Malattia renale cronica nell'anziano: problemi diagnostici e impatto della multimorbidità

Andrea Corsonello

IRCCS – INRCA, Cosenza

Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016

see commentary on page 462

OPEN

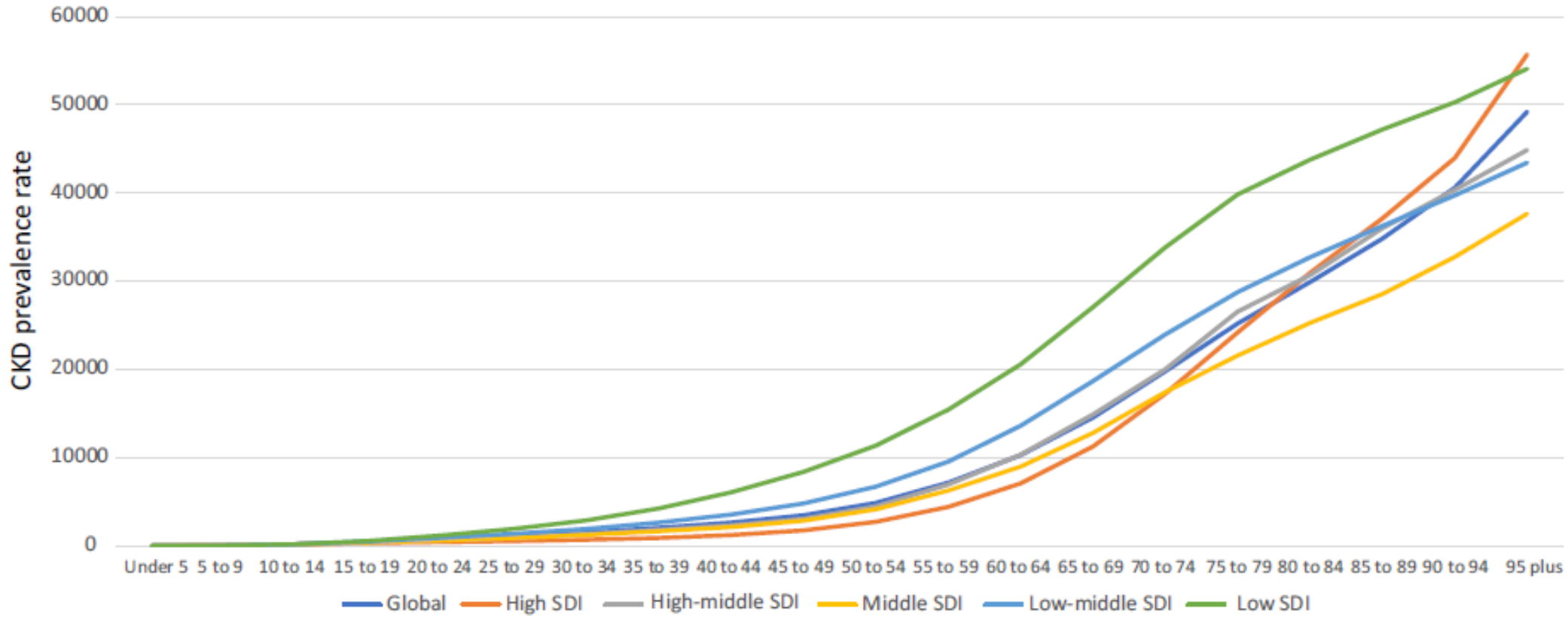
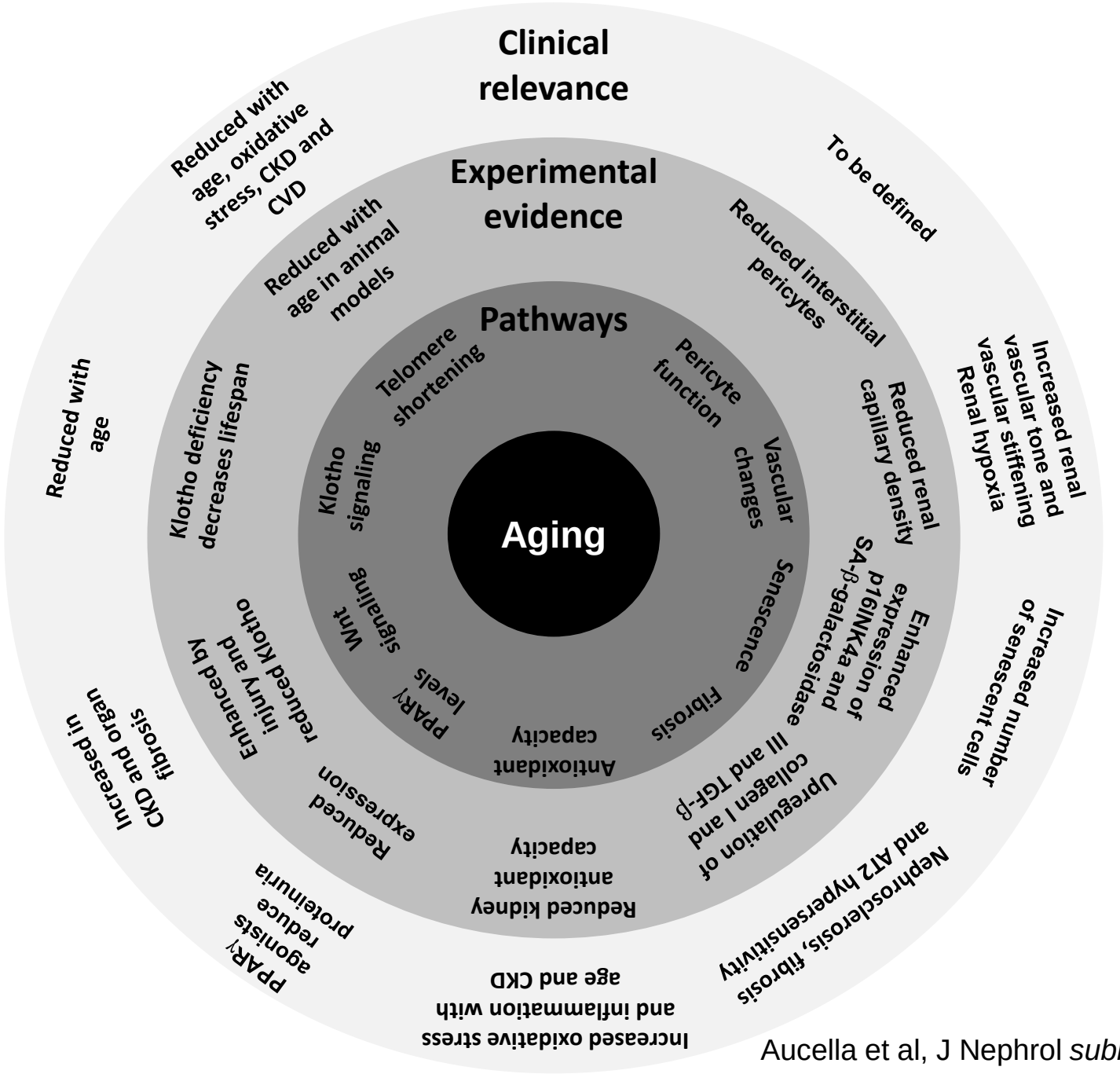


Figure 2| Chronic kidney disease (CKD) prevalence rate across age groups at the global level and by Sociodemographic Index (SDI) quintiles. Rate is per 100,000 population.



Aucella et al, J Nephrol *submitted*

Age-related structural changes

- Reduced renal mass
- Glomerulosclerosis
- Mesangial expansion
- Vascular changes
  - Renal atherosclerosis
  - Vascular dysautonomia
  - Arteriole subendothelial hyalinosis
  - Aglomerular circulation
- Tubular-interstitial changes
  - Tubular diverticuli
  - Tubular atrophy
  - Tubular fat degeneration
  - Reduced sodium reabsorption
  - Reduced potassium secretion
  - Interstitial fibrosis
  - Medulla hypotonicity

Age-related functional changes

- Decreased filtration, but with important interindividual variability.
- Decreased vascular autoregulation
- Defective Na+ retention under conditions of plasma volume contraction.
- Decline in the ability to adjust acid-base balance
- Decreased clearance of water soluble drugs in proportion to declining GFR, but variably from drug to drug due to tubular secretion and extrarenal clearance
- Declined renin-angiotensin system activity

Vulnerability to nephropathy

Similarities and difference between aging kidney and CKD in regards to selected kidney function parameters

	GFR	Urea FE*	Urea	Ca, Mg, P FE	K FE*	Erythropoietin
Aging kidney	< 60 ml/m	↑	=	=	↓	=
CKD	< 60 ml/m	↑	↑	↑	↑	↓

FE, fractional excretion.

*Reduced GFR may prevent full compensation by CKD-related increased urea and K FE

Aucella et al, J Nephrol *submitted*

RESEARCH ARTICLE

Assessing Nephrological Competence among Geriatricians: A Proof of Concept Internet Survey

PLOS ONE | DOI:10.1371/journal.pone.0141388 November 3, 2015

Table 1. The Nephrological Questionnaire for Geriatricians.

1	Do you systematically assess GFR?				
	Yes, 71.5%				
2	In the event of a confirmatory answer to question 1: through				
	Creatinine clearance: 8%	MDRD: 45.5%	C-G: 65%		
3	Do you routinely check the following parameters?				
	Urine[Na]: 25%	Urine[N]: 19%	Urine[P]: 16%	S-OH VitD: 30%	
4	Do you routinely perform 24 hour urine collection?				
	Yes, 69%				
5	At which CKD stage do you refer your patient to the nephrologist?				
	CKD 2: 5.4%	CKD 3a: 16.2%	CKD 3b: 34.7%	CKD 4: 32.9%	CKD 5: 10.8%
6	Do you think that EPO supplementation is useful to your patients?				
	Yes, 90.3%				
7	Do you usually prescribe D vitamin to your patients?				
	Yes, 90.3%				
8	In the event of a confirmatory answer to question 7, which D vitamin do you prescribe?				
	Cholecalciferol: 61.4%	25(OH)D3 calcidiol: 24.1%	Calcitriol: 23.1%	Other: 1.4%	
9	Do you usually check the albumin to creatinine ratio on spot urine sample?				
	Yes, 12%				
10	Do you usually order renal ultrasound scan?				
	Yes, 74.4%				
11	Do you use a standardized protocol to prevent the contrast induced nephropathy?				
	31%				
12	How do you rate your adherence to nephrological guidelines (from 1 to 5)?				
	1) 3.1%	2) 12%	3) 67.4%	4) 26.4%	5) 1.2%

Kidney functions	Relevance in clinical practice
Filtration function	➡ Heart failure, diabetes, hypertension, chronic obstructive pulmonary disease
Vascular autoregulation	➡ Long lasting hypertension, renal atherosclerosis, autonomic neuropathy
Water and electrolyte balance	➡ Water and Na+ retention in chronic respiratory failure, heart failure and liver failure
Acid-base balance	➡ Reduced response of the kidney to changes in blood pH (e.g. respiratory failure)
1α-hydroxilation of vitamin D	➡ In CKD, decreases for declining GFR (mineral bone disorder; supplementation)
Insulinase activity	➡ In CKD, decreases for declining GFR. Clinical relevance to be defined.
Renalase activity	➡ Increased sympathetic tone in CKD. Clinical relevance to be defined.
Synthesis of erythropoietin	➡ Decreases for declining GFR. Faster decline in diabetic CKD.
Clearance of water soluble drugs	➡ High risk of adverse events in CKD patients with multimorbidity taking several drugs
Renin-angiotensin system	➡ Upregulated in many CKD, but frequently depressed in diabetic CKD

