JIM Original Article

doi: 10.1111/joim.13146

Hypertensive nephrosclerosis: wider kidney biopsy indications may be needed to improve diagnostics

S. I. Hallan[1,2], M. A. Øvrehus[1,2], R. Bjørneklett[3,4], K. I. Aasarød[1,2], A. B. Fogo[5] & J. H. Ix[6,7,8]

From the [1]Department of Clinical and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology; [2]Department of Nephrology, St Olav Hospital, Trondheim University Hospital, Trondheim; [3]Department of Clinical Medicine, Faculty of Medicine, University of Bergen; [4]Emergency Care Clinic, Haukeland University Hospital, Bergen, Norway; [5]Division of Renal Pathology, Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, TN; [6]Nephrology Section, Veterans Affairs San Diego Healthcare System; [7]Division of Preventive Medicine, Department of Family Medicine and Public Health; and [8]Division of Nephrology-Hypertension, University of California San Diego, San Diego, CA, USA

Abstract. Hallan SI, Øvrehus MA, Bjørneklett R, Aasarød KI, Fogo AB, Ix JH (Norwegian University of Science and Technology, Trondheim; Trondheim University Hospital, Trondheim; University of Bergen, Bergen; Haukeland University Hospital, Bergen, Norway; Vanderbilt University Medical Center, Nashville, TN; Veterans Affairs San Diego Healthcare System, San Diego, CA; University of California San Diego, San Diego, CA; University of California San Diego, San Diego, CA, USA). Hypertensive nephrosclerosis: wider kidney biopsy indications may be needed to improve diagnostics (Original Article). *J Intern Med*; 2020;

Background. Hypertensive nephrosclerosis is the presumed underlying cause in many end-stage kidney disease (ESKD) patients, but the diagnosis is disputed and based on clinical criteria with low diagnostic accuracy.

Objective. To evaluate and improve the diagnostic process for nephrosclerosis patients.

Methods. We included adults from the population-based HUNT study (n = 50 552), Norwegian CKD patients referred for kidney biopsy 1988–2012 (n = 7261), and unselected nephrology clinic patients (n = 193) used for matching. Decision tree analysis and ROC curve-based methods of optimal cut-offs were used to improve clinical nephrosclerosis criteria.

Results. Nephrosclerosis prevalence was 2.7% in the general population, and eGFR decline and risk for kidney-related hospital admissions and ESKD were comparable to patients with diabetic kidney disease. In the biopsy cohort, current clinical criteria had very low sensitivity (0.13) but high specificity (0.94) for biopsy-verified arteriolonephrosclerosis. A new optimized diagnostic algorithm based on proteinuria (<0.75 g d^{-1}), systolic blood pressure (>155 mm Hg) and age (>75 years) only marginally improved diagnostic accuracy (sensitivity 0.19, specificity 0.96). Likewise, there were still false-positive cases with treatable diagnoses like glomerulonephritis, interstitial nephritis and others (40% of all test positive). Decision curve analysis showed that the new criteria can lead to higher clinical utility, especially for patients considering the potential harms to be close to the potential benefits, while the more risk-tolerant ones (harm:benefit ratio < 1:4) should consider kidney biopsy.

Conclusion. Further improvements of the current clinical criteria seem difficult, so risks and benefits of kidney biopsy could be more actively discussed with selected patients to reduce misclassification and direct treatment.

Keywords: chronic kidney disease, clinical criteria, diagnostics, harm-to-benefit analysis, kidney biopsy, nephrosclerosis.

Introduction

The incidence of patients with end-stage kidney disease (ESKD) ascribed to hypertensive nephrosclerosis has increased strongly in Europe and the United States over the past 20 years and now constitutes 15% and 28% of all new cases, respectively [1,2]. However, only a few of these patients have a biopsy-verified diagnosis, and the accuracy of clinical criteria used to diagnose nephrosclerosis has long been questioned [3–5]. These problems are also reflected by the wide range of incidence estimates for end-stage nephrosclerosis reported across Europe (5%–33% of ESKD

cases) [2]. In addition, the prevalence and prognosis of hypertensive nephrosclerosis in population-based studies are not well established.

The clinical diagnosis of nephrosclerosis is one of exclusion and typically consists of long-standing hypertension, the absence of diabetes, haematuria, overt proteinuria and the absence of other known CKD causes. Studies on the diagnostic accuracy of these clinical criteria are few, and prior studies have often had suboptimal designs [6–11]. Positive predictive value of 97% in African American patients (n = 39), 75% in Chinese (n = 63), 65% in Brazilian (n = 81) and 48% in Italian (n = 56) patients has been reported [7,9–11]. However, positive (and negative) predictive values are influenced by the prevalence in the population being evaluated. Sensitivity and specificity are better measures of diagnostic accuracy, but this necessitates biopsy verification of both test-positive and test-negative cases. We recently demonstrated that the current clinical nephrosclerosis criteria have very low sensitivity (17%) but high specificity (94%) in a large cohort of patients referred to kidney biopsy [12]. However, these findings could be influenced by the inevitable selection bias of kidney biopsy registries. Others have suggested that hypertensive nephrosclerosis patients should demonstrate subclinical organ damage like left ventricular hypertrophy, [6,8] but these stricter criteria are used more seldom in clinical practice and fewer scientific reports are available.

We therefore studied prevalence, phenotype and prognosis in subjects with hypertensive nephrosclerosis based on clinical criteria who are living in the general population. We aimed to optimize the current clinical diagnostic criteria using patients with arterionephrosclerosis and other relevant biopsy-verified diagnoses after matching these patients to unselected nephrology outpatient clinic patients. Diagnostic challenges in hypertensive nephrosclerosis are closely linked to kidney biopsy indications and the risk for complications, and we therefore included patient's perception of the trade-off between harm and benefit in our evaluation of clinical utility of diagnostic algorithms.

Material and methods

Patient populations

We included subjects from the Norwegian population-based Nord-Trøndelag Health Studies (HUNT) as indicated in Fig. 1. Nord-Trøndelag county has a population of 130 000 residents (>97% white) and is representative of Norway in regard to demographics, income, mortality and morbidity, including ESKD risk. Furthermore, relevant aspects of Norwegian health care in general and kidney medicine, in particular, are not substantially different from that in the rest of Europe and the United States [13]. HUNT invites all residents of Nord-Trøndelag County to participate every 10 years, and the participation rates have been very high with more than 50% of all adults in the county included in the examinations [14]. The study comprises extensive data on medical history and risk factors, a clinical examination, and donation of blood and urine. Information on total CKD prevalence, trends, patient characteristics and methods in the HUNT studies has been published previously [13,15,16]. Hypertensive nephrosclerosis was defined as long-standing hypertension (blood pressure ≥ 140/90 mm Hg or antihypertensive treatment in both HUNT-2 (1995–1997) and HUNT-3 (2006–2008)) with estimated glomerular filtration rate (eGFR) <60 mL^{-1} min^{-1} 1.73 m^2, no diabetes, no history of glomerulonephritis or other kidney diseases, no haematuria and only mild to moderate proteinuria (albumin creatinine ratio (ACR) <30 mg $mmol^{-1}$ or <0.5 g protein day^{-1}) at the HUNT-3 examination [17]. Hypertensive participants were not evaluated for secondary causes, and CKD cases were not referred for further diagnostic evaluations. Diabetic kidney disease (DKD) was defined as physician-verified diabetes mellitus with severely increased urinary albumin excretion (ACR ≥ 30 mg $mmol^{-1}$) or eGFR < 60 mL^{-1} min^{-1} 1.73 m^2. Subjects fulfilling the CKD criteria put forward by KDIGO (eGFR < 60 mL^{-1} min^{-1} 1.73 m^2 or ACR > 3 mg $mmol^{-1}$) but not classified as nephrosclerosis or DKD were grouped as 'other CKD'.

