5.4-19.9)[a]
Other	Death	3.6 (1.9-6.6)	7 (4.3-11.5)[a]	9.1 (3.4-24.3)	11.6 (4.8-27.9)[a]	2.6 (0.4-18.3)	8.3 (2.7-25.6)[a]	3 (0.4-21)	6.9 (1.7-27.6)[a]
All	Listing	7.6 (7.1-8.3)	8.6 (7.9-9.4)[b]	16.1 (14.4-18.1)	17.1 (15.2-19.2)[a]	12.6 (10.8-14.8)	12 (10.2-14.2)[a]	6.3 (4.8-8.1)	6.1 (4.7-8.1)[a]
1995-2000	Listing	6.1 (5.4-7)	7.3 (6.4-8.3)[a]	15.5 (12.8-18.8)	16.8 (13.9-20.3)[a]	12.6 (9.7-16.2)	10.9 (8.3-14.4)[a]	6.2 (4.1-9.2)	6.3 (4.2-9.6)[a]
2001-2005	Listing	7.9 (6.9-9)	8.2 (7-9.5)[a]	14.8 (12-18.3)	15.8 (12.7-19.5)[a]	14.1 (10.9-18.2)	12.8 (9.7-16.9)[a]	6.4 (4.2-9.9)	4.9 (3-8.2)[a]
2006-2010	Listing	12 (10.3-14.1)	13.4 (11.4-15.7)[a]	18.4 (15.1-22.6)	18.8 (15.3-23.1)[a]	10.9 (7.8-15.2)	12.8 (9.3-17.5)[a]	6.1 (3.6-10.6)	7.8 (4.6-13.2)[a]
< 5	Listing	13.2 (10.6-16.4)	11.5 (9-14.8)[a]	32.8 (24-44.6)	38.9 (28.4-53.3)[a]	15.4 (8.9-26.4)	13.1 (6.8-25.2)[a]	7.1 (3-17.1)	8.8 (3.7-21.2)[a]
5-19	Listing	10.6 (8.7-12.9)	14.9 (12.4-17.9)[b]	28.1 (21.1-37.4)	36.4 (28-47.4)[a]	16.5 (10.7-25.6)	24.5 (16.7-35.9)[a]	8.9 (4.6-17.2)	9.7 (4.8-19.3)[a]
20-39	Listing	8.9 (7.8-10.3)	11.6 (10.1-13.4)[b]	19.2 (15.5-23.8)	23.7 (19.3-29.1)[a]	16 (12.2-21.1)	18.7 (14.2-24.7)[a]	10.3 (6.9-15.2)	9.2 (5.8-14.5)[a]

40-64	Listing	7.3 (6.4-8.4)	6.7 (5.7-7.7)[a]	14.9 (12.3-18)	13.2 (10.7-16.2)[a]	13.9 (10.9-17.7)	9.3 (6.9-12.4)[b]	4.5 (2.8-7.4)	5 (3.2-8)[a]
≥ 65	Listing	1.4 (0.9-2.3)	2.1 (1.4-3.3)[a]	2.9 (1.6-5.5)	2.3 (1.2-4.7)[a]	1.8 (0.7-4.9)	3.7 (1.8-7.3)[a]	1.9 (0.6-5.9)	1.5 (0.4-5.8)[a]
Male	Listing	8.2 (7.2-9.4)	9.1 (8-10.4)[a]	15.8 (13-19.3)	19.8 (16.5-23.7)[a]	11.6 (8.8-15.3)	12.3 (9.3-16.3)[a]	7.6 (5.1-11.3)	6.5 (4.2-10.3)[a]
Female	Listing	7.4 (6.7-8.1)	8.3 (7.5-9.3)[a]	16.3 (14.1-18.9)	15.6 (13.4-18.1)[a]	13.2 (10.9-16.1)	11.9 (9.7-14.6)[a]	5.6 (4-7.8)	5.9 (4.2-8.4)[a]
White	Listing	7.7 (7-8.4)	8 (7.3-8.9)[a]	16.7 (14.6-19.1)	16.8 (14.7-19.3)[a]	13 (10.8-15.7)	11 (8.9-13.5)[a]	6 (4.4-8.2)	4.6 (3.2-6.7)[a]
AA	Listing	7.2 (6-8.7)	9.3 (7.8-11.1)[b]	12.2 (9-16.6)	15.9 (12.1-20.9)[a]	11 (7.6-16.1)	12.2 (8.4-17.7)[a]	8.3 (5.1-13.5)	11.8 (7.6-18.4)[a]
Hispanic	Listing	7.6 (5.6-10.4)	11.8 (8.7-15.8)[b]	17.6 (11.2-27.6)	21.6 (14.2-32.7)[a]	12.8 (6.9-23.8)	22 (13.3-36.5)[a]	4.5 (1.5-14.1)	4.2 (1.1-16.9)[a]
Other	Listing	11.7 (7-19.4)	17.2 (10.4-28.5)[a]	30.2 (16.2-56)	22.6 (10.8-47.5)[a]	13.6 (4.4-42.1)	19.9 (7.5-53)[a]	0 (0-0)	7.9 (1.1-55.8)
All	Transplant	6.9 (6.3-7.5)	9 (8.3-9.8)	8 (6.8-9.4)	11.8 (10.3-13.6)	12 (10.2-14)	10.7 (9-12.7)[a]	8.7 (7-10.7)	9.1 (7.3-11.3)[a]
1995-2000	Transplant	6.6 (5.8-7.5)	8.9 (7.9-10.1)	7.5 (5.7-9.9)	12.2 (9.8-15.2)[c]	14.6 (11.6-18.4)	12.4 (9.6-16)[a]	10.3 (7.6-14)	9.1 (6.4-12.8)[a]
2001-2005	Transplant	6.9 (6-8)	8.9 (7.8-10.3)[b]	9.4 (7.2-12.2)	11.8 (9.2-15)[a]	9.2 (6.8-12.5)	10.3 (7.6-13.8)[a]	8.6 (6-12.2)	9.9 (7-13.9)[a]
2006-2010	Transplant	7.7 (6.4-9.4)	9.3 (7.8-11.2)[a]	7 (5.1-9.6)	11.5 (8.9-14.8)[b]	11.7 (8.7-15.7)	8.7 (6-12.5)[a]	6.2 (3.7-10.2)	7.9 (4.8-12.9)[a]
< 5	Transplant	21 (17.1-25.6)	40.4 (32.6-50.1)	18 (11.9-27.1)	46 (34-62.2)	50.9 (37.6-68.9)	53.4 (36.1-79)[a]	12.6 (6-26.4)	39.3 (20.4-75.4)[b]
5-19	Transplant	17.3 (14.3-20.9)	26.9 (22.6-32)	31.3 (23.7-41.4)	40.5 (31.3-52.4)[a]	21.3 (14-32.3)	33.1 (23.1-47.3)[a]	21.5 (13.4-34.6)	34.7 (22.4-53.7)[a]
20-39	Transplant	7.7 (6.6-8.9)	11 (9.5-12.7)	9.6 (7.1-12.9)	13.8 (10.7-17.8)[a]	11 (8-15)	13.1 (9.7-17.7)[a]	11.6 (8.2-16.4)	10 (6.7-15)[a]
40-64	Transplant	4.9 (4.2-5.7)	5.4 (4.6-6.3)[a]	3.7 (2.5-5.4)	6.1 (4.6-8.2)[b]	9 (6.8-11.9)	6.1 (4.4-8.5)[a]	7.1 (4.9-10.1)	5.7 (3.8-8.5)[a]
≥ 65	Transplant	0.9 (0.5-1.6)	1 (0.5-1.9)[a]	0.6 (0.1-2.3)	0.9 (0.3-2.7)[a]	2.2 (0.9-5.3)	0.9 (0.2-3.5)[a]	0.6 (0.1-4.3)	2.7 (1-7.2)[a]
Male	Transplant	8.2 (7.2-9.4)	10.2 (9-11.7)[b]	10.4 (8.2-13.2)	15.1 (12.3-18.5)[b]	13.3 (10.3-17.1)	9.3 (6.8-12.6)[a]	6.9 (4.6-10.4)	10.8 (7.7-15.2)[a]
Female	Transplant	6.3 (5.6-7)	8.4 (7.5-9.3)	6.6 (5.3-8.3)	10.1 (8.4-12.1)[c]	11.3 (9.3-13.8)	11.4 (9.3-14)[a]	9.6 (7.5-12.2)	8.2 (6.2-10.9)[a]
White	Transplant	8 (7.2-8.8)	10.1 (9.2-11.1)	9.7 (8.2-11.6)	14.1 (12.2-16.4)[c]	13.8 (11.6-16.5)	12.8 (10.6-15.5)[a]	10.2 (8-12.9)	9.1 (7-11.9)[a]
AA	Transplant	3.8 (3-4.8)	6.1 (5-7.5)[c]	2 (0.9-4.2)	5.7 (3.7-8.9)[b]	5.6 (3.4-9.1)	6.1 (3.8-9.8)[a]	5.5 (3.2-9.4)	6.7 (4.1-11.2)[a]
Hispanic	Transplant	6.5 (4.7-9.1)	9.4 (6.9-12.8)[a]	6.2 (2.9-13)	8.2 (4.2-15.7)[a]	14.9 (8.7-25.7)	6.8 (3.1-15.2)[a]	4.2 (1.3-12.9)	12.2 (6.1-24.5)[a]
Other	Transplant	8.4 (4.9-14.4)	6.7 (3.6-12.5)[a]	8 (2.6-24.7)	2.6 (0.4-18.3)[a]	6.8 (1.7-27.1)	3.3 (0.5-23.2)[a]	12.3 (4-38.3)	23 (9.6-55.2)[a]

Chapter 7

ESRD from Scleroderma in the US

In the era of ACE inhibitor usage what is the trend in ESRD from Scleroderma?