Aucella et al, J Nephrol *submitted*

Staging – KDIGO 2012 guidelines

Prognosis of CKD by GFR and albuminuria category

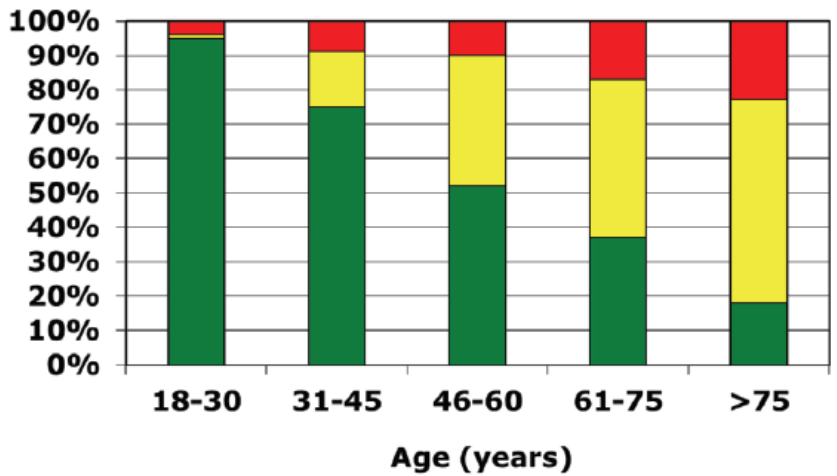
Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

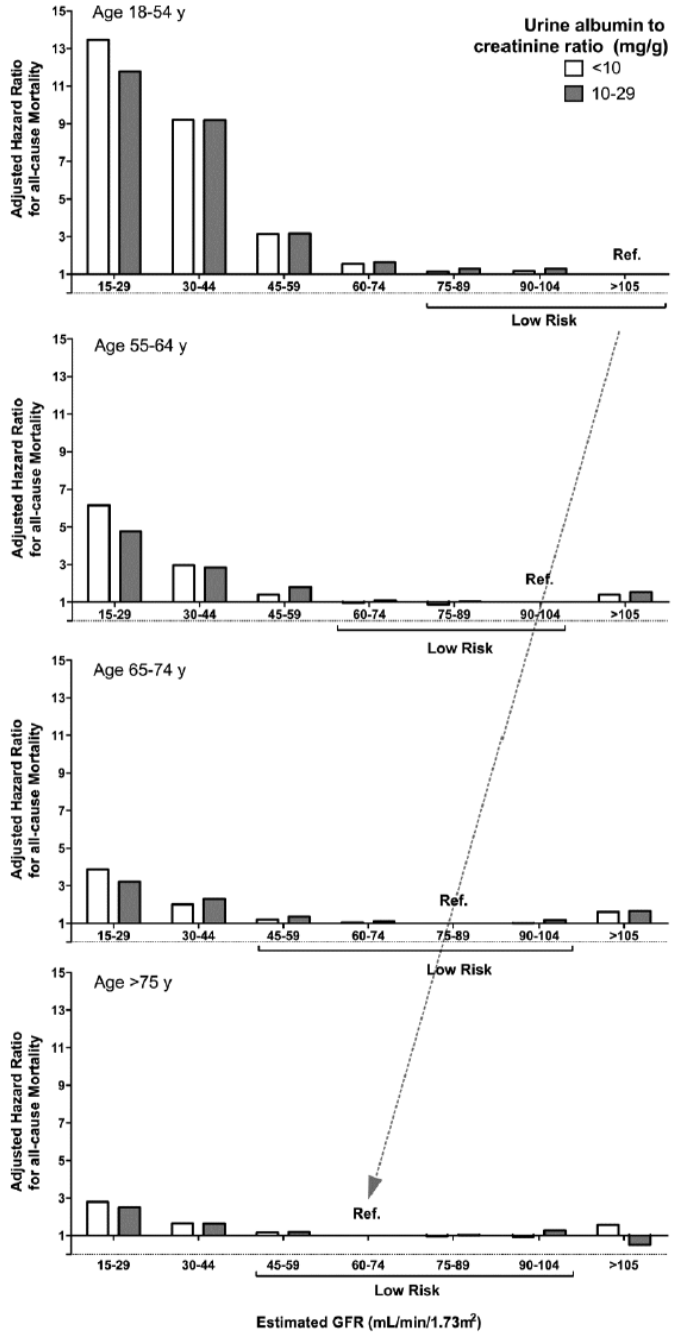
Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Percentage of US Population by eGFR and Albuminuria Category: KDIGO 2012 and NHANES 1999-2006

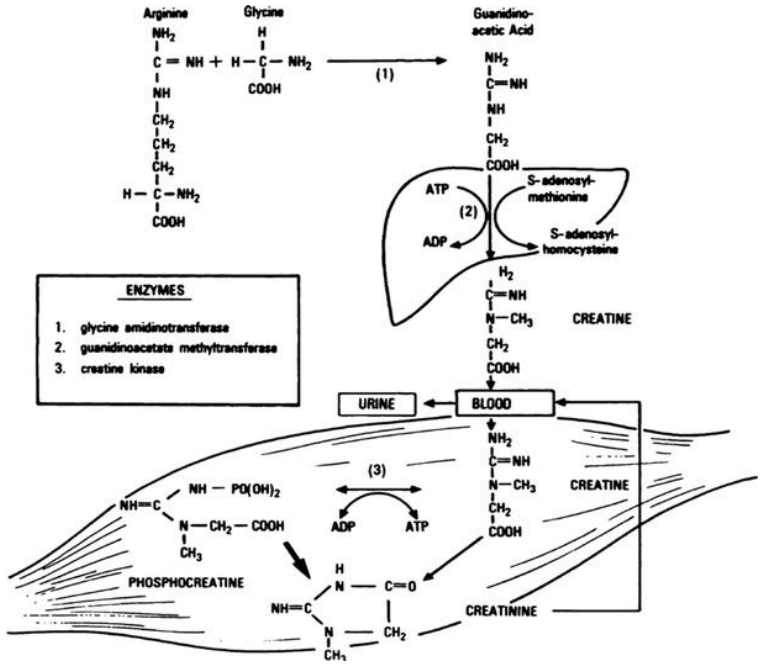
GFR categories (ml/min/ 1.73m^2) Description and range				Persistent albuminuria categories Description and range			
				A1	A2	A3	
				Normal to mildly increased	Moderately increased	Severely increased	
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30mg/mmol	
	G1	Normal or high	≥90	55.6	1.9	0.4	57.9
	G2	Mildly decreased	60-89	32.9	2.2	0.3	35.4
	G3a	Mildly to moderately decreased	45-59	3.6	0.8	0.2	4.6
	G3b	Moderately to severely decreased	30-44	1.0	0.4	0.2	1.6
	G4	Severely decreased	15-29	0.2	0.1	0.1	0.4
	G5	Kidney failure	<15	0.0	0.0	0.1	0.1
				93.2	5.4	1.3	100.0

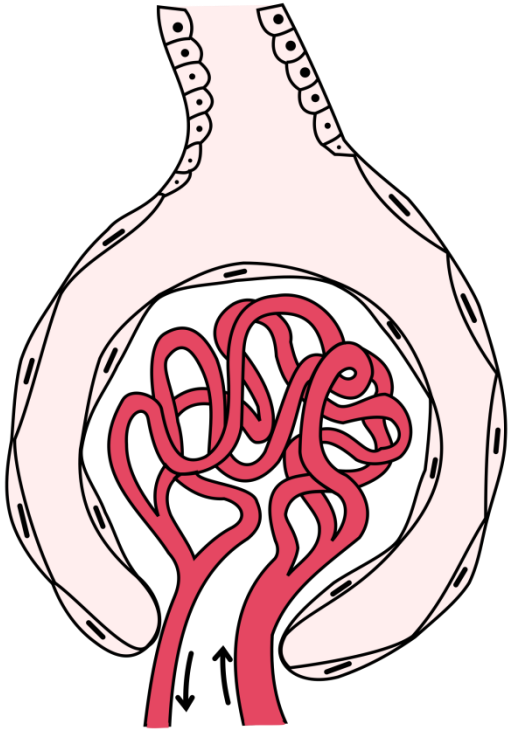


Clin Biochem Rev 37 (1) 2016



Low serum creatinine in older patients





Reduced creatinine production due to reduced muscle mass

Lindeman RD, Clin Lab Med 1993
Montesanto A, Age 2014

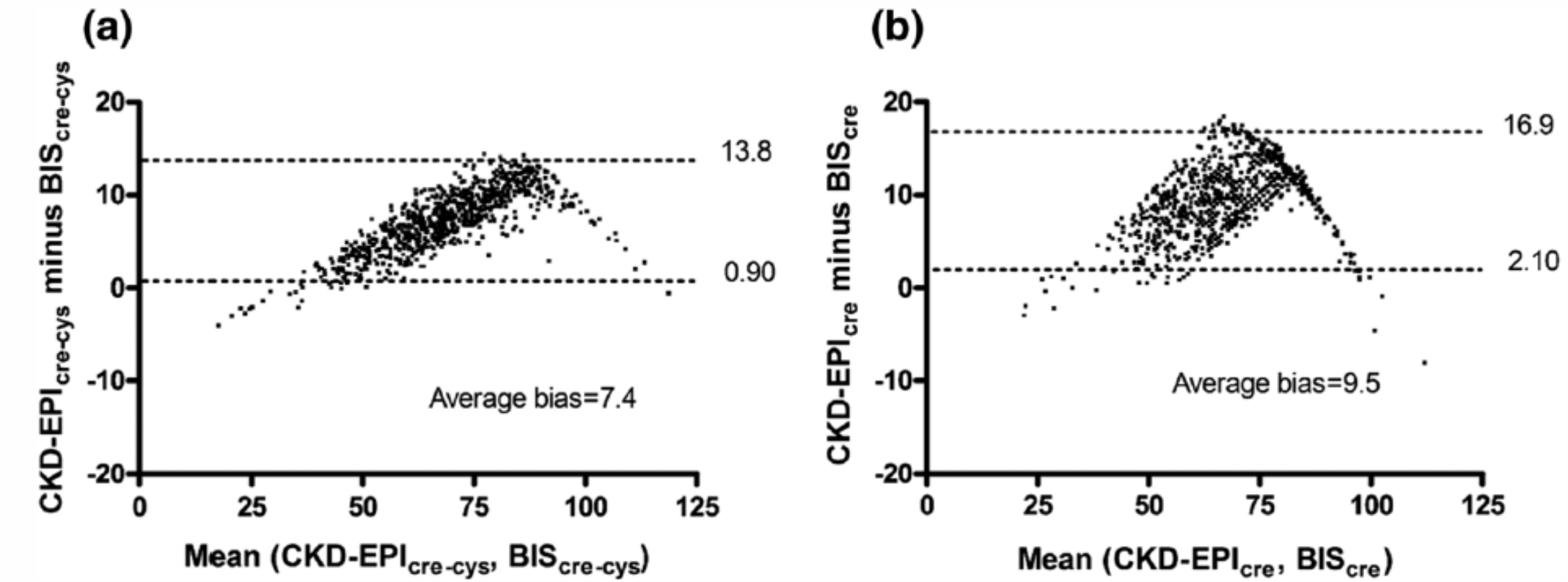
Hyperfiltration reduces circulating creatinine

Altay S, BMC Nephrol 2014
Park M, J Am Soc Nephrol 2015

↑Mortality

Agreement between Chronic Kidney Disease Epidemiological Collaboration and Berlin Initiative Study equations for estimating glomerular filtration rate in older people: The Invecchiare in Chianti (Aging in Chianti Region) study

Andrea Corsonello,[1†] Claudio Pedone,[2] Stefania Bandinelli,[3] Luigi Ferrucci[4] and Raffaele Antonelli Incalzi[2,5]



Geriatr Gerontol Int 2017; **17:** *1559–1567*

Table 1. Baseline demographic and clinical findings of 205 patients who underwent percutaneous ultrasound-guided renal biopsy.