The Norwegian Kidney Biopsy Registry (NKBR) collects clinical and histopathological data for all Norwegian patients who undergo kidney biopsy. The cohort consists of >90% whites, and the biopsy frequency was 150 per million inhabitants per year in 2013 [18]. The registry classifies the biopsy as arterionephrosclerosis if typical findings occur in the absence of other primary renal diagnoses. In patients with other findings like diabetes, glomerulonephritis and amyloid combined with arterionephrosclerosis, the latter is registered as an additional diagnosis only and not considered in the current study. Further details on the

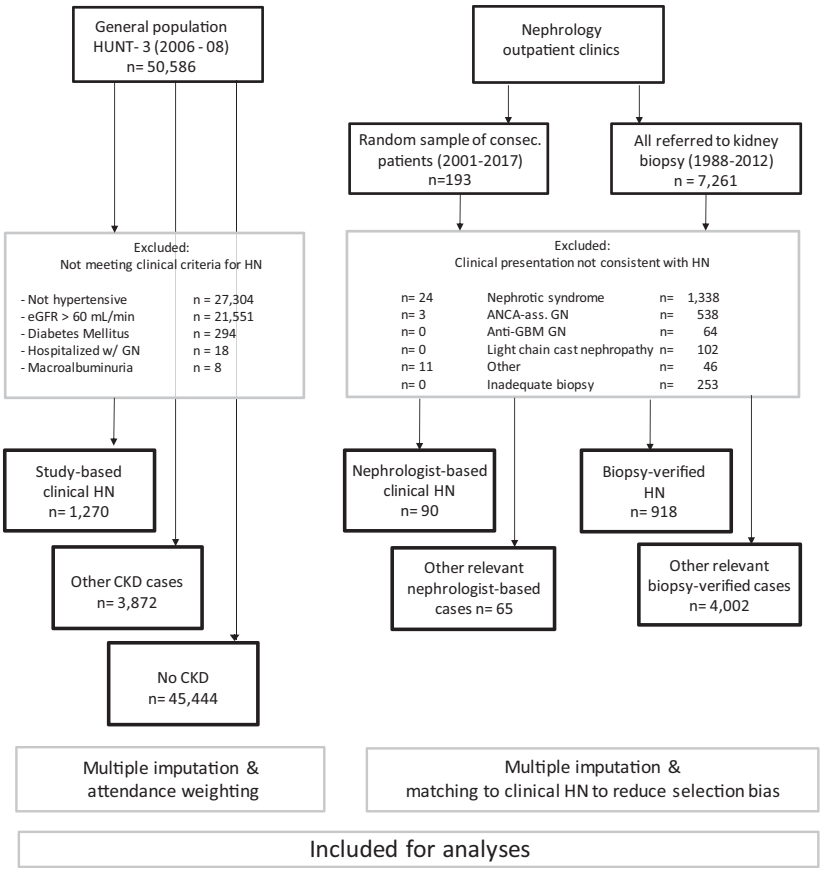

Fig. 1 *Flow chart showing selection of study participants from the population-based HUNT studies and nephrology outpatient clinics (including the Norwegian Kidney Biopsy Registry (NKBR), HN, hypertensive nephrosclerosis).*

histopathological diagnosis of arterionephrosclerosis are given in the Appendix S1 [19]. In addition, representative clinical data obtained prior to the biopsy are provided by the local nephrologist: indication for kidney biopsy (nephrotic syndrome, nephritic syndrome, proteinuria, haematuria, progressive decline in kidney function or acute decline in kidney function), age, sex, height, weight, blood pressure, antihypertensive medication use, and selected blood and urine laboratory values.

We excluded patients from the kidney biopsy registry who either had a clinical presentation that made arterionephrosclerosis very unlikely, or where a specific diagnosis could be made with high probability based on clinical criteria or noninvasive blood testing alone (Fig. 1): nephrotic syndrome, ANCA-associated vasculitis, anti-glomerular basement membrane glomerulonephritis, thrombotic microangiopathy and light-chain cast nephropathy. Included patients therefore comprise a relevant mix of arterionephrosclerosis and other cases where this diagnosis could not be accurately ruled out by clinical presentation or noninvasive tests.

We also studied patients from three hospital-based outpatient clinics considered representative for Norway (one local hospital covering the same area as the HUNT study and two large university hospitals). We included patients where an experienced nephrologist, without doing a kidney biopsy, had concluded that hypertensive nephrosclerosis was the most probable CKD diagnosis: clinical history, physical examination, urine and blood findings, and radiological examinations were integrated with information from the patient's general practitioner and other sources over time as well as the nephrologist's clinical experience. We registered important clinical variables like age, sex, systolic and diastolic blood pressure, diabetes status, BMI, eGFR,

urinary protein excretion, haematuria, total cholesterol and HDL cholesterol. This information was used for matching biopsy-verified arterionephrosclerosis to reduce selection bias [20].

All patients were observed until December 2017 by linkage to the Norwegian Cause of Death Registry and the Norwegian Nephrology Registry, which are both regarded as more than 99% complete regarding death and ESKD status, respectively. For HUNT participants, we also retrieved information on hospital admissions as well as all serum creatinine tests taken by their general practitioners or at outpatient clinics after HUNT3 (2006–2008) to provide information on individual eGFR slopes.

Statistics

We used STATA 13 for statistical analysis (StataCorp LP, College Station, TX, USA). The proportion of missing data for central variables used for clinical diagnosis of arterionephrosclerosis was low to medium in the Norwegian Kidney Biopsy Registry and in HUNT (2%–16%). However, ACR measurements in three urine samples were only done in HUNT participants with diabetes, hypertension or a 5% random subsample, that is these data were missing by design for 85% of HUNT participants. 26% of HUNT-3 participants did not have blood pressure measurements from the HUNT-2 examination. We used multiple imputation with chained equations creating 20 datasets of each database, which were then combined according to Rubin's rules and used in standard statistical analysis [13,16,21–27].

Baseline characteristics were described as mean (standard deviation) and percentage. Prevalence estimates in the HUNT cohort were adjusted for nonattendance. Prognosis was described with Kaplan–Meier plots, and we calculated age-adjusted rates of outcomes using standardized margins (STATA commands *logistic* with adjustment for age, followed by *margins*). Relative risk associations with adjustment for multiple covariates were assessed with Cox regression analysis. For ESKD, we used competing-risks regression based on Fine and Gray's proportional subhazards model. Diagnostic accuracy was evaluated as sensitivity/specificity and positive/negative likelihood ratios since these measures are less dependent of prevalence and enable proper adjustment of pretest probability in individual patients. However, these measures are still influenced by spectrum bias, so we used coarsened exact matching (CEM) to select subjects and generate weights to match relevant kidney biopsy patients to the more typical arterionephrosclerosis patient diagnosed at the outpatient clinics by a nephrologist without biopsy. Variables were first compared using t-test or chi-square test, and those with a false detection rate < 0.05 using Benjamini Hochberg ranking procedure were used for matching.

We used several analytical approaches to evaluate and improve the clinical criteria for nephrosclerosis. Multiway decision tree analysis was performed with the RapidMiner Studio 6.1 software (RapidMiner Inc., Cambridge, MA, USA), which uses a C.4-5 like algorithm to study the type, order and cut-off values of variables. Optimal cut-offs for important variables were also assessed with 'Optimal Cutpoints' package using various evaluations of receiver operating characteristics (ROC) analysis (ROC 01, Youden index, specificity > 0.90, equal sensitivity and specificity, and likelihood ratios of 2.0 and 0.5 for positive and negative tests, respectively) [28]. ROC 01 chooses the ROC curve point closest to the upper left corner (i.e. minimizes $(\text{specificity} - 1)^2 + (\text{sensitivity} - 1)^2$). Youden index is the ROC curve point with the largest difference between the true-positive rate and the false-positive rate (i.e. maximizing sensitivity + specificity − 1). We also built a logistic regression model based on information from the previous analysis for diagnosing arterionephrosclerosis. Internal validation with 10-fold cross validation was used to assess realistic performance measures (RapidMiner X-validation process).