Ref:

End Stage Renal Disease from Scleroderma in the US, 1996-2012.
Sexton DJ, Reule S, Foley RN.

In press – Kidney International Reports 2017.

End Stage Renal Disease from Scleroderma in the United States, 1996 to 2012.

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Running title: ESRD from Scleroderma.

Key words: End-stage renal disease, scleroderma.

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Word count: 2928

We the authors of this manuscript report no conflict of interest with the subject matter. Dr Sexton was funded by the Health Research Board of Ireland.

Abstract

Objectives:

Though the management of scleroderma (SD) continues to evolve it is unknown whether the burden of ESRD from SD has changed.

Methods:

We examined United States Renal Data System data (*n* = 1,677,303) for the years 1996-2012 to quantify incidence and outcomes of ESRD from SD treated with renal replacement therapy (RRT, N=2398). Outcomes assessed through case-control comparisons included mortality, listing for transplant, renal transplant, graft failure and recovery of independence from dialysis.

Results

Overall ESRD rates from SD were 0.5 per million per year. Adjusted incidence ratios [AIRs] fell over time to 0.58 per ten years [PTY] by 2012 (95% confidence interval 0.54-0.63). AIRs for ESRD from SD fell in both sexes, in the majority of age and race/ethnicity categories as well as all regions of the US studied. Followed from RRT initiation, SD cases had a higher likelihood of death [AHR 1.44 (1.34-1.54) versus unrestricted controls] and a lower likelihood of renal transplant than controls [AHR 0.68 (0.58-0.79) vs. unrestricted controls]. However following listing for transplant, Living donor renal transplant was more likely in SD than matched controls [AHR 1.71 (1.16-2.53) versus unrestricted controls]. Recovery of independence from dialysis was more likely in SD than unrestricted matched controls, AHR (95%CI) 1.42 (1.08, 1.87).

Conclusions:

The incidence of ESRD from SD appears to have declined in the United States since 1996. While mortality on RRT was higher in SD cases than controls, recovery of independence from dialysis was more likely in SD.

Introduction

Scleroderma (systemic sclerosis) is a rare disorder associated with considerable morbidity and mortality with an estimated annual incidence of 10 to 12 per million in the United States. [1 2] End stage renal disease (ESRD) is a feared complication, which may occur due to an abrupt onset of scleroderma (SD) renal crisis, or an indolent progressive deterioration of kidney function. [3-11] SD renal crisis is a poorly understood phenomenon, which results in elevated serum renin and malignant hypertension resulting in endothelial damage with occlusion of arterioles resulting in organ ischaemia, particularly in the kidney.

The therapeutic approach to scleroderma has evolved substantially in recent years, particularly with regard to angiotensin-converting-enzyme (ACE) inhibitor use in SD renal crisis and vasodilator therapy for pulmonary hypertension.[12-14] As management of SD has continued to evolve, it seems natural to question whether reductions in associated ESRD have occurred, and, if so, whether salutary trends have been generalized across major demographic subgroups. Hence, we set out to describe the clinical epidemiology of ESRD from scleroderma between 1996 and 2012.

Methods

Objectives

The principal objectives of this study were to evaluate trends in demography-adjusted incidence ratios of ESRD from scleroderma necessitating RRT in the US between 1996 and 2012. For clinical outcomes after initiation of renal replacement therapy (RRT), we set out to compare likelihoods of listing for renal transplant, transplantation, death and graft failure in matched patients with and without scleroderma. We further aimed to calculate hazards ratios for these

outcomes amongst patients with scleroderma and calculate cause specific hazards for recovery of dialysis independence in scleroderma and unrestricted matched controls from 1995-2010.

Participants

In this retrospective study, we used data for patients who initiated maintenance RRT in the United States between 1996 and 2012 (N = 1,677,303). Baseline characteristics at initiation of RRT were determined from the Centers for Medicare & Medicaid (CMS) Medical Evidence Report (form CMS-2728). By federal requirement, this form must be submitted for all new patients starting RRT in the US and resultant data are housed in the United States Renal Data System Medevid95 and Medevid05 files. The Medical Evidence Form changed in 2005. Unlike previous iterations, the 2005 form includes information about pre-dialysis nephrologist care and vascular access for hemodialysis. On both forms, one of 82 causes is entered as the primary cause of ESRD, with identical options in the 1995 and 2005 forms. For this study, cases of ESRD from scleroderma were those with the primary cause of ESRD listed as 'Scleroderma' in the Medical Evidence Form. Dates of death, and first renal transplant were obtained from the Patients file, while those for first listing for transplant and transplant were determined from the Waitlist_ki and Waitlist_kp files. Dates of renal recovery were obtained from the Recovery file and date of graft failure from the Transplant file.

Analysis

Mid-year US census data were used for population denominators for the years examined, with age in 5-year increments. Poisson regression was used to calculate incidence ratios of RRT-requiring ESRD from scleroderma, as well as for ESRD from glomerulonephritis and ESRD from either diabetes or glomerulonephritis respectively. The Chi-square test was employed for unadjusted comparisons of patients with and without ESRD from SD, and logistic regression for

adjusted comparisons. For comparisons of clinical outcome rates of cases with SD, controls without SD were matched by calendar year, age, sex, race, ethnicity and region of the US. Poisson regression and Cox regression, were used to calculate incidence rates and adjusted hazards ratios (AHRs) for events occurring after initiation of RRT, with follow-up ending on June 30, 2013. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to estimate glomerular filtration rate at RRT initiation.

We also calculated the cause specific hazard ratios for recovery of dialysis independence between SD and unrestricted matched controls using competing risks time to event analysis as described by Fine and Gray, [15] allowing for death and renal transplant as competing events. SAS, v9.1.4 (Cary, North Carolina) was used for data analysis.

Results

The crude incidence rate of ESRD from SD between 1996 and 2012 was 0.5 cases per million per year (N=2398 total). ESRD from SD was associated with age over 20 years, and particularly age 40-64 and 65-79 years, female sex, African American/Black race and residence in the Northeast and Midwest (adjusted incidence ratios, Table 1). As can be seen in figure 1, with calendar year as continuous variable over all years examined, a declining adjusted incidence trend was seen in the overall population in SD (adjusted incidence ratio [AIR] 0.58 per ten years [PTY] (95% confidence interval 0.54-0.63 Table 1); with corresponding estimates for glomerulonephritis as primary cause of ESRD and ESRD from entities other than glomerulonephritis and diabetes reported as 0.80 [0.79 to 0.81] and 1.12 [1.12-1.13] PTY.

Trends in AIR fell in those aged 20-39 years [AIR 0.55 (0.43-0.72) PTY], 40-64 years [AIR 0.56 (0.5-0.62) PTY], 65-79 years [AIR 0.65 (0.56-0.76) PTY] and ≥ 79 years [AIR 0.55 (0.34-0.88) PTY], males [AIR 0.6 (0.51-0.72) PTY], females [AIR 0.58 (0.52-0.63) PTY], white

race [AIR 0.65 (0.53-0.79) PTY], African American/Black race [AIR 0.64 (0.58-0.71) PTY], Native American race [AIR 0.35 (0.13-0.92) PTY], Hispanic ethnicity [AIR 0.53 (0.39-0.72) PTY], and Non-Hispanic ethnicity [AIR 0.65 (0.59-0.7) PTY] but not in the subgroups defined by Asian race [AIR 0.77 (0.44-1.36) PTY] or age < 20 years [AIR 0.57 (0.2-1.65) PTY]. Adjusted Incidence ratios also declined according to residence in all geographic locations studied including Northeast [AIR 0.69 (0.58-0.82) PTY], Midwest [AIR 0.67 (0.56-0.78) PTY], South [AIR 0.47 (0.41-0.55) PTY] and West [AIR 0.59 (0.49-0.71) PTY].

Compared to ESRD from other causes, associations of SD at initiation of RRT (Vs. other causes of ESRD, Table 2) included earlier era (adjusted odds ratio [AOR] 0.82 (0.74-0.9) for 2001-2005, and AOR 0.53 (0.48-0.59) for 2006-2012 versus 1996-2000), female sex [AOR 4.13 (3.76-4.54)], age < 40 years or 40-64 years [AOR 0.52 (0.45-0.6) for age 65-79 years, AOR 0.15 (0.12-0.2) for age ≥ 80 years Vs. < 40], White race [African American/Black race AOR 0.41 (0.37-0.46), other race AOR 0.44 (0.35-0.54), and Hispanic ethnicity AOR 0.43 (0.36-0.5) vs White race], residence in the Northeast [AOR 0.87 (0.78-0.98) for residence in the Midwest, AOR 0.72 (0.64-0.8) for residence in the South, and AOR 0.84 (0.74-0.96) for residence in the West Vs. Northeast], hemodialysis as initial mode of RRT [AOR 0.64 (0.54-0.75) for PD and AOR 0.21 (0.13-0.34) for pre-emptive transplant as initial RRT Vs. HD], an absence of vascular disease [AOR 0.49 (0.44-0.54)], diabetes [AOR 0.07 (0.06-0.08)], or malignancy [AOR 0.58 (0.46-0.73)], and a body mass index < 30 kg/m^2 [AOR 0.15 (0.13-0.17) for BMI ≥ 30 kg/m^2], and serum albumin < 3.5 g/dl [AOR 1.42 (1.29-1.58) versus ≥ 3.5 g/dl].