Baseline characteristic	Value
Age (years)	58.0 (44.0 – 70.0)
Male/female	125/80
Hospital stay (days)	7.0 (1.0 – 21.0)
Systolic blood pressure (mmHg)	130.0 (120.0 – 140.0)
Diastolic blood pressure (mmHg)	80.0 (70.0 – 80.0)
Hemoglobin (g/L)	116.0 (99.0 – 132.0)
Platelet number (× 10^3/mm^3)	243.5 (189.8 – 303.0)
Partial thromboplastin (s)	29.0 (27.0 – 31.0)
Prothrombin time (INR)	1.0 (1.0 – 1.1)
Serum creatinine (mg/dL)	2.1 (1.1 – 3.8)
Urea (< 71 mg/dL)	69.0 (42.0 – 107.5)
Albumin (g/dL, normal range 3.5 – 5.0 g/dL))	2.6 (2.1 – 3.2)
C3 (mg/dL, normal range 90 – 180 mg/dL))	115.0 (96.0 – 134.0)
C4 (mg/dL, normal range 10 – 40 mg/dL))	30.4 (22.0 – 36.8)
Positive antinuclear antibodies	41/205
Anti-dsDNA antibodies	12/205
Positive MPO antibodies	17/205
Positive PR3 antibodies	18/205
CrP (< 0.5 mg/dL)	0.6 (0.2 – 1.8)
Proteinuria (spot urine, < 0.25 g/g creatinine)	2.2 (0.8 – 5.4)
Hematuria (> 10 erythrocytes/ visual field)	165/205
Active urinary sediment	83/205
Nephrotic syndrome	54/205
aHT	135/205
DM	48/205
Length and diameter of right kidney (cm)	11.3 (10.5 – 12.0)
Length and diameter of left kidney (cm)	11.2 (10.3 – 12.0)

INR = international normalized ratio; C3 = complement factor 3; C4 = complement factor 4; MPO = myeloperoxidase; PR3 = proteinase 3; CrP = c-reactive protein; aHT = arterial hypertension; DM = diabetes mellitus.

The biopsy dilemma

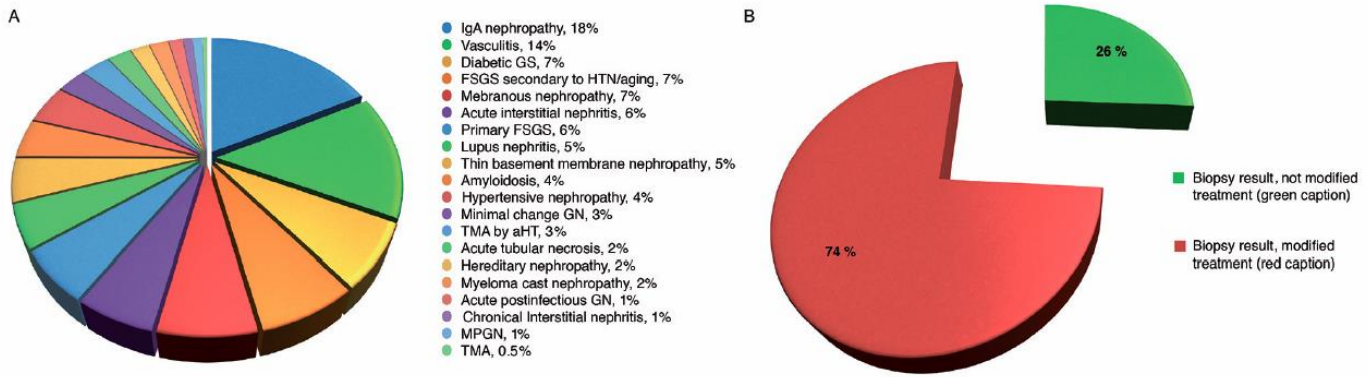


Figure 2. A: Frequency of histological findings in 205 patients who underwent percutaneous ultrasound-guided renal biopsy; (B) frequency of biopsy results that led to a treatment modification or did not lead to treatment modification.

Clinical Nephrology, Vol. 84 – No. 6/2015 (311-322)

Clinical Nephrology, Vol. 82 – No. 4/2014 (225-230)

Renal biopsy in patients over 75: 131 cases

Cristiana Rollino, Michela Ferro, Giulietta Beltrame, Giacomo Quattrocchio, Carlo Massara, Francesco Quarello, and Dario Roccatello

Nephrology, S.G. Bosco Hospital, Turin, Italy

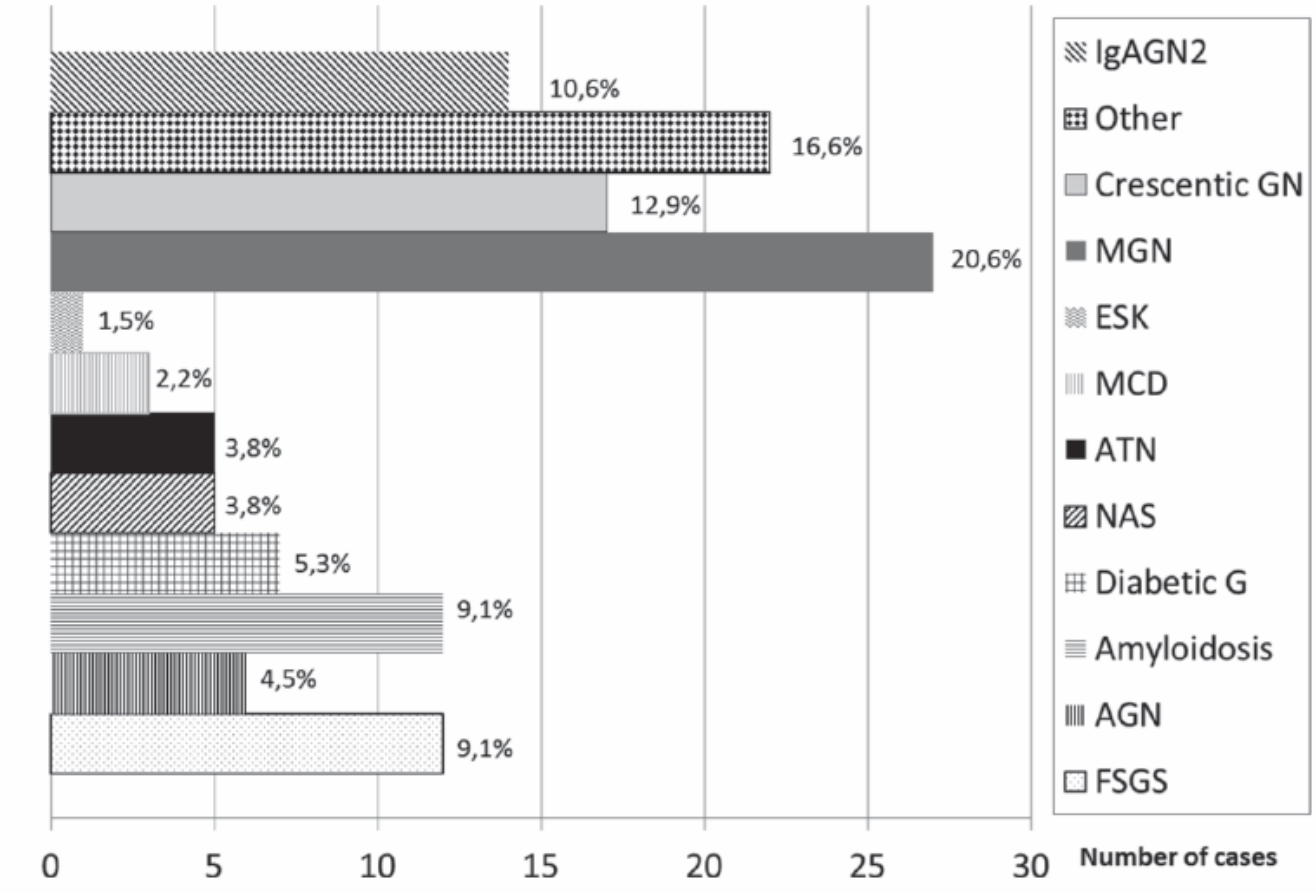
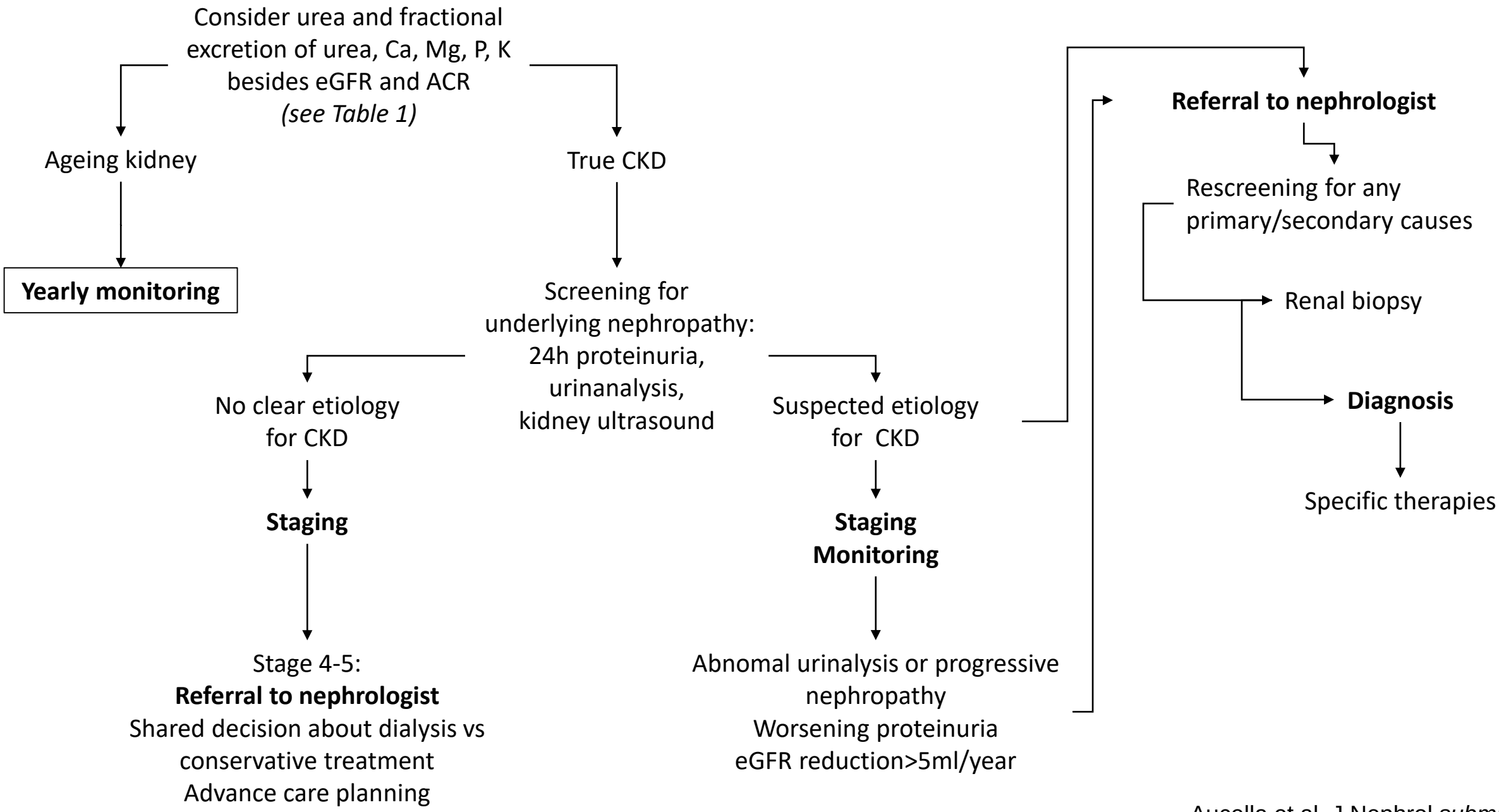
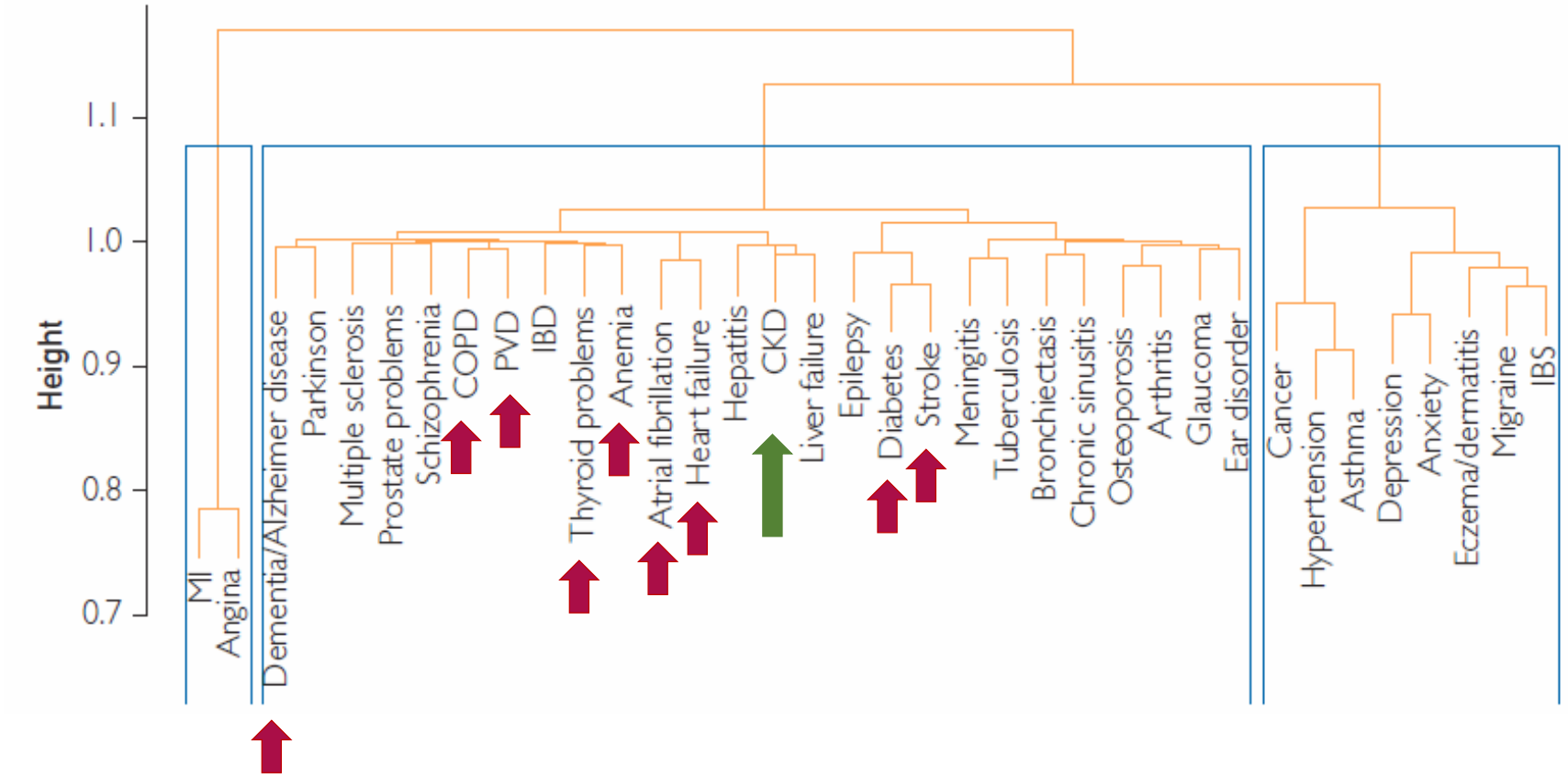