Finally, decision curve analysis (DCA) was used to compare the clinical utility of different diagnostic strategies: biopsy all relevant cases, biopsy none, or biopsy if a 'test' for nephrosclerosis is negative [29–32]. DCA describes the relationship between disease prevalence, predictive characteristics of the test (e.g. a referral algorithm) and individual patient perceived harm-to-benefit ratio for the intervention. Clinical utility (net benefit) = $(\text{true positives}/N) - (\text{false positives}/N) \times (\text{Pt}/1-\text{Pt})$, where Pt (probability threshold) is the level of diagnostic certainty above which the patients would choose to have the intervention. The $(\text{Pt}/1-\text{Pt})$ factor is equivalent to the harm:benefit ratio, that is a factor to incorporate the patient's perception of harms and benefits associated with kidney biopsy and, potentially, disease-specific treatment. No specific harm:benefit ratio is substantiated for

individual patients, rather the DCA visualizes the clinical utility of all referral algorithms over the full range of harm:benefit ratios. See Appendix S1 for further DCA details and statistical methods in general.

All participants gave informed consent when included in the NKBR and the HUNT study. The current study was approved by the Regional Committee for Medical and Health Research Ethics, the Norwegian Data Protection Authority and the Norwegian Ministry of Health.

Results

We included subjects from the general population, nephrology outpatient clinics, and a national kidney biopsy registry (Fig. 1). The prevalence of hypertensive nephrosclerosis, diabetic kidney disease, and other CKD diagnoses was 2.7%, 2.0% and 6.3%, respectively, in the general Norwegian population, 2006–2008, after adjusting for nonparticipation. The 1270 included subjects with a clinical nephrosclerosis diagnosis were, by definition, all hypertensive with a mean blood pressure of 143/73 mm Hg, without diabetes mellitus, and with no or only moderate albuminuria (A1–A2) (Table 1). Compared to other CKD patients in the general population, they had higher age and lower eGFR.

The mean eGFR decline in subjects without CKD was 0.71 mL^{-1} min^{-1} 1.73 m^2 per year (95% confidence interval 0.70–0.72). The eGFR decline in patients with nephrosclerosis, diabetic kidney disease, and other CKD diagnoses was 1.99 (1.95–2.04), 1.54 (1.49–1.60), and 0.97 (0.94–1.00) mL^{-1} min^{-1} 1.73 m^2 per year, respectively. Long-term prognosis for patients with hypertensive nephrosclerosis and other diagnoses in the general population is displayed in Fig. 2. Nephrosclerosis patients had the highest absolute mortality risk; half of patients had died within 10 years (Fig. 2a). On the contrary, ESKD was a very rare event in the general population, and the ESKD-free survival lines for hypertensive nephrosclerosis and DKD were not different (Fig. 2b). However, the nephrosclerosis patients were substantially older than the other groups. Table 2 displays age-adjusted rates for death and ESKD as well as rates for hospital admittance due to acute or chronic kidney disease. In general, subjects without CKD had a low absolute 10-year risk for these kidney-related outcomes (<1%), while the age-adjusted risk in nephrosclerosis patients was several times higher and similar to DKD patients. Table 3 displays relative risks after further adjustments for age, sex, blood pressure, body mass index and smoking. Total mortality risk was significantly lower in patients with nephrosclerosis compared to DKD patients but worse than the other CKD patient group. The multi-adjusted relative risk for ESKD was similar for nephrosclerosis and DKD. Therefore, patients with clinically diagnosed hypertensive nephrosclerosis experience substantially increased risks for kidney-related outcomes.

However, diagnosing hypertensive nephrosclerosis based on clinical criteria in a population-based registry can be inaccurate, while on the other hand biopsy-verified cases are selected and could potentially lead to biased results. Cases diagnosed by nephrologists at outpatient clinics with access to extensive clinical, biochemical and imaging data collected over time are a more representative cohort. We therefore studied clinical characteristics in 90 nonbiopsied patients with a diagnosis of hypertensive nephrosclerosis based on a nephrologist, as well as 4920 patients with biopsy-verified kidney diagnoses who presented with characteristics consistent with nephrosclerosis (Table 1). Many biopsy-verified arterionephrosclerosis patients suffered from diabetes (9.5%), had a positive dipstick for haematuria (34%) and excreted substantial amounts of protein (mean 1.7 g d^{-1}) (Table 1). This was atypical compared to current clinical criteria, but similar characteristics were found in the nonselected outpatient clinic cases. The biopsy-verified cases did have younger age and lower BMI (FDR < 0.05 after adjusting for multiple testing), so further analyses on the biopsy-verified cases were therefore matched on these variables.

The diagnostic accuracy of current clinical criteria and other diagnostic algorithms were tested in the biopsy cohort after matching to the nonbiopsied outpatient nephrosclerosis group to reduce selection bias. When comparing the discriminative potential of various components of the current clinical nephrosclerosis criteria, low proteinuria (<0.5 g d^{-1}) and hypertension had the highest specificity (0.66 and 0.55, respectively) (Table 4). The combination of these two variables had high specificity (0.88) and adding absence of haematuria increased specificity even further (0.94). However, the sensitivity was low for most individual criteria and for their combinations. Overall, the

Table 1. *Baseline characteristics in hypertensive nephrosclerosis (HN) and other relevant patients in various study populations*

	General population (HUNT3)				Nephrology outpatient clinics		
	No CKD (n = 45 444)	HN (n = 1270)	DKD (n = 978)	Other CKD (n = 2894)	Unselected HN (n = 90)	BX-verified HN (n = 918)	Other BX-verified (n = 4002)
Age (years)	51.5 (15.5)	77.2 (8.3)	70.1 (10.7)	62.9 (13.5)	69.5 (67.0–72.1)	56.8 (55.9–57.7)	48.4 (47.8–48.9)
Male sex (%)	45.2	40.3	50.1	48.3	62.9 (52.7–73.2)	68.8 (65.8–71.8)	60.6 (59.1–62.1)
BMI (kg m^{-2})	27.1 (4.4)	28.3 (4.3)	29.8 (5.0)	27.6 (4.4)	28.0 (27.0–29.1)	25.8 (25.4–26.1)	25.5 (25.3–25.7)
DM (%)	2.9	0.0	100.0	1.7	15.7 (8.0–23.4)	9.5 (7.6–11.4)	10.7 (9.8–11.7)
Systolic BP (mm Hg)	129.4 (18.1)	142.8 (22.5)	141.6 (20.9)	137.0 (20.3)	159.1 (153.3–164.9)	152.5 (150.6–154.4)	140.7 (139.9–141.5)
Diastolic BP (mm Hg)	73.0 (11.1)	72.9 (12.6)	73.4 (12.2)	75.3 (11.6)	88.3 (84.1–92.5)	90.0 (88.9–91.1)	83.7 (83.2–84.1)
Cholesterol (mmol L^{-1})	5.49 (1.10)	5.55 (1.22)	5.06 (1.20)	5.64 (1.12)	5.2 (5.0–5.5)	5.4 (5.2–5.6)	5.5 (5.4–5.6)
HDL cholesterol (mmol L^{-1})	1.35 (0.35)	1.28 (0.34)	1.18 (0.34)	1.34 (0.36)	1.3 (1.2–1.4)	1.3 (1.2–1.4)	1.3 (1.3–1.3)
Proteinuria (g/24 h)	0.04 (0.02)	0.08 (0.07)	0.17 (0.40)	0.06 (0.11)	1.7 (1.1–2.3)	1.7 (1.5–1.8)	2.1 (2.0–2.2)
Haematuria (%)	??				38.2 (27.9–48.5)	34.2 (31.1–37.3)	53.7 (52.2–55.3)
eGFR (mL^{-1} min^{-1} 1.73 m^2)	98.0 (16.2)	48.6 (9.8)	71.6 (20.2)	81.4 (20.8)	40.3 (37.1–43.5)	42.4 (40.5–44.2)	52.3 (51.2–53.4)