These age, sex, race and era associations were also relatively consistent at the time points defined by Listing for renal transplant and by transplant (Table 2). In addition, being on dialysis for > 1 year at listing for transplant [AOR 1.6 (1.31-1.97)] and at renal transplant [AOR 2.69 (2-

3.63)] was more likely in SD. At renal transplant, Living donor transplantation was associated with ESRD from SD [AOR 1.45 (1.13-1.85)].

Mean follow up from initiation of RRT in SD was 3.3 years. Table 3 shows outcome rate comparisons with matched controls, reported for three separate time intervals of observation, from initiation of renal replacement therapy, listing and transplant respectively.

Outcomes in cases with SD compared with controls followed from initiation of RRT were as follows: a higher likelihood of death [AHR 1.44 (1.34-1.54) versus unrestricted controls, AHR 1.95 (1.82-2.09) vs primary glomerulonephritis as controls, and AHR 1.54 (1.44-1.65) versus controls without glomerulonephritis or DM], a higher likelihood of listing for transplant [AHR 1.25 (1.16-1.34) vs. unrestricted controls, AHR 1.61 (1.5-1.73) vs. glomerulonephritis as primary disease and AHR 1.33 (1.24-1.43) versus primary disease without DM or glomerulonephritis]. Renal transplant overall was less likely in SD [AHR 0.68 (0.58-0.79) vs. unrestricted, AHR 0.48 (0.41-0.55) vs. primary glomerulonephritis and AHR 0.62 (0.53-0.73) vs. controls without glomerulonephritis or DM as primary disease]. This was similar for the deceased donor transplant component [AHR 0.59 (0.47-0.73) vs unrestricted controls, AHR 0.43 (0.35-0.53) vs glomerulonephritis as primary disease, and AHR 0.51 (0.41-0.63) compared to controls without glomerulonephritis or diabetes mellitus]. In the living donor component of transplant, while there was also a lower likelihood of transplant in SD vs controls with glomerulonephritis as primary disease [AHR 0.55 (0.44-0.68)] this was not the case for the comparison with unrestricted controls [AHR 0.82 (0.64-1.05)] or controls without glomerulonephritis or DM [AHR 0.84 (0.66-1.07)].

When focusing on the interval from listing for transplant: mortality did not differ from unrestricted matched controls [AHR 1.23 (0.98-1.53)] but was higher in SD compared to

glomerulonephritis controls [AHR 1.46 (1.16-1.82)] and controls without glomerulonephritis or diabetes [AHR 1.39 (1.11-1.74)]. Mortality on the transplant list and transplantation following listing for transplant did not differ in comparison to any set of controls. However, receiving a deceased donor transplant after listing for transplant was less likely in SD than both glomerulonephritis controls [AHR 0.75 (0.59-0.96)] and controls without glomerulonephritis or diabetes [AHR 0.7 (0.55-0.89)] but was not different compared to unrestricted controls [AHR 0.8 (0.63-1.03)]. Of interest Living donor renal transplant was more likely in SD than each set of matched controls following listing for transplant: [AHR 1.71 (1.16-2.53) versus unrestricted controls, AHR 1.8 (1.21-2.67) vs controls with glomerulonephritis as primary disease and AHR 2.1 (1.39-3.17) vs controls without glomerulonephritis or DM as primary cause of ESRD.

When followed from transplant; mortality in SD was not different in comparison to unrestricted matched controls [AHR 0.97 (0.73-1.29)] or controls without glomerulonephritis or DM as primary cause of ESRD [AHR 1.19 (0.89-1.6)] but was inferior to matched cases with glomerulonephritis as primary cause of ESRD [AHR 1.61 (1.18-2.21)]. Graft failure following renal transplant was not more likely in SD compared to any paired control set [AHR 0.58 (0.06-5.87) vs unrestricted controls, AHR 0.84 (0.17-4.2) vs controls with glomerulonephritis as primary cause of ESRD, and AHR 1.43 (0.14-14.22) vs controls without glomerulonephritis or DM as primary cause of ESRD].

Outcomes specific to ESRD from SD are shown in Table 4, reported over three different intervals of observation, from initiation of RRT, from listing for transplant and from transplant. Focusing on the interval from RRT initiation, mortality increased with age and differed by sex [AHR 0.83 (0.74-0.93) for female sex]. The likelihood of listing for transplant did not differ by race/ethnicity, however, Hispanic ethnicity was associated with lower mortality [AHR 0.76

(0.62-0.92)] and although mortality did not differ for African American/Black race, the likelihood of transplant was lower in African American/Black race [AHR 0.4 (0.26-0.61) Vs White]. Mortality and renal transplant in SD did not vary by region. PD was not associated with lower mortality, or a higher likelihood of listing for transplant or renal transplant in comparison to HD as RRT, but transplant as initial RRT was associated with lower mortality AHR 0.18 (0.07-0.47). Factors associated with a higher likelihood of death included: vascular disease [AHR 1.41 (1.26-1.58)], diabetes [AHR 1.26 (1.06-1.49)], malignancy [AHR 1.42 (1.1-1.83)], eGFR > 15 ml/min/1.73m^2 [AHR 1.31 (1.11-1.54)], serum albumin < 3.5 g/dl [AHR 1.45 (1.28-1.65)] at RRT initiation. A BMI ≥ 30 kg/m^2 was associated with a higher likelihood of listing for [AHR 1.76 (1.3-2.37)] and receiving a transplant [AHR 1.72 (1.18-2.52)].

When focusing on the interval from the date of listing for transplant, mortality was lower in the more recent era [AHR 0.59 (0.38-0.91) for RRT 2006-2012 vs 1996-2000], and similarly the likelihood of transplant was lower in this era [AHR 0.64 (0.44-0.92) vs 1996-2000]. The likelihood of death and transplant in SD did not differ by region in this interval of observation but was lower in female sex [AHR 0.66 (0.47-0.93]. While mortality risk did not differ by race, African American/Black race was associated with a lower likelihood of renal transplant [AHR 0.47 (0.31-0.72)] in contrast to other races studied.

When focusing on the period of observation following renal transplant, mortality and graft failure did not differ by era of RRT initiation. Although increasing age was associated with a higher likelihood of death [AHR 2.84 (1.15-7.06) for age 40-64 years, and AHR 8.64 (3.16-23.64) for age 65-79 years Vs. < 40 yrs), mortality and graft failure did not differ by sex [AHR 0.65 (0.41-1.02) and 0.73 (0.48-1.09)], race/ethnicity, location of residence in the US or dialysis modality (Table 4). Living donor renal transplant in SD was associated with a lower likelihood

of mortality [AHR 0.57 (0.37-0.87)] and graft failure [AHR 0.65 (0.45-0.94] following renal transplant.

Recovery of Dialysis Independence

Recovery of independence from dialysis reported from 1995 to 2010 was more likely in SD cases than matched ESRD controls without SD, cause-specific adjusted hazard ratio 1.42 (1.08, 1.87) P=0.01 (censoring for death and renal transplant as competing risks, and adjusting for age, sex, race and year of RRT initiation). Recovery was uncommon overall in both groups (N=131 or 5.6% in Scleroderma and N=90 or 3.9% in controls) as can be seen in the cumulative incidence curves in Figure 2. With censoring for death and renal transplant as competing risks, median (IQR) time to recovery was 117 (80) days in SD and 61 (67) days in ESRD controls without SD (P<0.001).

Discussion

We found that the incidence of ESRD from SD declined during the 16-year interval of observation. The burden of ESRD has fallen in both sexes, and in all but one race/ethnicity category and age group. While it is tempting to hypothesize that the encouraging trends in SD-related RRT may reflect improvements in the management of SD, the non-experimental design of our study precludes a definitive answer.

Possible explanations for this might include a combination of improvements in overall management despite the lack of specific therapies, such as; the widespread use of ACE inhibitors and/or calcium channel blockers and directed therapy for SD related vascular phenomena such as pulmonary arterial hypertension, Raynaud's phenomenon and digital ulceration.[8 12 13 16-20] While the incidence of SD renal crisis in itself is also thought to be falling, the impact of this on ESRD may theoretically be counterbalanced by improving survival with mortality falling from

approximately 76% at one year initially to less than 10% following the introduction of ACE inhibitor use in SD renal crisis.[14]

There are other possible explanations for these observed trends such as a reduced incidence of scleroderma in the general population, an increased mortality as a competing risk for ESRD amongst those with scleroderma, or a failure to capture ESRD cases not treated with dialysis or transplant.[21] As with other uncommon conditions with varied severity and presentation, an accurate assessment of incidence is difficult due to a lack of a reliable population denominator. [14 22 23] While the mortality in SD overall and in SD renal crisis is thought to be falling, the incidence of SD as of 2008 was thought to be stable, which may make the salutary trends in ESRD even more interesting, as one might expect an increase in ESRD incidence in this setting. [14 22 23]

Although more likely in SD cases than matched controls, recovery of dialysis independence was rare overall, and appeared to occur relatively early after dialysis initiation in both SD cases and controls. In contrast to one smaller registry study based on ANZDATA, we found that average time to recovery was longer in SD than controls with other causes of ESRD.[24] The reasons for the higher recovery rate in SD compared to controls is unknown but is thought to represent recovery of kidney function following the ischaemic insult of scleroderma renal crisis.