Figure 1. Main histological diagnosis.
IgAGN = IgA glomerulonephritis; MGN = membranous glomerulonephritis; ESK = end-stage kidney; MCD = minimal change disease; ATN = acute tubular necrosis; NAS = nephroangiosclerosis; Diabetic G = diabetic glomerulosclerosis; AGN = acute post-infectious glomerulonephritis; FSGS = focal segmental glomerulosclerosis.
The complete list of diagnoses is: MGN in 27 patients (20.6%), crescentic GN in 17 (12.9%; ANCA-associated in 11 cases, cANCA in 2 and pANCA in 9, including anti-glomerular basement membrane in 2), IgAGN in 14 (10.6%; in 1 with cholesterol embolism), FSGS in 12 (9.1%; in 1 with cholesterol embolism), AGN in 6 (4.5%), amyloidosis in 12 (9.1%; 7 AL, 5 AA), diabetic G. in 7 (5.3%), NAS in 5 (3.8%), ATN in 5 (3.8%), thrombotic microangiopathy (TMA) in 3 (2.2%), MCD in 3 (2.2%), membrano-proliferative GN (MPGN) in 4 (3%) (in 2 cases secondary to cryoglobulinemia), light chain disease (LCD) in 3 (2.2%), non-specific changes in 2 (1.5%), cholesterol embolism (CE) in 1 (0.7%), cast nephropathy in 2 (1.5%), ESK in 2 (1.5%), acute interstitial nephropathy in 1 (0.7%), sarcoidosis in 1 (0.7%), IgMGN in 2 (1.5%), mesangial GN in 1 (0.7%), and immunotactoid GN in 1 (0.7%).



Aucella et al, J Nephrol *submitted*

CKD in the context of multimorbidity conceptual framework



Mayo Clin Proc. ■ XXX 2018;▬(■):1-10

Clinical and laboratory findings suggesting CKD

Clinical clues

- Fatigue, dyspnea, tachypnea
- Water retention
- Anorexia, nausea
- Sleep disorders
- Difficult to control hypertension
- Osteoporosis
- Arterial calcifications
- ADRs to normally dosed kidney cleared drugs
- Unexplained peripheral neuropathy
- Itching
- Gastrointestinal bleeding
- Weight loss
- In diabetic patient: reduced cumulative amount of insulin

Confounded by and shared with coexsistent chronic diseases

Laboratory clues

- Anemia
- Hypo- or hypercalcemia
- Hyperkalemia or hypokalemia (tubular dysfunction)
- Metabolic acidosis
- Hypocapnia (hyperventilation compensating for metabolic acidosis)
- Hyposthenuria (low urine osmolarity: nephrogenic diabetes?)
- Oliguria or Polyuria
- Proteinuria or hematuria
- Hyperchloremia: renal metabolic acidosis?
- Hyperphosphatemia
- Hyperuricemia
- Increased ESR and/or CRP
- Increased D-dimer

Aucella et al, J Nephrol *submitted*

Table 1. Chronic Conditions Categorized as Concordant or Discordant/Unrelated Based on Nephrologist Agreement and Chronic Kidney Disease (CKD) Clinical Practice Guidelines

Concordant	Discordant/Unrelated
Hypertension[a]	Heart failure[a]
Diabetes[a]	Arthritis[a]
Atrial fibrillation[a]	Osteoporosis[a]
Anemia[a]	Hypothyroid[a]
Gout[a]	Epilepsy[a]
Benign prostatic hypertrophy[a]	Parkinson's disease [a]
Peripheral arterial disease[a]	Cancer[b]
Hyperlipidemia[b]	Prostate cancer[c]
Coronary heart disease[b]	Dementia[c]
Cerebrovascular disease[b]	Depression[c]
	GERD/Peptic ulcer[c]
	COPD/Asthma[c]

[a]Nephrologist agreement.
[b]CKD guidelines discuss management of condition in context of CKD.
[c]CKD guidelines do not discuss management of condition in the context of CKD.