Data are mean (SD) or percentages after imputation of missing values. In the general population, 'Other CKD' means all CKD patients except those fulfilling the arterionephrosclerosis criteria using the HUNT database. For the outpatient clinic and the kidney biopsy registry, 'Other CKD' means patients with glomerulonephritis, diabetic nephropathy or interstitial nephritis in most cases since we excluded those with nephrotic syndrome, acute kidney injury, ANCA-associated vasculitis, anti-GBM glomerulonephritis, thrombotic microangiopathy and paraprotein-related disease to create a relevant group of patients where arterionephrosclerosis could be a reasonable differential diagnosis.

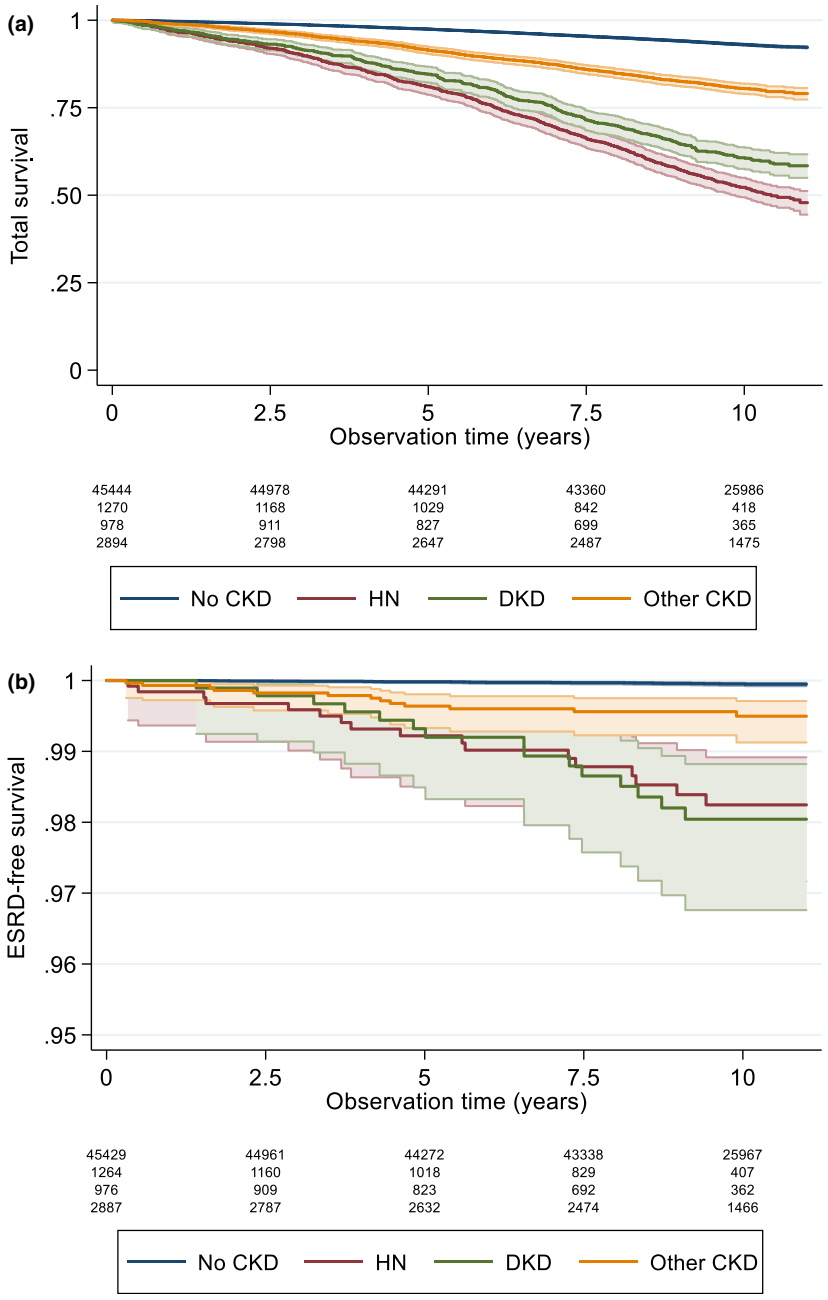

Fig. 2 *Total and ESKD-free survival by kidney diagnosis in the general population (figures a and b: 4827 deaths and 67 patients starting RRT over 494 892 observation years).*

current criteria had a sensitivity of 0.13 and a specificity of 0.94.

We therefore performed additional analyses to explore the potential for improving the clinical diagnostic criteria. Decision tree analysis was used to evaluate the order, cut-off and type of variables to include in a model. Lower proteinuria (<0.75 g d^{-1}), higher systolic blood pressure (>155 mmHg) and higher age (>75 years) were suggested as major criteria (Fig. 3). Additional evaluation with various receiver operation curve

Table 2. *Ten-year age-adjusted rates for death and kidney-related outcomes in the general population (HUNT-3) by CKD diagnoses*

Outcome	No CKD (n = 45 444)	HN (n = 1270)	DKD (n = 978)	Other CKD (n = 2894)
Death risk (%, n = 4827)	23.3 (22.6–23.9)	30.9 (29.1–32.8)	37.0 (34.6–39.4)	27.7 (26.2–29.3)
ESKD risk (%, n = 67)	0.05 (0.03–0.08)	1.3 (0.6–1.9)	1.5 (0.8–2.3)	0.5 (0.2–0.7)
CKD hospital admittance (%, n = 309)	0.5 (0.3–0.6)	5.7 (4.7–6.8)	4.8 (3.5–6.1)	2.4 (1.7–3.0)
AKI hospital admittance (%, n = 271)	0.9 (0.7–1.0)	2.7 (2.0–3.4)	3.2 (2.1–4.3)	1.6 (1.1–2.1)

Marginal standardization (*logistic regression* followed by *margins*) was used to estimate 10-year rates (% with outcome within 10 years) adjusted for age (95% confidence intervals).
DKD, diabetic kidney disease; HN, hypertensive nephrosclerosis.

(ROC)-based methods confirmed that these cut-offs were optimal in most sensitivity/specificity trade-off scenarios (Table 5). Based on these findings, we suggested a new dichotomous model ('New Clinical Criteria') for diagnosing nephrosclerosis with slightly higher proteinuria cut-off (<0.75 g d^{-1}) as the first criterion and adding age (>75 years) to the subgroup with high systolic blood pressure (>155 mm Hg) while those with lower blood pressure should have very low proteinuria (<0.10 g d^{-1}), see Fig. 3. We also suggested a regression-based model ('New Regression Model') using continuous (age, blood pressure and proteinuria) as well as dichotomous (sex, haematuria and diabetes) variables. The 'New Clinical Criteria' had improved sensitivity (0.19) and specificity (0.96) compared to 'Current Clinical Criteria' with the diagnostic odds ratio (DOR, i.e. the likelihood ratio for a positive test divided by the likelihood ratio for a negative test) increasing from 2.4 to 5.7 (Table 6). However, there was still many false-positive cases with other treatable diagnoses like glomerulonephritis, interstitial nephritis and other diagnoses (40% of all with positive test). The 'New Regression Model' had slightly higher sensitivity (17% vs. 13%) for the equivalent level of specificity (94%) compared to the current criteria, which combined into a moderately improved DOR value (3.3).