Unfortunately we found that mortality in the contemporary era remains high for ESRD patients with SD in comparison to ESRD controls from other primary diseases, however this discrepant mortality risk was not evident after renal transplant. [14 18 22] SD is thought to be more common in African Americans, and we did find a higher rate of ESRD associated with African American/Black race along with a lower likelihood of receiving a renal transplant at each interval under scrutiny. The reasons for this are unclear but possibly relate to disease-specific

factors in African American/Black race, as well as possible racial heterogeneity in access to medical care in the US.[20 23 25]

When focusing on the interval following RRT initiation, we found that SD patients were more likely to be listed for renal transplant as matched controls, but were less likely to receive a transplant in this time frame. Although our findings pertaining to deceased donor transplant in SD may be concerning, that for living donor transplant in SD and indeed outcomes following transplant are perhaps more encouraging. These data are consistent with the available literature to date, which although limited, suggests a survival benefit to renal transplantation in SD.[26 27]

This study has several limitations, including retrospective registry-based design and a lack of information about earlier stage kidney disease and treatments received. The lack of facility to identify participants initiating RRT from SD renal crisis specifically resulted in the reporting of an overall estimation of renal recovery in ESRD from SD rather than in SD renal crisis itself. In spite of its limitations, we feel that our study provides some useful information.

Though research efforts to develop alternative efficacious treatments are clearly needed, it is encouraging that rates of RRT from scleroderma appear to be declining. It is perhaps encouraging to observe such a falling ESRD burden synchronous with a reported improvement in survival in those at risk.

Disclosures

The authors report no competing financial interests with the subject matter of this manuscript.

Acknowledgments

The data reported here have been supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US government. The Health Research Board of Ireland funded Dr Donal Sexton. The authors have no conflict of interest with its subject matter.

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Table 1. Adjusted incidence ratios of ESRD due to scleroderma, requiring renal replacement therapy, 1996-2012 (N=2398).

	Incidence Ratios, Overall Population			
Era	Unadjusted Incidence Ratio	Adjusted Incidence Ratio		
Year as a continuous variable, per 10 years	0.61 (0.56-0.66)	0.58 (0.54-0.63)		
Categorical				
1996	1 (Reference)	1 (Reference)		
1997	0.96 (0.78-1.19)[ns]	0.96 (0.78-1.19)[ns]		
1998	0.96 (0.78-1.19)[ns]	0.95 (0.77-1.18)[ns]		
1999	0.9 (0.73-1.12)[ns]	0.89 (0.72-1.1)[ns]		
2000	0.98 (0.79-1.21)[ns]	0.96 (0.78-1.18)[ns]		
2001	0.98 (0.8-1.21)[ns]	0.96 (0.78-1.19)[ns]		
2002	0.9 (0.72-1.11)[ns]	0.87 (0.7-1.08)[ns]		
2003	0.82 (0.66-1.02)[ns]	0.79 (0.64-0.99)[a]		
2004	0.78 (0.62-0.97)[a]	0.75 (0.6-0.94)[a]		
2005	0.74 (0.59-0.93)[b]	0.71 (0.57-0.89)[b]		
2006	0.66 (0.52-0.83)	0.63 (0.5-0.79)		
2007	0.72 (0.57-0.9)[b]	0.68 (0.55-0.86)		
2008	0.54 (0.42-0.69)	0.51 (0.4-0.65)		
2009	0.54 (0.42-0.69)	0.51 (0.4-0.65)		
2010	0.54 (0.42-0.69)	0.5 (0.4-0.64)	Incidence Ratios for Calendar Year as Continuous Variable Within Subgroups, Per Decade	
2011	0.51 (0.4-0.65)	0.47 (0.37-0.6)		
2012	0.45 (0.35-0.58)	0.42 (0.32-0.54)	Unadjusted	Adjusted
Age				
< 20 yrs.	1 (Reference)	1 (Reference)	0.56 (0.19-1.62)[ns]	0.57 (0.2-1.65)[ns]
20-39 yrs.	16.41 (9.75-27.63)	16.53 (9.81-27.83)	0.56 (0.43-0.72)	0.55 (0.43-0.72)
40-64 yrs.	80.96 (48.67-134.67)	82.23 (49.42-136.8)	0.55 (0.49-0.62)	0.56 (0.5-0.62)
65-79 yrs.	135.79 (81.4-226.5)	132.15 (79.19-220.53)	0.64 (0.54-0.74)	0.65 (0.56-0.76)
> 79 yrs.	40.46 (23.26-70.4)	36.59 (21.02-63.7)	0.54 (0.34-0.86)[b]	0.55 (0.34-0.88)[a]

Male	1 (Reference)	1 (Reference)	0.65 (0.55-0.76)	0.6 (0.51-0.72)
Female	3.06 (2.78-3.36)	2.83 (2.58-3.11)	0.6 (0.55-0.66)	0.58 (0.52-0.63)
Race				
White	1 (Reference)	1 (Reference)	0.54 (0.45-0.66)	0.65 (0.53-0.79)
Black	1.49 (1.35-1.65)	1.84 (1.65-2.04)	0.66 (0.6-0.72)	0.64 (0.58-0.71)
Native American	0.73 (0.47-1.15)[ns]	1.07 (0.68-1.68)[ns]	0.35 (0.14-0.91)[a]	0.35 (0.13-0.92)[a]
Asian	0.47 (0.36-0.63)	0.56 (0.43-0.75)	0.86 (0.49-1.51)[ns]	0.77 (0.44-1.36)[ns]
Non-Hispanic	1 (Reference)	1 (Reference)	0.7 (0.64-0.76)	0.65 (0.59-0.7)
Hispanic	0.47 (0.41-0.55)	0.83 (0.71-0.98)[a]	0.57 (0.42-0.78)	0.53 (0.39-0.72)
Location				
Northeast	1 (Reference)	1 (Reference)	0.72 (0.6-0.86)	0.69 (0.58-0.82)
Midwest	0.98 (0.87-1.11)[ns]	1.02 (0.91-1.15)[ns]	0.7 (0.59-0.82)	0.67 (0.56-0.78)
South	0.83 (0.74-0.93)[b]	0.84 (0.75-0.94)[b]	0.5 (0.43-0.58)	0.47 (0.41-0.55)
West	0.72 (0.64-0.82)	0.89 (0.78-1.01)[ns]	0.62 (0.51-0.75)	0.59 (0.49-0.71)

Note:

2314 of 2398 (96.5%) cases of Scleroderma had documentation of age, sex, ethnicity and geographic region and had race categories corresponding to those used in the census summaries ('Native American', 'Asian', 'Black', 'White'). Incidence ratios are reported with 95% confidence intervals in parentheses. Adjustment factors were year, age, sex, race, ethnicity and region.
P-values < 0.001 unless otherwise indicated. ns. *P*-value ≥ 0.05; a. 0.01 ≤ *P*-value < 0.05; b. 0.001 ≤ *P*-value < 0.01.

Table 2. Baseline characteristics at initiation of dialysis (N = 2398)

ESSD/All (%)	At initiation of Renal Replacement Therapy 2398/1682471 (0.1%)		AOR SD	At Listing for Renal Transplant 392/246813 (0.2%)		AOR SD	At Renal Transplant 260/203854 (0.1%)		AOR SD
	Yes	No		Yes	No		Yes	No	
ESRD from diabetes	0	44.5	-	0	40	-	0	30.2	-
ESRD from hypertension	0	27.9	.	0	22.2	.	0	18	.
ESRD from other cause	100	27.6	.	100	37.8	.	100	51.8	.
Era 1996 to 2000	35.2	24.9	-	23.2	19.1	-	20	17.2[a]	-
Era 2001 to 2005	32.7	29.6	0.82 (0.74-0.9)	36	29.8	1.05 (0.81-1.37)	38.5	32[a]	1.04 (0.74-1.45)
Era 2006 to 2012	32.1	45.6	0.53 (0.48-0.59)	40.8	51.1	0.73 (0.56-0.94)	41.5	50.9[a]	0.72 (0.51-1.01)
Age < 40 yrs.	11.2	9.4	-	15.1	24.8	-	12.3	29.1	-
Age 40-64 yrs.	57.5	41.4	1.13 (0.99-1.29)	74	62.3	2.01 (1.51-2.66)	76.2	58.3	3.23 (2.22-4.7)
Age 65-79 yrs.	28.1	35.9	0.52 (0.45-0.6)	11	12.7	1.38 (0.93-2.05)	11.5	12.4	2.36 (1.43-3.91)
Age ≥ 80 yrs.	3.2	13.3	0.15 (0.12-0.2)	0	0.2	0 (0-.)	0	0.2	0 (0-.)
Female sex	75.9	44.8	4.13 (3.76-4.54)	78.8	38.9	6.19 (4.85-7.89)	78.1	39.3	5.75 (4.28-7.71)
White race	77.6	66.1	-	78.8	60	-	86.2	70.2	-
Afr. Am./Black race	18.9	28.4	0.41 (0.37-0.46)	17.3	32.1	0.34 (0.26-0.45)	10.4	23.1	0.35 (0.23-0.52)
Other race	3.5	5.5	0.44 (0.35-0.54)	3.8	7.9	0.3 (0.18-0.51)	3.5	6.7	0.38 (0.19-0.75)
Hispanic	7.3	11.8	0.43 (0.36-0.5)	10.2	16.9	0.44 (0.31-0.61)	9.2	13[ns]	0.64 (0.42-0.99)
Northeast	21.7	18.2	-	23.5	18.9	-	26.5	19[b]	-
Midwest	25.1	21.8	0.87 (0.78-0.98)	25.5	19.7	0.94 (0.7-1.24)	25	24.3[b]	0.68 (0.49-0.96)
South	34.3	40.4	0.72 (0.64-0.8)	28.8	38.3	0.66 (0.5-0.86)	28.5	36[b]	0.61 (0.44-0.85)
West	18.9	19.7	0.84 (0.74-0.96)	22.2	23.1	0.83 (0.61-1.12)	20	20.7[b]	0.7 (0.49-1.01)
On dialysis > 1 yr.				57.1	48.7	1.6 (1.31-1.97)	77.3	62	2.69 (2-3.63)
Hemodialysis as RRT	92.5	90.5	-	79.8	81.4[ns]	-	91	92[ns]	-
Peritoneal dialysis	6.8	7.5	0.64 (0.54-0.75)	20.2	18.6[ns]	0.91 (0.71-1.18)	9	8[ns]	0.85 (0.52-1.39)
Transplant as RRT	0.8	2	0.21 (0.13-0.34)						
Vascular disease	19.2	34.2	0.49 (0.44-0.54)						
Diabetes	7.5	50.8	0.07 (0.06-0.08)						