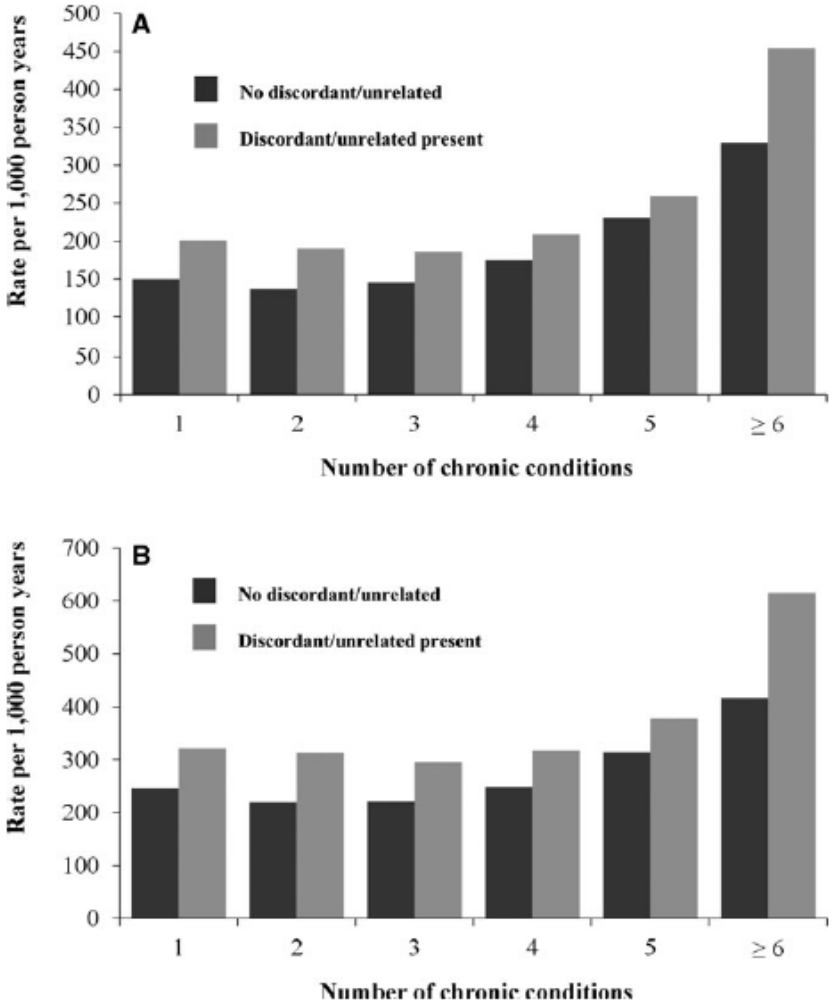
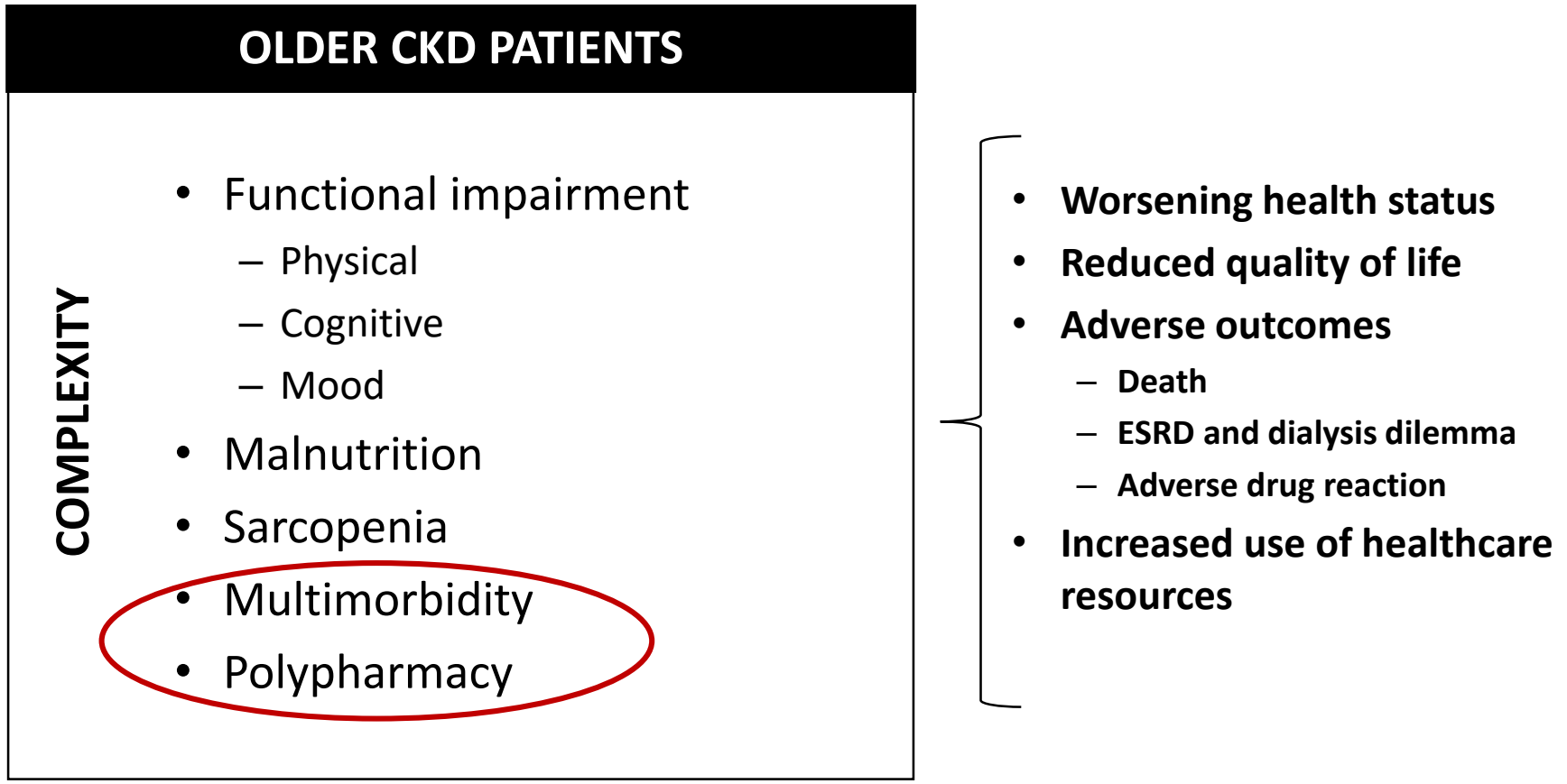


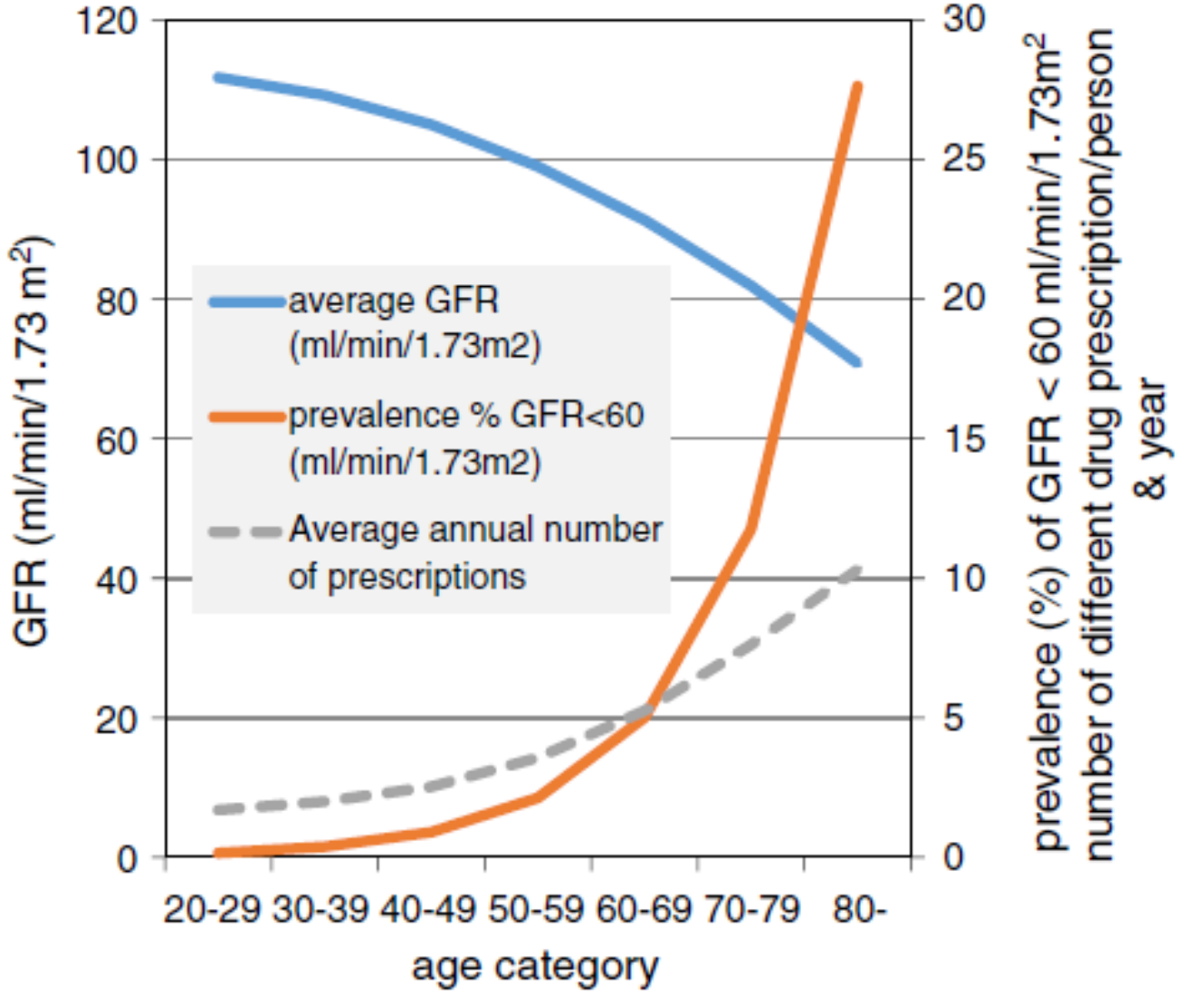
Figure 1. Crude rates (per 1,000 person years) among U.S. veterans with incident CKD between January 1, 2005 and December 31, 2008 for (A) hospitalizations and (B) emergency department visits by number of chronic conditions stratified by the presence of discordant/unrelated condition.

- **Concordant: having overlap in treatment goals**
- **Discordant: having opposing treatment recommendations**
- **Unrelated: having no overlap, but contributing to complexity via different resource requirements**

J Am Geriatr Soc 65:704–711, 2017.



Corsonello et al, Exp Rev Clin Pharmacol 2016



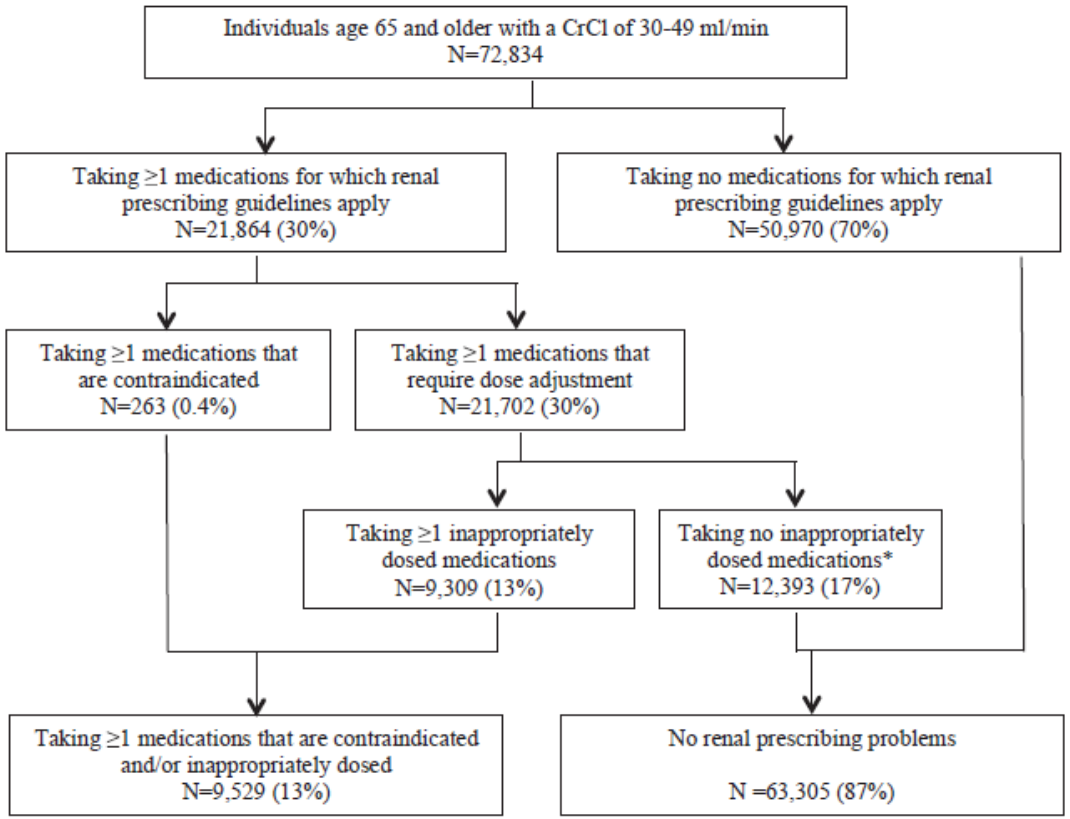
Drugs Aging (2014) 31:493–499
DOI 10.1007/s40266-014-0187-z