The clinical utility of these diagnostic algorithms also depends on the individual patient's valuation of harms (biopsy risk, financial costs, concerns, etc.) versus benefits (potential improved health outcomes due to more specific confirmation of the diagnosis and directed treatments). Fig. 4 shows that if a patient and his or her provider judge that the risks of biopsy equals the benefits (harm: benefit ratio 1:1), the best overall strategy to diagnose nephrosclerosis was to use the 'New Clinical Criteria' model (red line), while all other alternatives would do more harm than good (negative utility). The 'New Clinical Criteria' model also remains the best option for patients considering the harm:benefit ratio to be more favourable, i.e. decreasing (e.g. harm:benefit ratios from 1:1 to 1:4). However, since algorithms based on clinical variables have a low diagnostic accuracy, patients considering the harm:benefit ratio to be <1:4 should choose the 'Biopsy All' option.

Discussion

The prevalence of hypertensive nephrosclerosis was high in the general population, but the current clinical criteria had low diagnostic accuracy. However, the diagnosis nevertheless carried a substantially increased risk for ESKD and death. Diagnostic strategies based on new optimized clinical criteria had, after considering patients' valuation of risks and benefits, a small but significantly higher clinical utility than current clinical criteria. Risk-willing patients could consider the 'Biopsy All' option to avoid a false-positive diagnosis of nephrosclerosis and thereby losing the opportunity of more specific treatment of their kidney disease.

The true prevalence of nephrosclerosis in the general population is unknown since there has been a general advice against biopsying CKD patients without proteinuria or haematuria. Italian studies found that hypertensive/ischaemic nephropathy posed one quarter of CKD, which gave a prevalence of 3.4% at age over 40 years [33,34]. A Japanese study used nonproteinuric CKD as a proxy for hypertensive nephrosclerosis

Table 3. *Adjusted risk for death and ESKD in the general population by CKD diagnoses*

	Adjusted for age & sex		Adjusted for age, sex, sBP, BMI and smoking	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Death				
No CKD	1.00	(Ref.)	1.00	(Ref.)
Hypertensive nephrosclerosis	1.43 (1.31–1.57)	<0.001	1.47 (1.33–1.62)	<0.001
Diabetic kidney disease	1.93 (1.73–2.14)	<0.001	1.91 (1.70–2.15)	<0.001
Other CKD	1.32 (1.21–1.44)	<0.001	1.27 (1.15–1.40)	<0.001
ESKD				
No CKD	1.00	(Ref.)	1.00	(Ref.)
Hypertensive nephrosclerosis	19.2 (6.1–60.0)	<0.001	15.4 (4.6–51.9)	<0.001
Diabetic kidney disease	17.7 (6.3–49.9)	<0.001	18.8 (6.4–55.8)	<0.001
Other CKD	7.8 (3.1–19.2)	<0.001	6.8 (2.7–17.6)	<0.001

Data are hazard ratios for experiencing death during the 10-year observation period (Cox regression) and sub hazard ratios for experiencing ESKD before death (Fine Grey competing risk regression).

and estimated a prevalence of 10% in women and 15% in men above the age of 40, but these diagnostic criteria were much wider than in most other studies [35]. We found that the current clinical criteria classified 2.8% of the general adult population as hypertensive nephrosclerosis (3.8% at age 40+), but the true prevalence could be substantially higher given the high number of false-negative cases versus the number of false-positive cases.

The prognosis for patients diagnosed with hypertensive nephrosclerosis in the general population using clinical criteria is studied in few cohorts. A very interesting Japanese study followed 50 patients with diabetic kidney disease and 50 patients with hypertensive nephrosclerosis diagnosed with biopsy or extensive clinical examinations from CKD stage 2/3a to renal replacement therapy initiation [36]. The overall kidney function decline was not very different between DKD and nephrosclerosis patients over this up to 20-year observation period, but the DKD patients followed a trajectory on the KDIGO heat map with an initial phase with rather stable kidney function but increasing albuminuria followed by a rapid decline in kidney function. Hypertensive nephrosclerosis patients, on the other hand, displayed a slower but inexorable decline in kidney function from the start of the study. Our population-based nephrosclerosis patients were, except for a higher age, quite similar to these Japanese cases and displayed a rather similar mortality and ESKD risk. Current data therefore indicate that even population-based hypertensive nephrosclerosis patients have a substantially increased risk and are not merely normal ageing.

The diagnostic accuracy of the current clinical criteria has only been studied in a few studies and has been hampered with suboptimal designs. The positive predictive value ranged 40%–97%, [7,9–12] and the full diagnostic accuracy was not studied until we recently gave estimates of both sensitivity and specificity (0.17 and 0.94, respectively) [12]. To improve this very disappointing accuracy, we need more data on the performance of the individual clinical criteria and suggestions of new diagnostic algorithms, but we are not aware of any such studies. Our current study indicates that hypertension and proteinuria add specificity, while absence of haematuria and high eGFR contribute to sensitivity. However, the two latter criteria were not selected by the decision tree analysis used to build a more optimal diagnostic model. Instead, age was selected, and >75 years was suggested as cut-off in ROC-based analyses. Correspondingly, we suggest higher cut-offs for proteinuria and systolic blood than the current clinical criteria (<0.75 g d^{-1} and >155 mm Hg, respectively). Selecting the optimal cut-off is a trade-off between sensitivity and specificity. Traditionally, higher sensitivity is prioritized when picking up more true-positive cases is important, while higher

Table 4. *Discriminative potential of the various components of clinical nephrosclerosis criteria*

	+HT	+HT + Proteinuria	+HT + Proteinuria + Haematuria	+HT + Proteinuria + Haematuria + DM
Hypertension (140/90)				
Sensitivity (%)	64.0 (60.8–67.2)			
Specificity (%)	54.5 (52.9–56.1)			
Proteinuria (<0.5 g d^{-1})				
Sensitivity (%)	40.8 (37.4–44.1)	23.5 (20.6–26.4)		
Specificity (%)	66.1 (64.5–67.6)	87.7 (86.6–88.8)		
Haematuria (absent)				
Sensitivity (%)	65.8 (62.7–68.9)	43.0 (39.7–46.2)	16.1 (13.6–18.5)	
Specificity (%)	53.8 (52.2–55.3)	76.8 (75.5–78.1)	93.9 (93.1–94.7)	
Diabetes (absent)				
Sensitivity (%)	90.5 (88.6–92.4)	57.7 (54.4–61.0)	21.4 (18.6–24.1)	14.0 (11.7–16.3)
Specificity (%)	10.7 (9.8–11.7)	61.3 (59.7–62.8)	88.9 (87.8–89.9)	94.8 (94.0–95.5)
eGFR (<60 mL min^{-1})				
Sensitivity (%)	75.4 (72.6–78.2)	50.6 (47.3–53.9)	18.0 (15.5–20.6)	13.7 (11.4–16.0)
Specificity (%)	40.1 (38.6–41.6)	66.4 (64.9–67.9)	90.9 (89.9–91.9)	94.8 (94.0–95.5)
				11.8 (9.5–13.9)
				95.6 (94.9–96.3)

Sensitivity and specificity with 95% confidence intervals of the various components and their combinations were calculated using biopsy-verified arterionephrosclerosis as gold standard.