Malignancy	3.3	6.6	0.58 (0.46-0.73)			
Smoking	5.8	5.7[ns]	0.93 (0.78-1.1)			
Alcohol/drug abuse	2	2.4[ns]	0.99 (0.74-1.32)			
eGFR > 15 ml/min/1.7	9.2	11.2[b]	0.93 (0.81-1.07)			
Body mass index ≥ 30	8.5	32.2	0.15 (0.13-0.17)			
Serum albumin < 3.5	71.9	64.5	1.42 (1.29-1.58)			
Hemoglobin ≥ 9 g/dL	70.7	71.3[ns]	1.02 (0.93-1.12)			
Living donor				49.2	38.3	1.45 (1.13-1.85)

Note: Abbreviations: AOR, adjusted odds ratio; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease from scleroderma; RRT, renal replacement therapy. Parameter estimates are presented as column percentages (except for 'All', with row percentages) or odds ratios, with 95% confidence intervals in parentheses. Estimates for age, duration of dialysis therapy and mode of dialysis therapy refer to the day of initiation of RRT, listing for transplant and renal transplant. Comorbid conditions were only assessed at initiation of RRT. Statistical comparisons are of patients with and without SD at initiation of RRT, listing for transplant and renal transplant. Logistic regression-adjusted for age, sex, race, ethnicity and geographic region was used to calculate odds ratios; reference categories for binary variables were those without the characteristic.
P-values < 0.001 unless otherwise indicated. ns. *P*-value ≥ 0.05; a. 0.01 ≤ *P*-value < 0.05; b. 0.001 ≤ *P*-value < 0.01. Missing data at initiation of renal replacement therapy: eGFR, 0.5%; body mass index, 3.0%; serum albumin, 24.8%; hemoglobin, 9.4%.

Table 3. Adjusted hazards ratios for outcomes on dialysis therapy, patients with scleroderma (N =2398).

Outcome	Rate, Cases SD+	Matched controls		
		Hazard ratio Unrestricted controls	Hazard ratio Primary Disease Glomerulonephritis	Hazard ratio Primary Disease Not DM, Not Glomerulonephritis
Followed from Initiation of Renal Replacement Therapy (2398 pairs, mean follow-up 3.3 years)				
Death	22 (21, 23.1)	1.44 (1.34-1.54)	1.95 (1.82-2.09)	1.54 (1.44-1.65)
Listing for transplant	25.4 (24.2, 26.6)	1.25 (1.16-1.34)	1.61 (1.5-1.73)	1.33 (1.24-1.43)
Transplant	3.6 (3.2, 4.1)	0.68 (0.58-0.79)	0.48 (0.41-0.55)	0.62 (0.53-0.73)
Deceased-donor transplant	1.9 (1.6, 2.3)	0.59 (0.47-0.73)	0.43 (0.35-0.53)	0.51 (0.41-0.63)
Living-donor transplant	1.7 (1.4, 2.1)	0.82 (0.64-1.05)[ns]	0.55 (0.44-0.68)	0.84 (0.66-1.07)[ns]
Followed from Listing for Transplant (392 pairs, mean follow-up 5.1 years)				
Death	8.6 (7.4, 9.9)	1.23 (0.98-1.53)[ns]	1.46 (1.16-1.82)[b]	1.39 (1.11-1.74)[b]
Death on transplant list	5.2 (4.3, 6.4)	0.84 (0.64-1.11)[ns]	0.99 (0.74-1.31)[ns]	0.99 (0.75-1.31)[ns]
Transplant	21.9 (19, 25.1)	1.01 (0.82-1.25)[ns]	0.97 (0.79-1.19)[ns]	0.95 (0.78-1.16)[ns]
Deceased-donor transplant	13.2 (11.1, 15.8)	0.8 (0.63-1.03)[ns]	0.75 (0.59-0.96)[a]	0.7 (0.55-0.89)[b]
Living-donor transplant	8.6 (6.9, 10.8)	1.71 (1.16-2.53)[b]	1.8 (1.21-2.67)[b]	2.1 (1.39-3.17)
Followed from Transplant (260 pairs, mean follow-up 5.6 years)				
Death	6.4 (5.2, 7.9)	0.97 (0.73-1.29)[ns]	1.61 (1.18-2.21)[b]	1.19 (0.89-1.6)[ns]
Graft failure	1.2 (0.4, 3.8)	0.58 (0.06-5.87)[ns]	0.84 (0.17-4.2)[ns]	1.43 (0.14-14.22)[ns]

Abbreviations: DM, diabetes mellitus; GN, glomerulonephritis. Rates are reported per hundred person-years. 95% confidence intervals are shown in parentheses. Factors used for matching were calendar year, age, sex, race, ethnicity and region.
P-values < 0.001 unless otherwise indicated. ns. *P*-value ≥ 0.05; a. 0.01 ≤ *P*-value < 0.05; b. 0.001 ≤ *P*-value < 0.01.

Table 4. Adjusted hazards ratios for outcomes on renal replacement therapy, patients with end-stage renal disease from Scleroderma (N=2398)