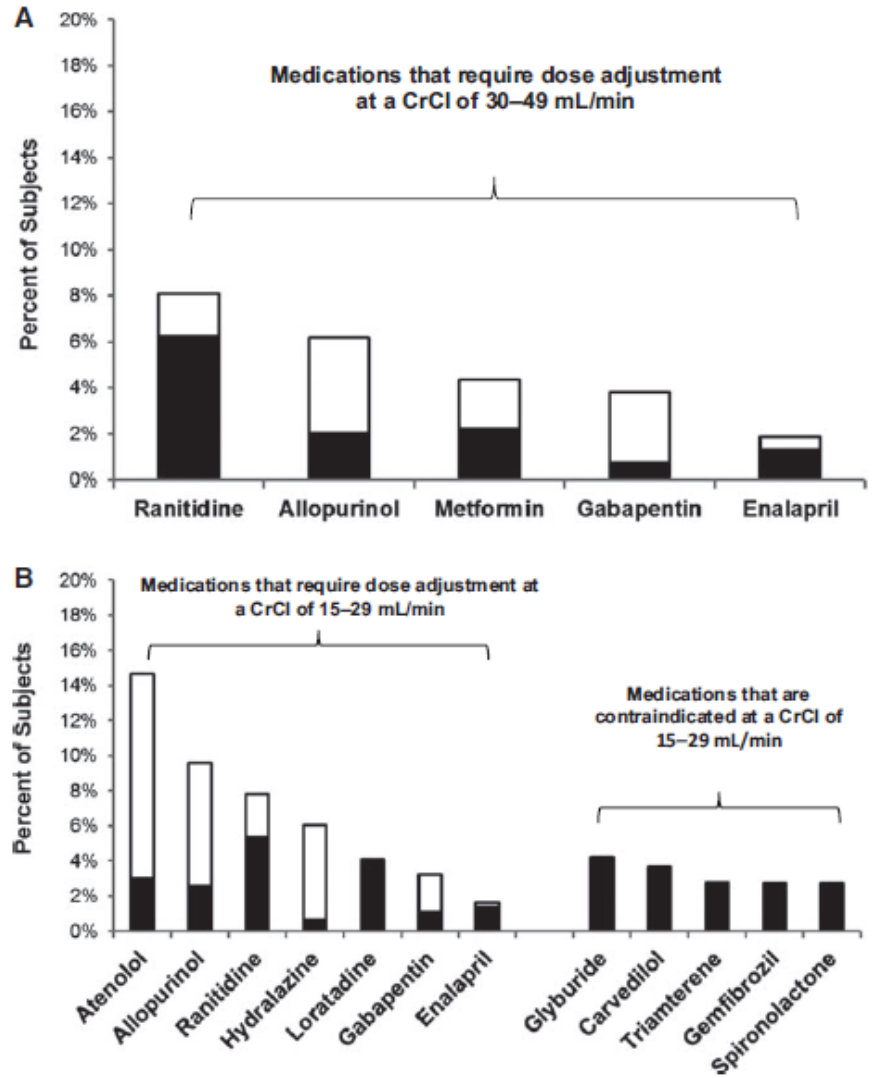

WORK IN
PROGRESS
COMING SOON!

Use of Renally Inappropriate Medications in Older Veterans: A National Study

Flora Chang, BA,[*†‡] *Ann M. O'Hare, MD,*[§‖] *Yinghui Miao, MPH,*[†‡] *and Michael A. Steinman, MD*[†‡]

JAGS 63:2290–2297, 2015





British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2018) •• ••–••

ORIGINAL ARTICLE

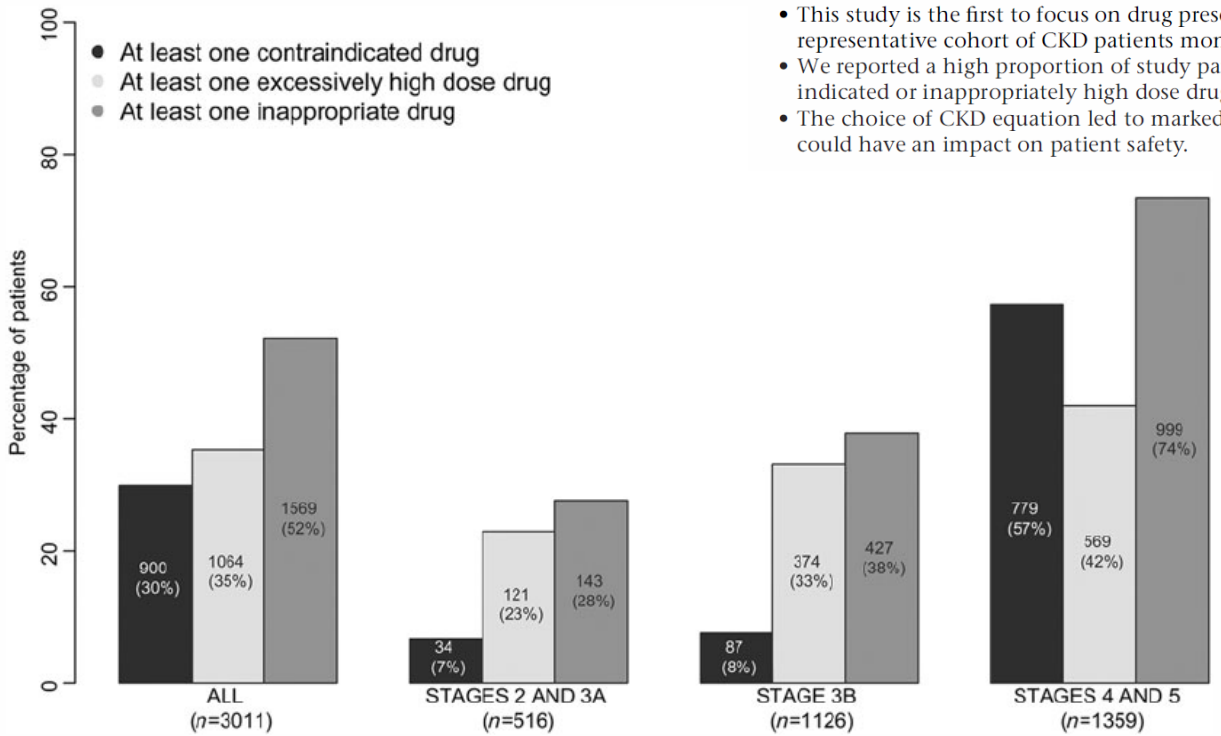
Evaluation of the adequacy of drug prescriptions in patients with chronic kidney disease: results from the CKD-REIN cohort

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

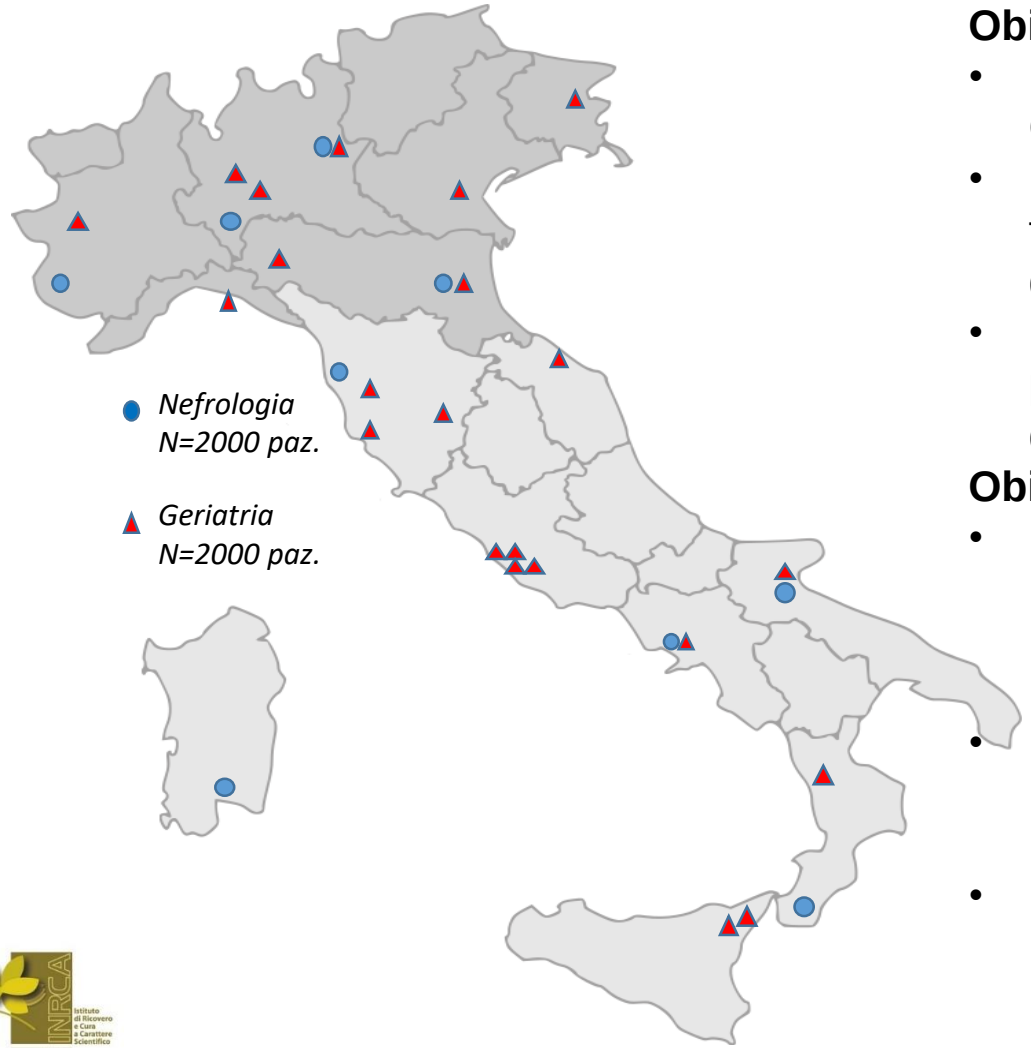
- Pharmacokinetics and pharmacodynamics are greatly altered by GFR decline.
- The dosage of many drugs may need to be reduced in patients with poor kidney function, in order to avoid drug accumulation and toxicity.

WHAT THIS STUDY ADDS

- This study is the first to focus on drug prescriptions and their adjustment to the kidney function in a large and representative cohort of CKD patients monitored by nephrologist.
- We reported a high proportion of study participants (52%) receiving one or more inappropriate prescriptions (a contraindicated or inappropriately high dose drug).
- The choice of CKD equation led to marked differences in the proportion of inappropriate prescriptions and this choice could have an impact on patient safety.



Retrospective study of CKD reporting and medication prescribing/dosing in older patients discharged from geriatric and nephrology unit in Italy



Obiettivi primari

- Prevalenza di omessa diagnosi di MRC nelle UO di Geriatria
- Prevalenza di inappropriata prescrizione/dosaggio di farmaci ad eliminazione renale al momento della dimissione in UO di Nefrologia e Geriatria
- Prevalenza di omessa prescrizione di farmaci potenzialmente appropriati al momento della dimissione in UO di Nefrologia e Geriatria

Obiettivi secondari

- Confronto fra diverse equazioni per la stima della eGFR nell'individuazione di inappropriata prescrizione/dosaggio di farmaci ad eliminazione renale
- Studio dei correlati di incremento dei livelli di creatinina (riduzione eGFR) tra ingresso in ospedale e dimissione
- Studio dell'impatto che l'incremento dei livelli di creatinina (riduzione eGFR) tra ingresso in ospedale e dimissione determina sull'appropriatezza prescrittiva.