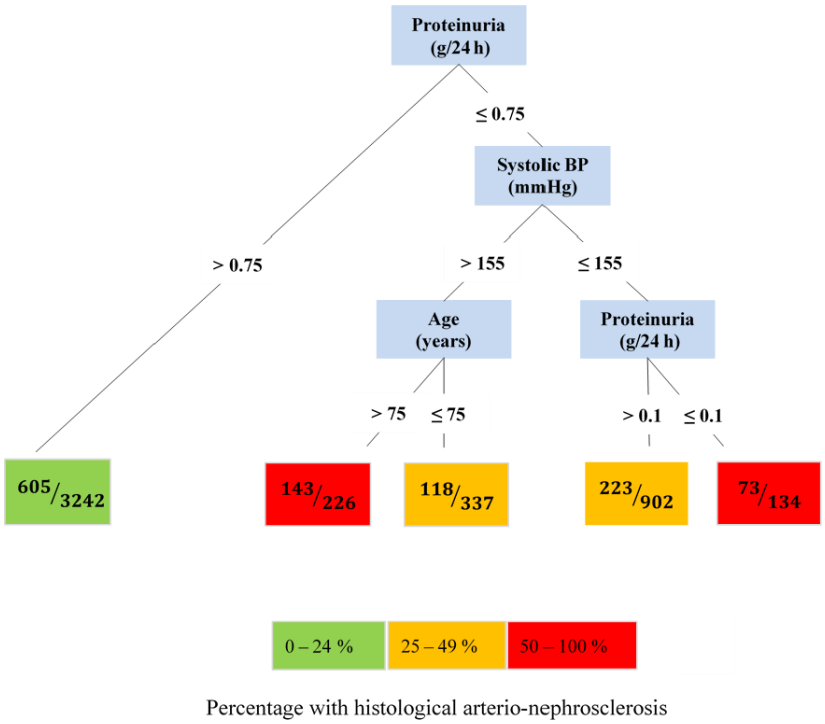

Fig. 3 *Decision tree analysis to evaluate the order, cut-off and type of variables to be included for diagnosing hypertensive nephrosclerosis. Proportion of biopsy-verified arterionephrosclerosis in each category is displayed.*

Table 5. *Optimal cut-offs with corresponding sensitivity and specificity for important nephrosclerosis variables based on different selection methods*

Method	Proteinuria (g d^{-1})	Systolic BP (mm Hg)		Age (years)	
			Subgroup A	All	Subgroup B
Subgroup	All (ROC 0.610)	All (ROC 0.575)	(ROC 0.581)	(ROC 0.497)	(ROC 0.600)
ROC 01	<0.8 (48/71)	>155 (51/65)	150 (56/59)	NA	>75 (53/73)
Youden index	<0.7 (47/72)	>155 (51/65)	155 (47/71)	NA	>75 (53/75)
Specificity ≥ 0.85	<0.3 (17/92)	>171 (23/86)	167 (20/86)	NA	>80 (9/88)
Equal Sens & Spec	<1.3 (56/56)	>150 (59/54)	145 (56/57)	NA	>72 (57/54)
LR = 2.0 for positive test	<0.3 (16/92)	>205 (3/99)	205 (3/98)	NA	>75 (53/73)
LR = 0.5 for negative test	<3.2 (88/24)	>100 (99/1)	111 (97/7)	NA	>58 (93/14)

For example, when using ROC 01 (selecting the point on the ROC curve closest to the upper left corner to maximize overall accuracy), we find that the optimal cut-off for proteinuria is < 0.8 g d^{-1} and the corresponding sensitivity is 48% and specificity is 71%. Subgroups are chosen according to the results of the classification tree analysis: subgroup A is proteinuria < 0.75 g d^{-1}; subgroup B is proteinuria < 0.75 g d^{-1} and systolic blood pressure > 155 mm Hg.
NA, data not available since the overall ROC curve was not statistically different from a value of 0.500.

specificity is suitable when we want to exclude a diagnosis and avoid false-positive cases, for example in a screening situation [37]. In the current setting, these two goals are interwoven, and we therefore focused on ROC 01 and the Youden methods which prioritize total diagnostic accuracy (total area under the ROC curve). However, the optimized clinical criteria

Table 6. *Diagnostic performance of current and proposed diagnostic criteria for hypertensive nephrosclerosis*

	Current criteria	New clinical criteria	New regression model
Sensitivity (%)	13.2 (11.3–15.3)	19.2 (17.0–21.5)	16.9 (14.8–19.1)
Specificity (%)	93.9 (93.1–94.7)	96.0 (95.3–96.6)	94.1 (93.3–94.8)
Likelihood Ratio (+)	2.17 (1.79–2.63)	4.78 (3.93–5.82)	2.86 (2.39–3.42)
Likelihood Ratio (−)	0.92 (0.90–0.95)	0.84 (0.82–0.87)	0.88 (0.86–0.91)
Positive predictive value (%)	40.5 (35.9–45.2)	60.0 (55.2–64.6)	47.3 (42.8–51.8)
Negative predictive value (%)	77.6 (77.1–78.0)	79.1 (78.6–79.6)	78.3 (77.8–78.8)
Diagnostic Odds Ratio (LR+/LR−)	2.36	5.69	3.25

95% confidence intervals for the estimates are given in parentheses. Data are from CKD patients with relevant biopsy-verified diagnoses matched to clinical characteristics of typical arterionephrosclerosis patients diagnosed by a nephrologist at the outpatient clinic without biopsy.
Current clinical criteria: hypertension (>140/90 mm Hg), proteinuria < 0.5 g/24 h, no haematuria, no DM and no other CKD diagnosis.
New clinical criteria: proteinuria < 0.75 g/24 h, and age > 75 if systolic BP > 155 mm Hg or proteinuria < 0.10 g/24 h if systolic BP < 155 mm Hg. New regression model: age, systolic BP, diastolic BP and proteinuria as continuous variables; sex, haematuria and diabetes as dichotomous variables. (Probability cut-off for ± HN was set to p(D) > 0.40 to achieve the same specificity as the current clinical criteria to enhance the comparison between the diagnostic algorithms).

(proteinuria < 0.75 g d^{-1}, systolic blood pressure >
155 mm Hg, and age > 75 years) only led to a moderate improvement of the diagnostic accuracy. Further research is therefore strongly needed, and noninvasive methods based on new –omics technologies could push the field forward [38].

Our study has some important limitations. The optimal design should include all incident patients with a clinical phenotype compatible with nephrosclerosis and refer all patients to kidney biopsy to get a definitive diagnosis. This is, however, neither ethical nor practical possible, and all studies on the current topic will be influence by selection bias. We tried to reduce such bias by matching the biopsy-verified cases with nonbiopsied hypertensive nephrosclerosis cases from the nephrology clinic for central characteristics, but it is difficult to estimate the amount of residual bias. Missing data were imputed to avoid bias, and we used 10-fold cross validation to avoid overfitting of new models. We included only white Northern European subjects, and generalization to other regions should be done with caution (and for African Americans not at all). Although we did internal validation to avoid overoptimistic performance characteristics, external validation is needed. Finally, we did not have information on cardiovascular mortality, but it is reasonable to assume that a large proportion of our CKD patients died due to cardiovascular disease [39].