	Adjusted from RRT			Adjusted from Listing		Adjusted from Transplant	
Group	Death	Listing	Transplant	Death	Transplant	Death	Graft Failure
All	1727/2350	383/2326	234/2334	169/384	200/381	90/250	116/250
	(73.5%) over 3yrs	(16.5%) over 2.5yrs	(10%) over 2.8 yrs	(44%) over 5.1 yrs	(52.5%) over 2.4 yrs	(36%) over 5.6 yrs	(46.4%) over 4.9 yr
Era							
1st RRT 2001 to 2005	1 (0.9-1.12)^{ns}	1.07 (0.85-1.36)^{ns}	1.15 (0.86-1.52)^{ns}	0.75 (0.53-1.06)^{ns}	0.9 (0.64-1.26)^{ns}	0.7 (0.43-1.12)^{ns}	0.7 (0.46-1.07)^{ns}
1st RRT 2006 to 2012	0.94 (0.83-1.07)^{ns}	1.15 (0.89-1.49)^{ns}	0.74 (0.51-1.08)^{ns}	0.59 (0.38-0.91)^{a}	0.64 (0.44-0.92)^{a}	0.6 (0.32-1.13)^{ns}	0.57 (0.33-1)^{ns}
Age							
Age < 40 yrs.	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Age 40-64 yrs.	1.53 (1.28-1.82)	1 (0.76-1.32)	1.23 (0.86-1.76)	1.35 (0.85-2.15)	1.46 (0.96-2.21)^{ns}	2.84 (1.15-7.06)	1.58 (0.84-2.96)ns
Age 65-79 yrs.	3.03 (2.52-3.65)	0.31 (0.2-0.47)	0.46 (0.26-0.79)	2.64 (1.46-4.77)^{b}	1.41 (0.79-2.51)^{ns}	8.64 (3.16-23.64)	3.94 (1.85-8.42)
Age ≥ 80 yrs.	4.96 (3.72-6.61)	.	.				
Sex							
Female sex	0.83 (0.74-0.93)	1.02 (0.8-1.3)^{ns}	0.96 (0.71-1.31)^{ns}	0.66 (0.47-0.93)^{a}	0.88 (0.63-1.22)^{ns}	0.65 (0.41-1.02)^{ns}	0.73 (0.48-1.09)^{ns}
Race							
White race	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Afr. Am./Black race	0.91 (0.8-1.02)^{ns}	0.85 (0.65-1.1)^{ns}	0.4 (0.26-0.61)	0.9 (0.6-1.35)^{ns}	0.47 (0.31-0.72)^{b}	0.63 (0.28-1.45)^{ns}	0.93 (0.49-1.79)^{ns}
Other race	0.95 (0.73-1.24)^{ns}	1.09 (0.64-1.86)^{ns}	0.86 (0.43-1.75)	1 (0.44-2.27)^{ns}	0.81 (0.38-1.73)ns	0.86 (0.27-2.74)^{ns}	0.84 (0.31-2.3)^{ns}
Hispanic	0.76 (0.62-0.92)^{b}	1.29 (0.93-1.8)^{ns}	1.06 (0.68-1.66)^{ns}	0.99 (0.59-1.66)^{ns}	0.87 (0.54-1.42)^{ns}	0.99 (0.48-2.04)^{ns}	1.05 (0.56-1.96)^{ns}
Location							
Northeast	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Midwest	1.14 (0.99-1.31)^{ns}	0.94 (0.7-1.25)^{a}	0.86 (0.6-1.22)^{ns}	1.42 (0.92-2.21)^{ns}	0.83 (0.56-1.22)^{ns}	1.18 (0.66-2.08)^{ns}	1.38 (0.83-2.29)^{ns}
South	1.08 (0.95-1.23)^{ns}	0.73 (0.55-0.96)^{a}	0.65 (0.46-0.92)^{ns}	1.02 (0.65-1.6)^{ns}	0.91 (0.63-1.31)^{ns}	0.88 (0.49-1.59)^{ns}	0.91 (0.54-1.53)^{ns}
West	0.97 (0.84-1.13)^{ns}	1.05 (0.78-1.41)^{a}	0.8 (0.55-1.17)^{ns}	1.52 (0.97-2.36)^{ns}	0.7 (0.46-1.06)^{ns}	1.08 (0.59-1.98)^{ns}	1.08 (0.63-1.86)^{ns}
On dialysis > 1 yr.	-	-	-	1.27 (0.93-1.73)^{ns}	0.94 (0.71-1.24)^{ns}	1.2 (0.73-1.96)^{ns}	1.18 (0.77-1.82)^{ns}
Hemodialysis as RRT	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Peritoneal dialysis as RRT	0.91 (0.76-1.1)^{b}	0.89 (0.59-1.33)^{ns}	1.41 (0.92-2.17)^{ns}	0.68 (0.43-1.07)^{ns}	1.17 (0.83-1.66)^{ns}	0.81 (0.37-1.76)^{ns}	0.73 (0.37-1.45)^{ns}
Transplant as RRT	0.18 (0.07-0.47)^{b}	0.71 (0.18-2.86)^{ns}	-				
Vascular disease	1.41 (1.26-1.58)	0.73 (0.54-0.98)^{a}	0.62 (0.41-0.95)^{a}	-	-	-	-
Diabetes	1.26 (1.06-1.49)^{b}	1.02 (0.68-1.51)^{ns}	1.06 (0.63-1.78)^{ns}	-	-	-	-

Malignancy	1.42 (1.1-1.83)[b]	0.54 (0.24-1.2)[ns]	0.5 (0.16-1.56)[ns]	-	-	-	-
Smoking	1.03 (0.85-1.26)[ns]	0.55 (0.33-0.93)[a]	0.45 (0.21-0.95)[a]	-	-	-	-
Alcohol/drug abuse	0.85 (0.6-1.21)[ns]	0.32 (0.1-1)[a]	0.36 (0.09-1.43)[ns]	-	-	-	-
eGFR > 15 ml/min/1.73 m^2	1.31 (1.11-1.54)[b]	0.5 (0.3-0.85)[b]	0.63 (0.32-1.22)[ns]	-	-	-	-
Body mass index ≥ 30 kg/m^2	0.86 (0.72-1.03)[ns]	1.76 (1.3-2.37)	1.72 (1.18-2.52)[b]	-	-	-	-
Serum albumin < 3.5 g/dL	1.45 (1.28-1.65)	0.82 (0.65-1.04)[ns]	1.08 (0.78-1.49)[ns]	-	-	-	-
Hemoglobin ≥ 9 g/dL	1.02 (0.91-1.14)[ns]	1.01 (0.8-1.28)[ns]	0.89 (0.66-1.2)[ns]	-	-	-	-
Living donor	-	-	-	-	-	0.57 (0.37-0.87)[b]	0.65 (0.45-0.94)[a]

Abbreviations (units): Afr. Am., African American; BMI, body mass index (kg/m^2); eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy. Parameter estimates are presented as hazards ratios, adjusted for era, age, sex, race and Hispanic ethnicity, with 95% confidence intervals in parentheses. Estimates for age, duration of dialysis therapy and mode of dialysis therapy refer to the day of initiation of RRT, listing for transplant and renal transplant. Statistical comparisons are of patients with and without ESRD from SD at initiation of RRT, listing for transplant and renal transplant. Reference groups for statistical comparisons were 1996-2000 era, age < 40 yrs, male, white race, non-Hispanic ethnicity, residence in the Northeast, dialysis < 1 yr., hemodialysis, comorbid condition absent, substance abuse absent, eGFR ≤ 15 ml/min/1.73m^2, BMI < 30 kg/m^2, albumin ≥ 3.5 g/dl, hemoglobin < 9 g/dl and deceased donor. *P*-values < 0.001 unless otherwise indicated. ns. *P*-value ≥ 0.05; a. 0.01 ≤ *P*-value < 0.05; b. 0.001 ≤ *P*-value < 0.01

Figure 1. Incidence trends in ESRD from Scleroderma (SCL) 1996-2012.

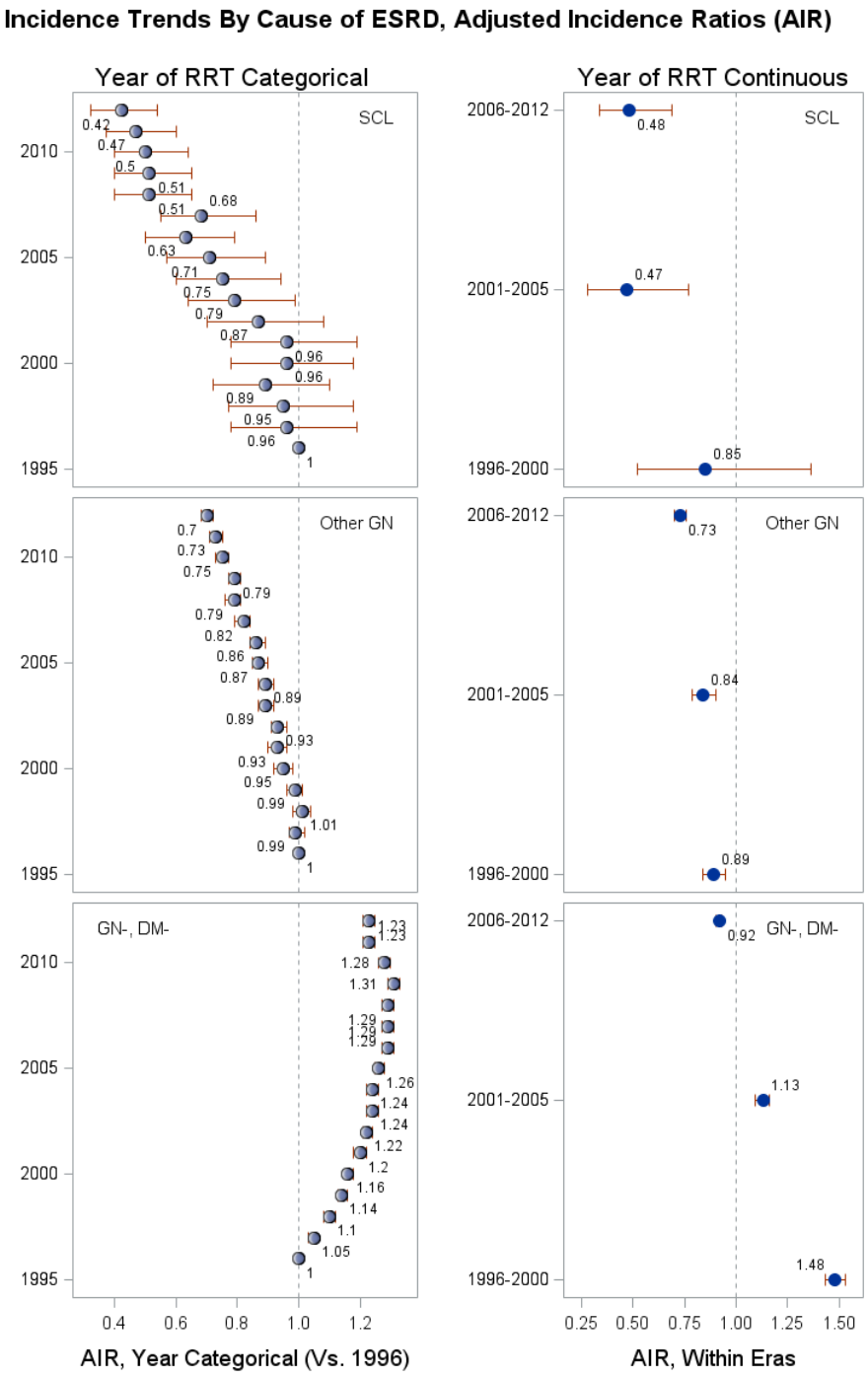
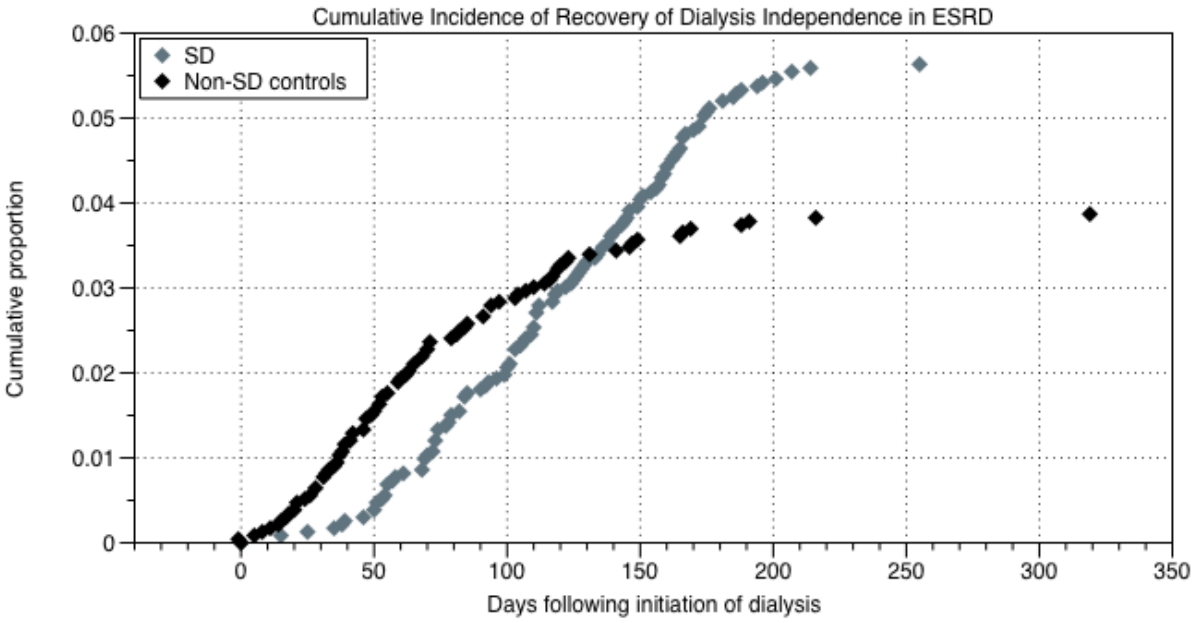