Project Coordinator

UPPSALA UNIVERSITET

Erasmus MC
Universitair Medisch Centrum Rotterdam

FAU

Bellvitge Hospital

Servicio Madrileño de Salud
SERMAS

Medical University of Graz

Ben-Gurion University of the Negev

SCOPE

Screening for CKD among Older People across Europe

SCOPE mission

Evaluating a 2-year screening program for CKD in the older patients to comprehend to which extent available screening methods may identify older people at risk of worsening kidney function

The SCOPE cohort

n = 2,450 in 7 Countries

Primary End-points

- Rate of eGFR decline
- Incidence of ESRD

Secondary End-points

Effects of CKD screening programs on conventional and geriatric outcomes

Corsonello et al. BMC Nephrology (2018) 19:260
https://doi.org/10.1186/s12882-018-1030-2

BMC Nephrology

STUDY PROTOCOL Open Access

Design and methodology of the screening for CKD among older patients across Europe (SCOPE) study: a multicenter cohort observational study

Andrea Corsonello[1], Lisanne Tap[2], Regina Roller-Wirnsberger[3*], Gerhard Wirnsberger[3], Carmine Zoccali[4], Tomasz Kostka[5], Agnieszka Guligowska[5], Francesco Mattace-Raso[2], Pedro Gil[6], Lara Guardado Fuentes[6], Itshak Meltzer[7], Ilan Yehoshua[8], Francesc Formiga-Perez[9], Rafael Moreno-González[9], Christian Weingart[10], Ellen Freiberger[10], Johan Ärnlöv[11,12,13], Axel C. Carlsson[11,13], Silvia Bustacchini[1], Fabrizia Lattanzio[1] on behalf of SCOPE investigators

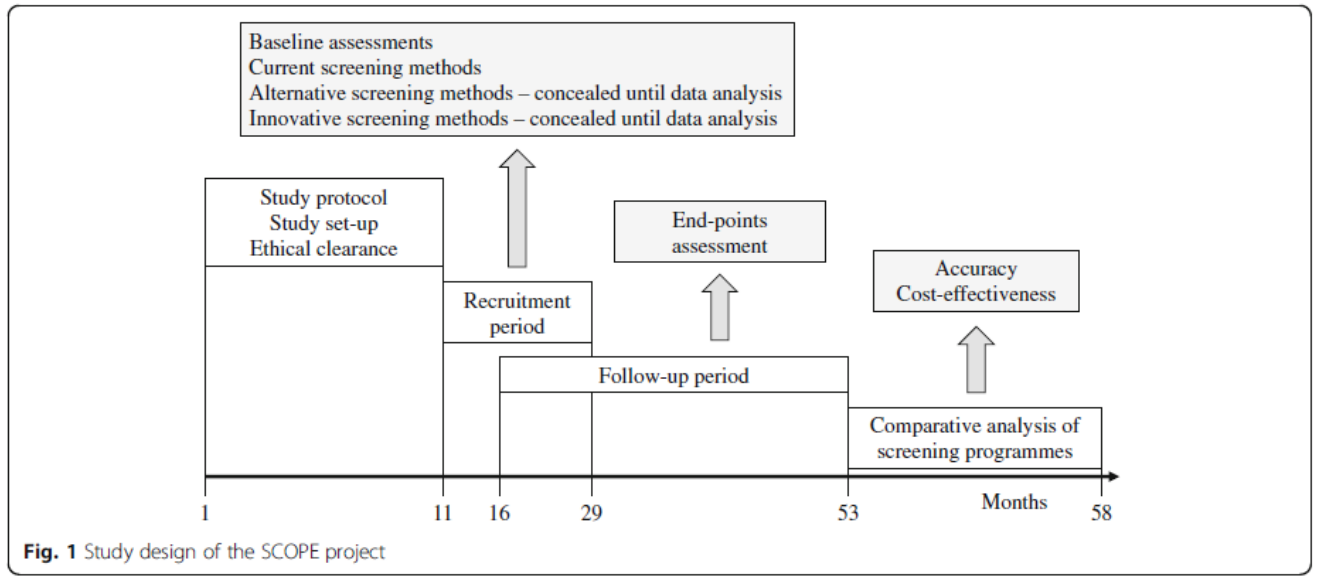


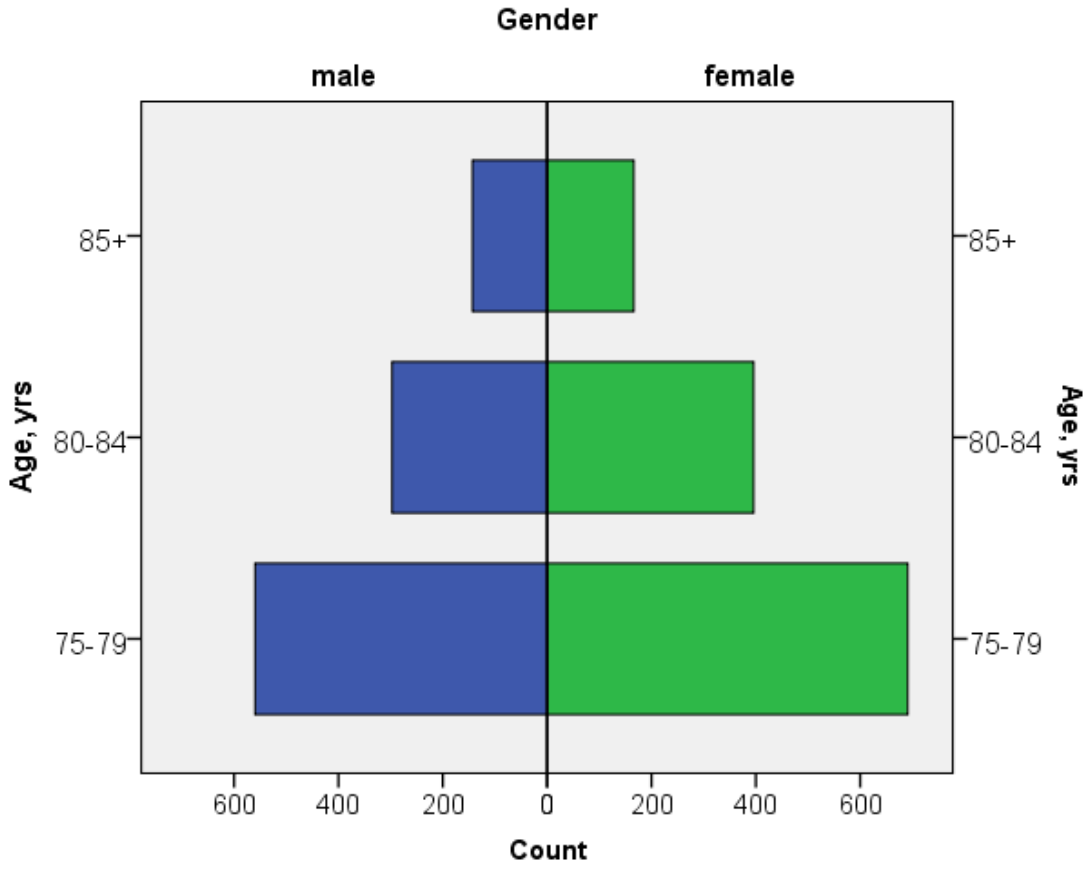
Fig. 1 Study design of the SCOPE project

Table 2 Comprehensive Geriatric Assessment domains tested during the SCOPE project

- Basic (ADL) and Instrumental Activities of Daily Living (IADL)/self-reported disability [39, 40]
- Mini Mental State Examination (MMSE)/cognitive status [41]
- 15-items Geriatric Depression Scale (GDS)/mood [42]
- Cumulative Illness Rating Scale (CIRS)/overall comorbidity [43]
- History of falls and incident falls
- Vision and hearing impairment will be coded on a scale from 0 (adequate) to 4 (no vision/hearing present) [44].
- Lower urinary tract symptoms (LUTS): The presence of LUTS will be ascertained by asking the patient to rate on a 5-point (0–4) Likert scale how big a problem, if any, has each of the following items been during the last 4 weeks: 1. Dripping or leaking urine, 2. Pain or burning in urination, 3. Bleeding with urination, 4. Weak urine stream or incomplete emptying, 5. Waking up to urinate, 6. Need to urinate frequently during the day [45].
- Nutritional status: anthropometric parameters (calf circumference, arm circumference, Body mass index (kg/m2), waist-hip ratio, waist-to-height ratio), Mini Nutritional Assessment (MNA) [46] and 24-h dietary recall[a] [47].
- Short Physical Performance Battery (SPPB) [48].
- Grip strength [49] measured by using JAMAR hydraulic dynamometer.
- Bioelectrical impedance analysis (BIA)[b] [50] Muscle mass will be calculated using the Janssen et al. equation [51], using the instrument Akern BIA101.
- Health related quality of life will be rated by the Euro-QoL 5D.

SCREENING FOR CKD AMONG OLDER PEOPLE ACROSS EUROPE

The SCOPE study cohort



Country	No. of patients
Austria	288
Germany	285
Israel	313
Italy	440
Netherland	297
Poland	354
Spain - Barcelona	141
Spain - Madrid	135
Total	2253

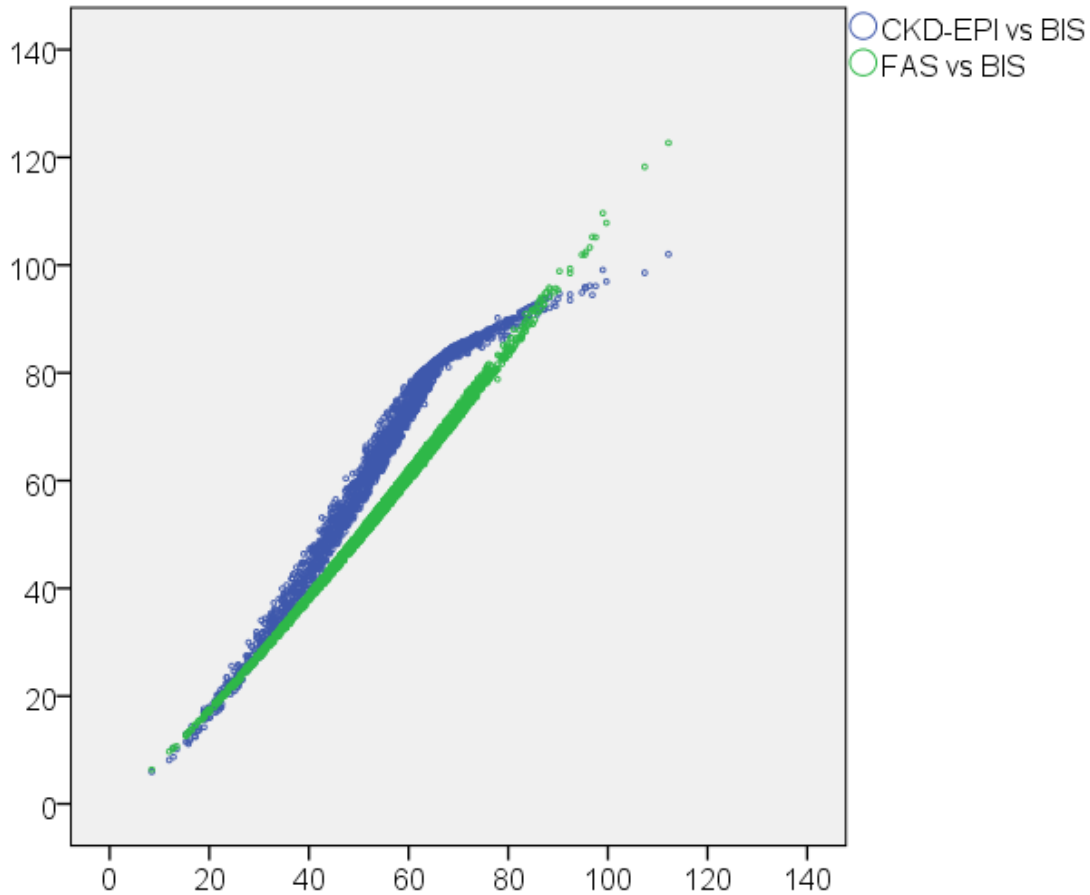
GFR (BIS equation)	ACR (mg/g) <30	30-300	>300
G1 (90 or more)	13 0.7%	3 0.8%	0
G2 (60-89.9)	721 41.2%	91 23.5%	5 4.3%
G3A (45-59.9)	717 41.0%	125 32.2%	16 13.7%
G3B (30-44.9)	259 14.8%	117 30.2%	45 38.5%
G4-5 (<30)	38 2.2%	52 13.4%	51 43.6%