All things considered, our findings could have important clinical consequences. Kidney biopsy is, in general, a safe procedure when performed *lege artis*, [40] but all recommendations highlight the need to be sure that the risk of the procedure and treatment is acceptable for the patient [41]. Decision curve analyses is a new technique to include patient preferences and risk willingness, [42] and the method has increasingly been used to evaluate nephrology prediction models for mortality and ESKD risk, residual kidney function, transplant outcomes and acute kidney injury risk [43–46]. Studies have demonstrated that serious (but nonlethal) biopsy complications occur in <5%, while the biopsy information changes the diagnosis in two thirds and the treatment in one third of cases [47]. However, the harm:benefit (H:B) ratio could be less advantageous in arterionephrosclerosis, and our 'New Clinical Criteria' model could perform less favourable in other cohorts. Currently, there are no studies on how patients evaluate the specific harm versus benefit relationship for diagnosing nephrosclerosis. In general, the majority of patients tend to be risk averse. However, patients often accept higher risk than their physician, and studies show that there is a substantial number of patients (15%–25% depending on the clinical situation) who are willing to take higher risks [48–51]. The risk willingness is only weakly associated with patient characteristics, and the biopsy complication risk and the clinical benefit from a more precise diagnosis are not different

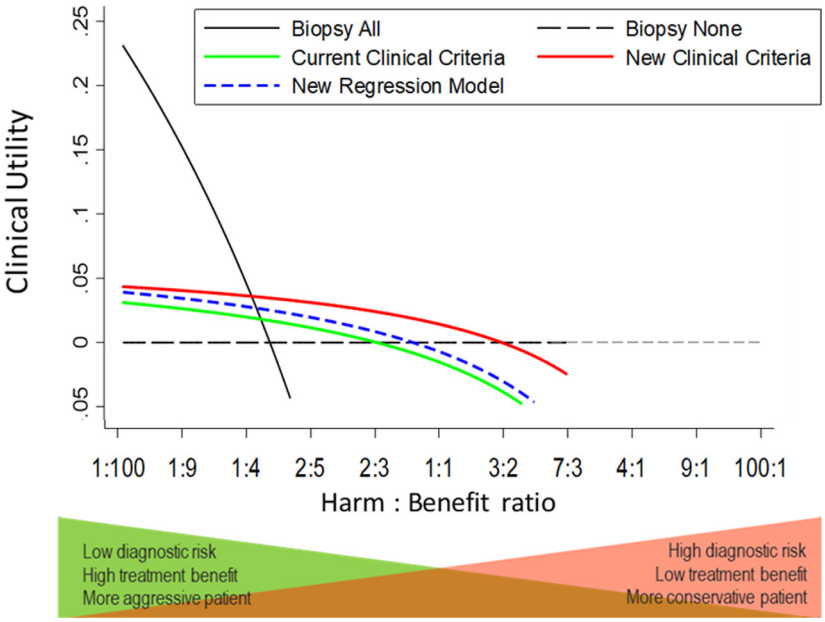

Fig. 4 *Decision curve analysis displaying clinical utility (net benefit) versus patient's preferences in a relevant group of kidney patients. A negative test ('Current Criteria', 'New Criteria' or 'New Regression Model') for nephrosclerosis is followed by a kidney biopsy and potentially disease-specific treatment. Net Benefit is the benefit minus the harm for the total group adjusted for the individual patient's perception of the trade-off between harm and benefit (Benefit = (true positives/*N*) − (false positives/*N*) × harm/benefit ratio).*

in younger versus older patients. Although we demonstrated that higher age increased the risk of hypertensive nephrosclerosis, the clinical criteria still had a low diagnostic accuracy. Kidney biopsy is a relevant option even in elderly patients, and physicians must therefore discuss or formally evaluate each patient to elicit their evaluation of these aspects.

In clinical practice, some patients and providers will consider the H:B ratio for arterionephrosclerosis to be rather disadvantageous (>3:2). None of the tested algorithms will give a positive clinical utility for these patients, so the 'Biopsy None' option is the best advice. Based on our clinical experience, we estimate that many patients would consider the H:B ratio to be in the 1:4 to 3:2 range. For these, the 'New Clinical Criteria' model is the best choice. For low-risk patients wanting a more aggressive diagnostic approach (H:B ratio < 1:4), the 'Biopsy All' strategy could give higher benefit than the clinical criteria-based options. However, whether and how much the indications for biopsy should be widened warrants further discussions and studies.

In conclusion, hypertensive nephrosclerosis is a common disease and carries an increased risk of kidney-related outcomes and death comparable to DKD in the general population. Optimizing the clinical criteria improved the clinical utility of the current diagnostic process only moderately. A more liberal biopsy policy could theoretically increase benefit by reducing misclassification and direct treatment for a subgroup of patients. Our study highlights the need for further research on the diagnostic process in patients suspected to have hypertensive nephrosclerosis.

Acknowledgements

The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre, (Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology), Trøndelag County Council, Central Norway Regional Health Authority and the Norwegian Institute of Public Health. The project was supported by a research grant from the Liaison Committee between The Central Norway Regional Health Authority (RHA) and The Norwegian University of Science and Technology (NTNU).

Author Contribution

Stein Hallan: Conceptualization (lead); Formal analysis (lead); Writing-original draft (lead); Writing-review & editing (equal). **Marius A Øvrehus:** Formal analysis (equal); Writing-review & editing (equal). **Rune Bjørneklett:** Data curation (equal); Resources (equal); Writing-review & editing (equal).

Knut I Aasarød: Data curation (equal); Methodology (equal); Writing-review & editing (equal). **Agnes Fogo:** Formal analysis (equal); Methodology (equal); Writing-review & editing (equal). **Joachim H Ix:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Methodology (equal); Supervision (equal); Writing-review & editing (equal).

Conflict of interest statement

None of the authors have any financial or other conflict that potentially could influence the current manuscript.