Figure 2. Cumulative incidence of recovery of dialysis independence in scleroderma ESRD and matched ESRD controls without scleroderma.



Summary & relevance of findings

Discriminatory ability of measures of Kidney function for all-cause mortality

Organisations such as the National Foundation Kidney Outcomes Quality Initiative (NKF-K/DOQI) and the Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference and 2012 KDIGO clinical practice guidelines for the evaluation and management of chronic kidney disease recommend that all individuals should be assessed as part of routine health examinations to determine whether they are at increased risk for developing CKD. [1 2] However the United States Preventive Services Task Force (USPSTF) concluded as of 2012 that there was insufficient evidence to advocate population screening for CKD.[3]

The topic of population screening for CKD is controversial for many reasons. Among these are the following: kidney function declines with age, and population studies based on eGFR have reported marked increases in prevalence by age.[4] Separating chronic kidney disease from age related decline per se is difficult, and it is possible that CKD by eGFR thresholds may be a separate entity such as a marker of dysfunctional or accelerated ageing. At a population level the prevalence of CKD when eGFR thresholds alone are used is much higher than when combined with microalbuminuria criteria, in many of those individuals the reduction in eGFR and even measured GFR is isolated without proteinuria or any discernible true cause of kidney disease.[5] This prevalence of CKD by eGFR also depends on which equation is used, serum cystatin C or serum creatinine or the combination of both serum creatinine and serum cystatin C. To suggest that 50% of the population over the age of 70 years have a true disease may be difficult to agree with.[5] Some may struggle to accept that this proportion of the population have a

disease which rarely progresses, is associated with comorbid conditions such as hypertension and diabetes and premature death, in which age is not only a key determinant but is actually embedded in the calculation for estimated kidney function. Since the majority of these individuals die from causes other than kidney disease and never develop end stage renal disease (ESRD),[6] calling this phenomenon a true disease may be difficult to conceive.

While applying the established threshold of an eGFR < 60 ml/min/1.73m^2 and/or ACR > 30 mg/g CKD is uncommon at a population level overall at approximately 12%, which may hamper the cost effectiveness of proposed screening programs. [7] One cost-effectiveness study evaluated screening for microalbuminuria and found that this strategy is likely only to be cost-effective for patients with established diabetes or hypertension, and was not likely to be cost effective in the absence of these two comorbidities.[8]

However our study suggests that as a community we may be disregarding a considerable amount of useful information above and below the accepted thresholds for defining chronic kidney disease. Proponents of CKD screening often focus on ESRD as the outcome of interest. If we critically apply the WHO general principles of screening (Wilson's) criteria, some of the limitations come into clear focus: although CKD by consensus thresholds is likely important, we don't have a specific treatment that is proven to reduce ESRD from randomized trials, nor do we have a specific intervention for mortality reduction beyond cardiovascular risk factor modification. We do have facility for diagnosis and we do have tests to diagnose CKD, however we probably don't know enough about these tests, such as their performance on repeated testing in a stratified random sample of the general population. The natural history of CKD in the population is not adequately understood; there is no agreed policy on who to treat or screen. Given these limitations, if the focus is on ESRD prevention then the cost is not likely to be

balanced by expenditure. In terms of natural history, the hypothesis of progression over time from stage 1 consecutively through to ESRD may or may not be true in the general population, while ESRD is a rare event most people with CKD die before ever reaching ESRD. [6 9]

However, regardless of the pathophysiology, the association of this phenomenon of reduced eGFR with adverse outcomes is consistent across many studies in different populations.[10] It is possible that an estimated GFR below what is expected for age may be a useful risk discriminator for mortality, which may be a more appropriate application rather than the focus on ESRD, which is a rare event in the general population. In the PREVEND study, a general population-based cohort study of 40,854 people aged 28-75 years, identified through linkage with ESRD registry data only 45 people started renal replacement therapy over a 9 year observation period. [9]

However since reduced eGFR and elevated ACR are consistently associated with premature mortality, it is possible that screening for a high risk cardiovascular phenotype through abnormalities in kidney function with mortality reduction as the outcome of interest achieved through cardiovascular risk modification could perhaps be more productive. However there are sparse data pertaining to the issue of screening based on measures of kidney function in order to reduce all-cause mortality. Perhaps eGFR and ACR are better used to identify community dwelling individuals at elevated risk of premature mortality, for who individualized intervention for CVD may reduce all cause mortality. Given the prevalence of hypertension in those with reduced GFR and the findings of the SPRINT trial, hypertension treatment alone may be beneficial, but with a focus on mortality reduction rather than ESRD prevention. [11]

In an ideal situation as a community we would conduct a large randomized trial, following large scale screening after which community dwelling participants are randomized to

attendance of nephrology clinics in the active arm and standard care in the control arm and are monitored for all cause mortality in the long term. However for practical reasons, cost and length of follow up time required we are unlikely to see such a trial conducted. There are a number of possible challenges to such a study including: the typically slow rate of decline in kidney function and the small proportion developing ESRD again makes progression to ESRD a difficult outcome to study without resorting to surrogate markers, and perhaps makes the required sample size prohibitively large. Also accounting for lead-time bias, length-time bias and possible volunteer bias, as well as premature mortality as a competing risk, and the likely high drop out rate for a trial of such duration pose additional challenges. In contrast to diseases such as breast cancer, in a screening paradigm we don't have a specific proven therapy for CKD other than cardiovascular risk modification. [12]

Paradoxically, in theory a strategy aimed at mortality reduction in those with CKD through cardiovascular disease modification and hypertension treatment might actually increase the rate of ESRD by inflating the size of the population at risk and increasing time at risk. This would be of course unless these strategies also reduce the progression to ESRD by a similar or greater magnitude in those with an eGFR between 20 and 60 ml/min/1.73m^2.

So perhaps all-cause mortality in community dwelling individuals is a more relevant outcome for the application of kidney function thresholds. With this in mind, we decided to explore the relative importance of measures of kidney function for mortality prediction in comparison to other well-established clinical parameters such as systolic BP and LDL cholesterol. We also deliberately investigated eGFR and ACR as continuous measures rather than dichotomized by current CKD diagnostic cut-offs. We searched for thresholds that gave equal weighting to false positives and false negatives for mortality at 13 years, since in a

screening context it would seem as important to equally weight these factors rather than maximising specificity and the cost of sensitivity or visa versa, which is the case with, established CKD thresholds.

Measures of kidney function (eGFR) and urinary albumin excretion (ACR) performed well overall in our study, and could perhaps be used in addition to established public health parameters to aid in mortality discrimination in community dwelling individuals. In classification trees considering age in addition to other parameters urinary ACR appeared in the third round within the subgroup defined by age 54-67 years and in the final node of this tree for those with hypertension aged 44-54 years. In trees excluding age from the parent nodes, ACR appeared in the second round and eGFR appeared in the third round in three out of four possible nodes. That is eGFR and ACR ranked higher in terms of Max (Sn/Sp) at these points than other health parameters studied.