References

1 Saran R, Li Y, Robinson B *et al.* Renal data system 2015 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis* 2016; **67:** Svii, S1–305.
2 ERA-EDTA Registry. Annual report 2017. Accessed March 1. 2020 at https://www.era-edta-reg.org/index.jsp?p=14
3 Weisstuch JM, Dworkin LD. Does essential hypertension cause end-stage renal disease? *Kidney Int* 1992; **36:** S33–37.
4 Luft FC. Hypertensive nephrosclerosis-a cause of end-stage renal disease? *Nephrol Dial Transplant* 2000; **15:** 1515–517.
5 Meyrier A. Nephrosclerosis: a term in quest of a disease. *Nephron* 2015; **129:** 276–82.
6 Schlessinger SD, Tankersley MR, Curtis JJ. Clinical documentation of end-stage renal disease due to hypertension. *Am J Kidney Dis* 1994; **23:** 655–60.
7 Guo YS, Yuan WJ, Yu JP *et al.* Clinical and pathological characteristics in patients with clinically presumed hypertensive nephrosclerosis. *Zhonghua Xin Xue Guan Bing Za Zhi* 2006; **34:** 391–95.
8 Zarif L, Covic A, Iyengar S, Sehgal AR, Sedor JR, Schelling JR. Inaccuracy of clinical phenotyping parameters for hypertensive nephrosclerosis. *Nephrol Dial Transplant* 2000; **15:** 1801–807.
9 Zucchelli P, Zuccala A. Recent data on hypertension and progressive renal disease. *J Hum Hypertens* 1996; **10:** 679–82.
10 Fogo A, Breyer JA, Smith MC *et al.* Accuracy of the diagnosis of hypertensive nephrosclerosis in African Americans: a report from the African American Study of Kidney Disease (AASK) Trial. AASK Pilot Study Investigators. *Kidney Int* 1997; **51:** 244–52.
11 Caetano ER, Zatz R, Saldanha LB, Praxedes JN. Hypertensive nephrosclerosis as a relevant cause of chronic renal failure. *Hypertension* 2001; **38:** 171–76.
12 Øvrehus MA, Oldereid TS, Dadfar A *et al.* Clinical phenotypes and long-term prognosis in whites with biopsy-verified hypertensive nephrosclerosis. *Kidney Int Rep* 2019; **5:** 339–347.
13 Hallan SI, Ovrehus MA, Romundstad S *et al.* Long-term trends in the prevalence of chronic kidney disease and the influence of cardiovascular risk factors in Norway. *Kidney Int* 2016; **90:** 665–73.
14 Krokstad S, Langhammer A, Hveem K *et al.* Cohort profile: the HUNT study. *Norway. Int J Epidemiol* 2013; **42:** 968–77.
15 Hallan SI, Coresh J, Astor BC *et al.* International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol* 2006; **17:** 2275–284.
16 Hallan SI, Ritz E, Lydersen S, Romundstad S, Kvenild K, Orth SR. Combining GFR and albuminuria to classify CKD improves prediction of ESRD. *J Am Soc Nephrol* 2009; **20:** 1069–77.
17 Wright JT Jr, Kusek JW, Toto RD *et al.* Design and baseline characteristics of participants in the African American Study of Kidney Disease and Hypertension (AASK) pilot study. *Control Clin Trials* 1996; **17:** S3–16.
18 Norwegian Kidney Biopsy Register. Annual reports. Accessed October 20, 2019, http://nephrono/nnr/AARSRAPPORT_NNR_2017pdf. 2018.
19 Churg J, Bernstein J, Glassock RJ. *Renal Disease: Classification and Atlas of Glomerular Diseases*, (2nd ed). New York: Igaku-Shoin, 1995.
20 Blackwell MIS, King G, Porro G. cem: Coarsened exact matching in Stata. *Stata Journal.* 2009; **9:** 524–46.
21 Newgard CD, Haukoos JS. Advanced statistics: missing data in clinical research–part 2: multiple imputation. *Acad Emerg Med* 2007; **14:** 669–78.
22 Rubin DB. *Multiple Imputations for Nonresponse in Surveys.* New York: J. Wiley & Sons, 1987.
23 Siew ED, Peterson JF, Eden SK, Moons KG, Ikizler TA, Matheny ME. Use of multiple imputation method to improve estimation of missing baseline serum creatinine in acute kidney injury research. *Clin J Am Soc Nephrol* 2013; **8:** 10–18.
24 Marshall A, Altman DG, Royston P, Holder RL. Comparison of techniques for handling missing covariate data within prognostic modelling studies: a simulation study. *BMC Med Res Methodol* 2010; **10:** 7.
25 Rassler S, Rubin DB, Zell ER. Incomplete data in epidemiology and medical statistics. In: Rao CR, Miller J, Rao DC, eds. *Handbook of Statistics.* vol 27. Amsterdam, The Netherlands: Elsevier, 2008; 569–601.
26 Schafer JL, Graham JW. Missing data: our view of the state of the art. *PsycholMethods* 2002; **7:** 147–77.
27 van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *StatMed* 1999; **18:** 681–94.
28 López Ratón M, Rodríguez Álvarez MX, Cadarso Suárez CM, Gude Sampedro F. OptimalCutpoints: An R package for selecting optimal cutpoints in diagnostic tests. *J Stat Softw* 2014; **61:** 1–36.
29 Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making* 2006; **26:** 565–74.
30 Kerr KF, Brown MD, Zhu K, Janes H. Assessing the clinical impact of risk prediction models with decision curves: guidance for correct interpretation and appropriate use. *J Clin Oncol* 2016; **34:** 2534–540.
31 Fitzgerald MS, Saville BR, Lewis RJ. Decision curve analysis. *JAMA* 2015; **313:** 409–10.
32 McNeil BJ, Keller E, Adelstein SJ. Primer on certain elements of medical decision making. *N Engl J Med* 1975; **293:** 211–15.
33 Gambaro G, Bonfante L, Abaterusso C *et al.* High chronic nephropathy detection yield in CKD subjects identified by the combination of albuminuria and estimated GFR. *Nephrol Dial Transplant* 2012; **27:** 746–51.

34 Gambaro G, Yabarek T, Graziani MS *et al.* Prevalence of CKD in northeastern Italy: results of the INCIPE study and comparison with NHANES. *Clin J Am Soc Nephrol* 2010; **5:** 1946–953.
35 Shiraishi N, Kitamura K, Kohda Y, Iseki K, Tomita K. Prevalence and risk factor analysis of nephrosclerosis and ischemic nephropathy in the Japanese general population. *Clin Exp Nephrol* 2014; **18:** 461–68.
36 Abe M, Okada K, Maruyama N, Takashima H, Oikawa O, Soma M. Comparison of clinical trajectories before initiation of renal replacement therapy between diabetic nephropathy and nephrosclerosis on the KDIGO guidelines heat map. *J Diabetes Res* 2016; **2016:** 5374746.
37 Chubak J, Pocobelli G, Weiss NS. Tradeoffs between accuracy measures for electronic health care data algorithms. *J Clin Epidemiol* 2012; **65:** 343–49.e2.
38 Schaub JA, Hamidi H, Subramanian L, Kretzler M. Systems biology and kidney disease. *Clin J Am Soc Nephrol* 2020; **15:** 695–703.
39 Thompson S, James M, Wiebe N *et al.* Cause of death in patients with reduced kidney function. *J Am Soc Nephrol* 2015; **26:** 2504–511.
40 Tondel C, Vikse BE, Bostad L, Svarstad E. Safety and complications of percutaneous kidney biopsies in 715 children and 8573 adults in Norway 1988–2010. *Clin J Am Soc Nephrol* 2012; **7:** 1591–597.
41 Hogan JJ, Mocanu M, Berns JS. The native kidney biopsy: update and evidence for best practice. *Clin J Am Soc Nephrol* 2016; **11:** 354–62.
42 Roy J, Shou H, Xie D *et al.* Statistical methods for cohort studies of CKD: prediction modeling. *Clin J Am Soc Nephrol* 2017; **12:** 1010–17.
43 Sawhney S, Marks A, Fluck N, McLernon DJ, Prescott GJ, Black C. Acute kidney injury as an independent risk factor for unplanned 90-day hospital readmissions. *BMC Nephrol* 2017; **18:** 9.
44 Gonzales MM, Bentall A, Kremers WK, Stegall MD, Borrows R. Predicting individual renal allograft outcomes using risk models with 1-year surveillance biopsy and alloantibody data. *J Am Soc Nephrol* 2016; **27:** 3165–174.
45 Achakzai MI, Argyropoulos C, Roumelioti ME. Predicting residual function in hemodialysis and hemodiafiltration-A population kinetic, decision analytic approach. *J Clin Med* 2019; **8:** 2080
46 Forzley B, Er L, Chiu HHL *et al.* External validation and clinical utility of a prediction model for 6-month mortality in patients undergoing hemodialysis for end-stage kidney disease. *Palliat Med* 2018; **32:** 395–403.
47 Cohen AH, Nast CC, Adler SG, Kopple JD. Clinical utility of kidney biopsies in the diagnosis and management of renal disease. *Am J Nephrol* 1989; **9:** 309–15.
48 Tischer B, Bilang M, Kraemer M, Ronga P, Lacouture ME. A survey of patient and physician acceptance of skin toxicities from anti-epidermal growth factor receptor therapies. *Support Care Cancer* 2018; **26:** 1169–179.
49 Rouyard T, Attema A, Baskerville R, Leal J, Gray A. Risk attitudes of people with 'manageable' chronic disease: an analysis under prospect theory. *Soc Sci Med* 2018; **214:** 144–53.
50 Hussain AI, Garratt AM, Brunborg C, Aakhus S, Gullestad L, Pettersen KI. Eliciting patient risk willingness in clinical consultations as a means of improving decision-making of aortic valve replacement. *J Am Heart Assoc* 2016; **5:** e002828.
51 Wee CC, Hamel MB, Apovian CM *et al.* Expectations for weight loss and willingness to accept risk among patients seeking weight loss surgery. *JAMA Surg* 2013; **148:** 264–71.

Correspondence: Stein I. Hallan, Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Prinsesse Kristinas gate 1, 7000 Trondheim, Norway.
(fax: +47 72825736; e-mail: stein.hallan@ntnu.no).

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Supplementary information on methods with a special focus on decision curve analysis.