We examined mortality over approximately 13 years, considering kidney function in addition to and in the absence of traditional mortality risk factors, and attempted to rank the optimal thresholds for each variable. Overall, age was the most discriminatory variable for all cause mortality. Since age is included in the calculating equations for eGFR it is also possible that some of the discriminatory ability associated with eGFR was actually attributable to the contribution by age.

The performance of clinical parameters of established public health importance for mortality discrimination in our study appeared to vary according to the demographic subgroup within which it is applied in a conditional manner. Kidney function may be at least as important as established mortality risk factors in the risk triage of community dwelling individuals. More studies are needed into the test performance characteristics of eGFR and ACR for CKD and

mortality. Perhaps the focus of studies of CKD screening should shift to mortality reduction at a population level as the primary outcome rather than ESRD prevention, although perhaps a utopian aspiration, a large scale randomized trial of screening community dwelling individuals for CKD and secondary prevention would be ideal.

There are a number of limitations to our study such as the lack of incorporation of socioeconomic factors, the lack of assessment of calibration and external validation of our models on other cohorts. In addition our study did not address morbidity, rather we focused on mortality. The main reason for this was that morbidity is not well captured as part of NHANES, or indeed in the USRDS dataset. We chose to look at mortality since it is a hard outcome, which is less susceptible to many forms of bias, whereas capturing morbidity is more difficult and also more susceptible to bias. While the incorporation of socioeconomic factors would likely increase the robustness of the models, our intention was to build models which could potentially be used in clinical practice to quickly estimate individual level probabilities of the outcome and this socioeconomic data is often not readily available.

Future directions

Since our recursive partitioning analysis was predicated on a sample representative of the general population of the US it may be of interest to assess its applicability to other populations. External validation will allow an assessment not only of the reproducibility of our findings but also the discrimination and calibration of or models. Possible cohorts studies of interest for this application include Northern Ireland Cohort for the Longitudinal study on Ageing (NICOLA), the Irish Longitudinal Study on Ageing (TILDA), and the Health and Retirement Study (HRS), the Berlin Initiative study and the English Longitudinal Study on Ageing (ELSA). The

comparison of model performance in European cohorts compared to the USA based NHANES will be of interest since healthcare in general may be more equitable in Europe.

In the immediate term we plan on applying this methodology to data from the Irish Longitudinal Study on Ageing (TILDA). This is a perfect opportunity to assess the performance of our models on another community dwelling population based cohort outside of the US. TILDA is a nationally representative prospective longitudinal cohort study of community-dwelling adults aged ≥ 50 years resident in the Republic of Ireland. Random sampling of geographical clusters was used to select households (RANSAM sampling framework). Data collection involved an in-home interview, a self-completion questionnaire (CAPI) and a comprehensive health assessment undertaken in the health center or in the respondent's home. The final wave 1 sample was 8,175 adults aged ≥ 50 years. Subsequently, N=5751 completed the health assessment.[13] This will be the first step toward validating our models in an external cohort.

Trends in the incidence and outcomes of ESRD from specific causes

For renal diseases affected by rare conditions such as HIV associated nephropathy, Scleroderma and Hemolytic Uremic Syndrome, we may never have adequately sized randomized trials to evaluate treatment efficacy of interventions. In addition to specific treatments, changes in the general management of patients with kidney disease have changed considerably in the last two decades. Trends in end stage renal disease (ESRD) in these diseases over time at a population level may be quite informative to give some indication as to whether contemporary management regimes are working to prevent the end stage disease scenario.

We observed encouraging declines in ESRD burden from Lupus nephritis, Scleroderma and HIV-associated nephropathy (HIVAN). We cannot glean cause and effect legitimately between treatments such as HAART in HIV, ACE inhibitor use in Scleroderma or Mycophenolate use in Lupus nephritis respectively. Nor can we assume reduced progression to ESRD in the face of a steady incidence of the primary disease since there may be alternative plausible explanations for the observed reductions. These include an under-capturing of ESRD cases, particularly in those not initiating renal replacement therapy, increased mortality as competing risk for ESRD amongst the population at risk, or even a falling incidence of the primary disease coupled with a steady or even an increased progression to ESRD. For example in the case of Lupus nephritis, in theory, declines in the population-level burden of SLE, the risk of kidney disease amongst patients with SLE, and the risk of ESRD among patients with lupus nephritis, could all lead to the apparent trends seen in our study. An additional challenge in our studies was the lack of representative disease-specific population denominators in the US over the same time period for these rare diseases. Difficulties in defining these denominators include

the inability to identify milder cases or account for sampling disparities in race/ethnicity and access to medical care in the US. Furthermore, improved detection of these rare diseases over time may confound comparisons of recent incidence rates to earlier studies.

For diseases such as lupus nephritis in which there are good quality randomized trials to inform management it is also of interest to be aware of the trends in the most severe manifestation of the disease at a population level, whilst acknowledging the limitations of our studies. Our study findings may contribute to a realistic assessment of disease specific management where effective treatments taken from randomized trials, general improvements in the general care of CKD, the delivery of these treatments as well as patient adherence may result in changes in the disease footprint at a national level in the US. We found that standardized incidence ratios of ESRD from lupus nephritis in the US remained static throughout most of the last decade, with an apparent decline in the 2009-2010 biennium. Groups for whom incidence declined included middle and older age groups, women, and Hispanic and non-Hispanic white race/ethnicity; while incidence was stagnant for African American/black race. This disappointing fact for lupus nephritis in African Americans may be related to racial differences in disease severity or response to therapy and/or reduced access to medical care in the United States.

In the case of HIVAN, we found that overall rates of RRT-requiring ESRD declined in the United States between 2001 and 2010. However we found, standardized incidence ratios rose for patients aged older than 64 years. This is consistent with other studies suggesting that with improving survival in HIV, there is an emergence of HIV related disease in older age groups.[14] We also highlighted areas of concern for the future attention such as racial disparities, stagnation of survival rates in the current millennium, and low rates of renal transplant. Moving legislature in the United States could change the landscape for patients with organ failure and HIV, such as

the sanctioning of organ transplantation between HIV-positive donors to HIV-positive recipients in some US states.[15]

For hemolytic uremic syndrome (HUS) we found that the incidence of ESRD remained largely unchanged over the past decade and indeed over the past 15 years of observation. In this study we could not differentiate between different causes of HUS such as Shiga toxin induced HUS vs. atypical and other secondary forms of HUS. Since Shiga toxin associated HUS is rarely associated with ESRD it is likely that HUS cases on maintenance dialysis in the US are due to atypical HUS and other secondary forms. However since HUS may result from heterogeneous causes for this disease in particular the findings may be difficult to interpret. Eculizumab has shown promising non-randomized evidence in atypical HUS for which it received FDA approval. For this reason, updated trends for HUS after 2012 will be of interest in future studies given the approval of Eculizumab in 2012. Whether the therapeutic effect of Eculizumab will result in a change in SIRs of ESRD overall in HUS remains to be seen.

For ESRD from Scleroderma we reported encouraging trends in ESRD. Although we could not identify those with or without scleroderma renal crisis, the overall trends in ESRD were encouraging. Although smaller studies have suggested improved outcomes in scleroderma following the introduction of ACE inhibitors, very few studies have looked at trends in ESRD over time. Studies have also suggested an improved survival in renal crisis and in scleroderma overall, and therefore the reduced trends we observed in the face of improved survival may be even more encouraging for those caring for individuals with SD in the contemporary era.

If death rates from causes other than ESRD have declined, competing risk considerations might suggest that incidence rates of ESRD might increase, because potential time at risk for ESRD would increase. In this scenario, a decline in ESRD rates in some of the diseases studied

may be more impressive considered in the light of survival rates having improved during the timeframe studied. As we stated in our individual studies, the availability of aggregated census data (as opposed to longitudinal data for individuals) precludes the accurate quantification of the true size of a competing death effect.

For many of the diseases under investigation in our studies there was apparent racial heterogeneity in outcomes such as mortality, and renal transplant. Configuration of nephrology care may also be important for patients with these conditions, with length of predialysis nephrology care, smoking, substance abuse, body mass index, and mode of RRT representing potentially modifiable determinants of poorer outcomes, which could at least in theory be improved.

Each of these studies was retrospective and registry-based and lack desirable data elements that a prospective design could provide. A lack of a true renal biopsy tissue diagnosis is a limitation common to each of these studies, since the diagnosis is based on the cause attributed to by the clinician rather than being linked with renal biopsy diagnosis data. While a true tissue diagnosis in all patients would be desirable, this aspiration is unlikely to occur in clinical practice. Thus, it is not possible to refute with certainty the hypothesis that the apparently salutary trends in these diseases reflect changing fashions in labelling the cause of renal disease in patients with these disorders rather than a true change in the incidence. Although perhaps in theory, one might consider this form of bias as a form of random error, and as such might be minimized by the large sample size of the USRDS dataset, however one might also argue that for certain diagnosis there could in fact an element of systematic error in labelling, for example focal segmental glomerulosclerosis (FSGS) in African American race may have been attributed to and HIVAN, and visa versa which may not be accounted for by the large sample size.

Overall, while alternative treatments with fewer side effects are needed for these rare diseases, we found encouraging trends in Lupus nephritis, Scleroderma and HIVAN. With falling mortality in the contemporary era both in the general population and the ESRD population, these trends are perhaps heartening. For conditions such as HUS in which we found plateaued burden for ESRD, time will tell whether approved treatment or other novel treatments will be associated with a reduced ESRD incidence.

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