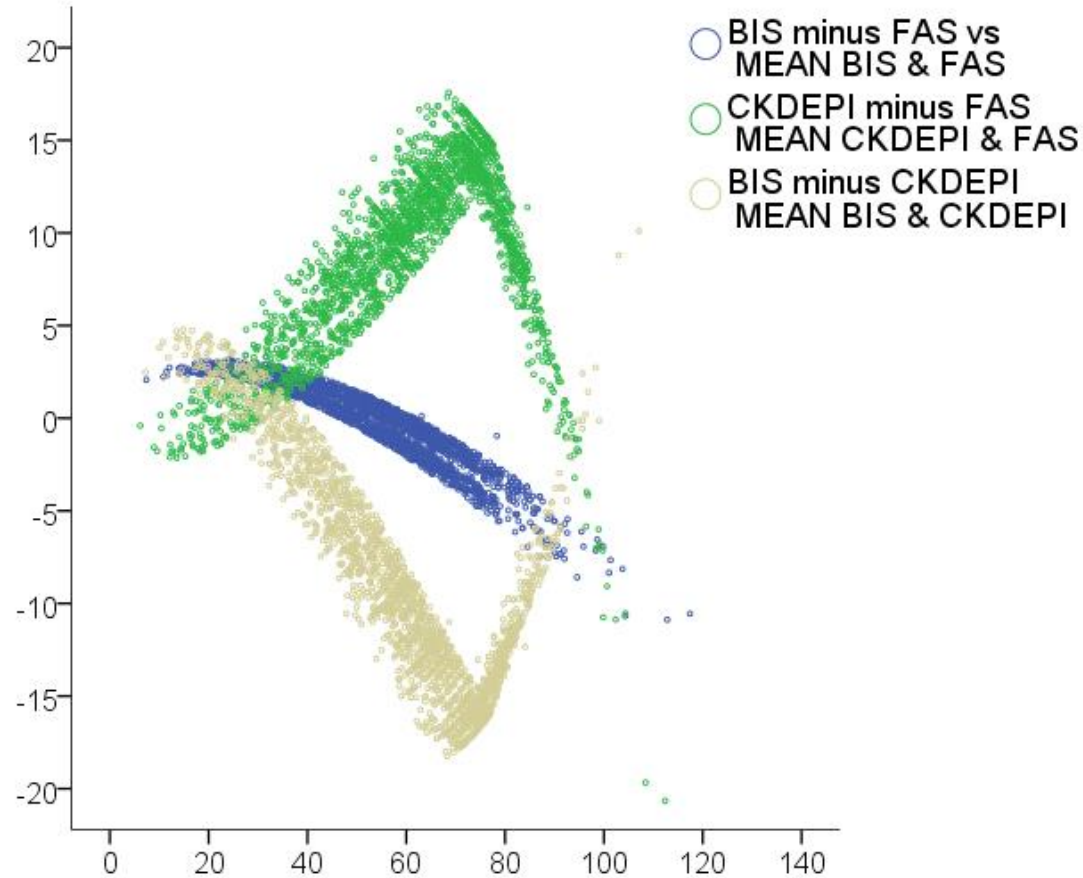
GFR (FAS equation)	ACR (mg/g) <30	30-300	>300
G1 (90 or more)	34 1.9%	5 1.3%	2 1.7%
G2 (60-89.9)	737 42.2%	97 25.0%	3 2.6%
G3A (45-59.9)	637 36.4%	112 28.9%	15 12.8%
G3B (30-44.9)	279 16.0%	104 26.8%	36 30.8%
G4-5 (<30)	61 3.5%	70 18.0%	61 52.1%

GFR (CKD-EPI equation)	ACR (mg/g) <30	30-300	>300
G1 (90 or more)	54 3.1%	7 1.8%	2 1.7%
G2 (60-89.9)	1189 68.0%	170 43.8%	10 8.5%
G3A (45-59.9)	311 17.8%	79 20.4%	16 13.7%
G3B (30-44.9)	150 8.6%	75 19.3%	35 29.9%
G4-5 (<30)	44 2.5%	57 14.7%	54 46.2%

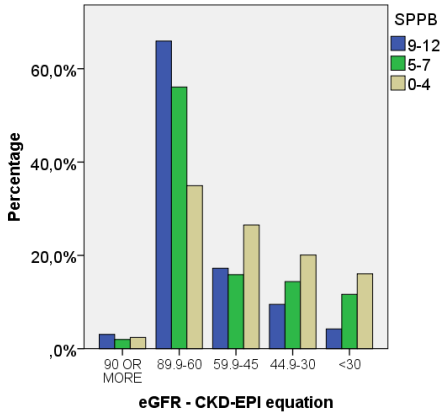
SCREENING FOR CKD AMONG OLDER PEOPLE ACROSS EUROPE

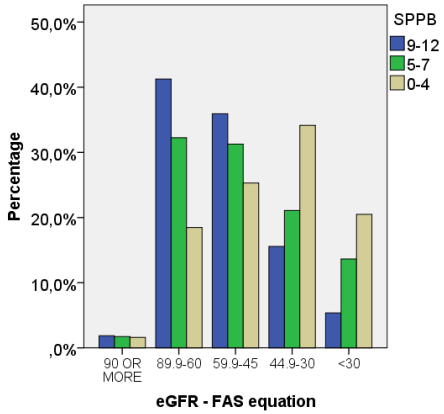
SCREENING FOR CKD AMONG OLDER PEOPLE ACROSS EUROPE

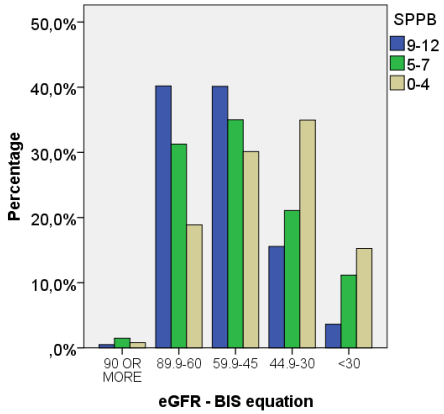




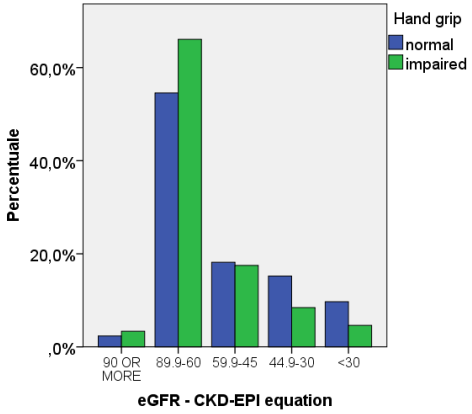
SPPB

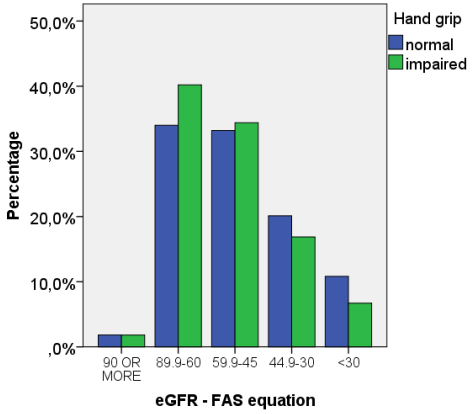


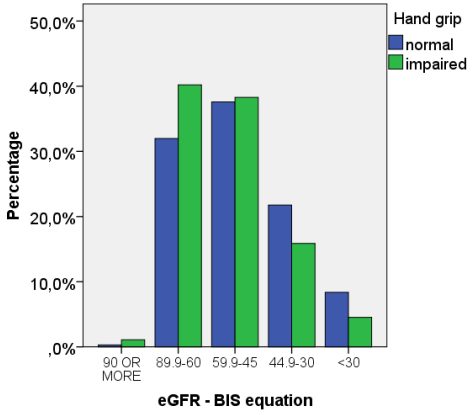




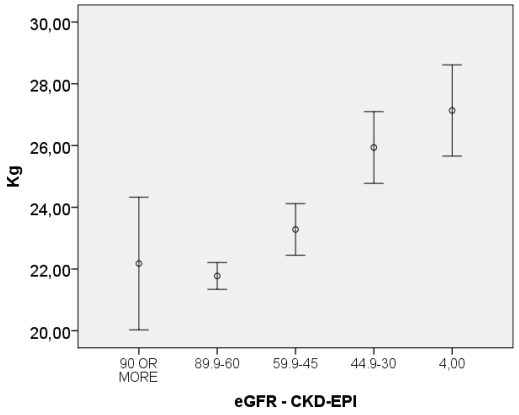
Hand grip

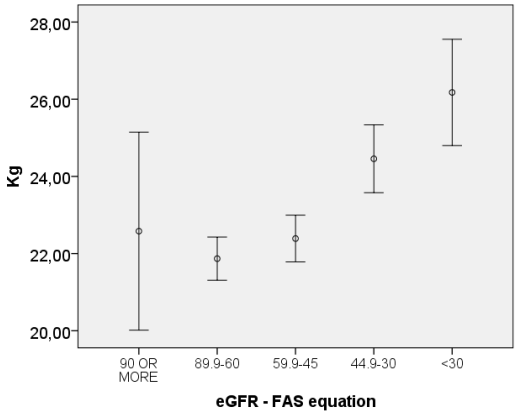


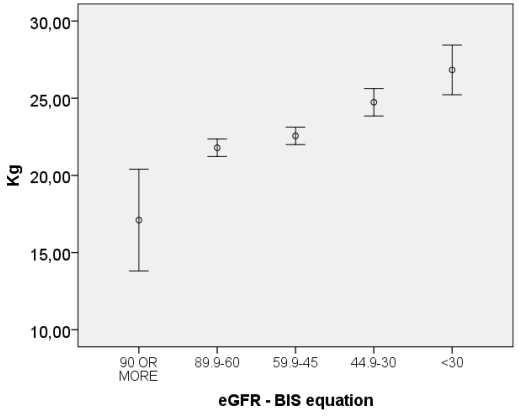




Muscle mass
(*Janssen et al)*







SCOPE
SCREENING FOR CKD AMONG OLDER PEOPLE ACROSS EUROPE

Corsonello et al. BMC Nephrology (2018) 19:260
https://doi.org/10.1186/s12882-018-1030-2

BMC Nephrology

STUDY PROTOCOL Open Access

Design and methodology of the screening for CKD among older patients across Europe (SCOPE) study: a multicenter cohort observational study

Andrea Corsonello[1], Lisanne Tap[2], Regina Roller-Wirnsberger[3*], Gerhard Wirnsberger[3], Carmine Zoccali[4], Tomasz Kostka[5], Agnieszka Guligowska[5], Francesco Mattace-Raso[2], Pedro Gil[6], Lara Guardado Fuentes[6], Itshak Meltzer[7], Ilan Yehoshua[8], Francesc Formiga-Perez[9], Rafael Moreno-González[9], Christian Weingart[10], Ellen Freiberger[10], Johan Ärnlöv[11,12,13], Axel C. Carlsson[11,13], Silvia Bustacchini[1], Fabrizia Lattanzio[1] on behalf of SCOPE investigators

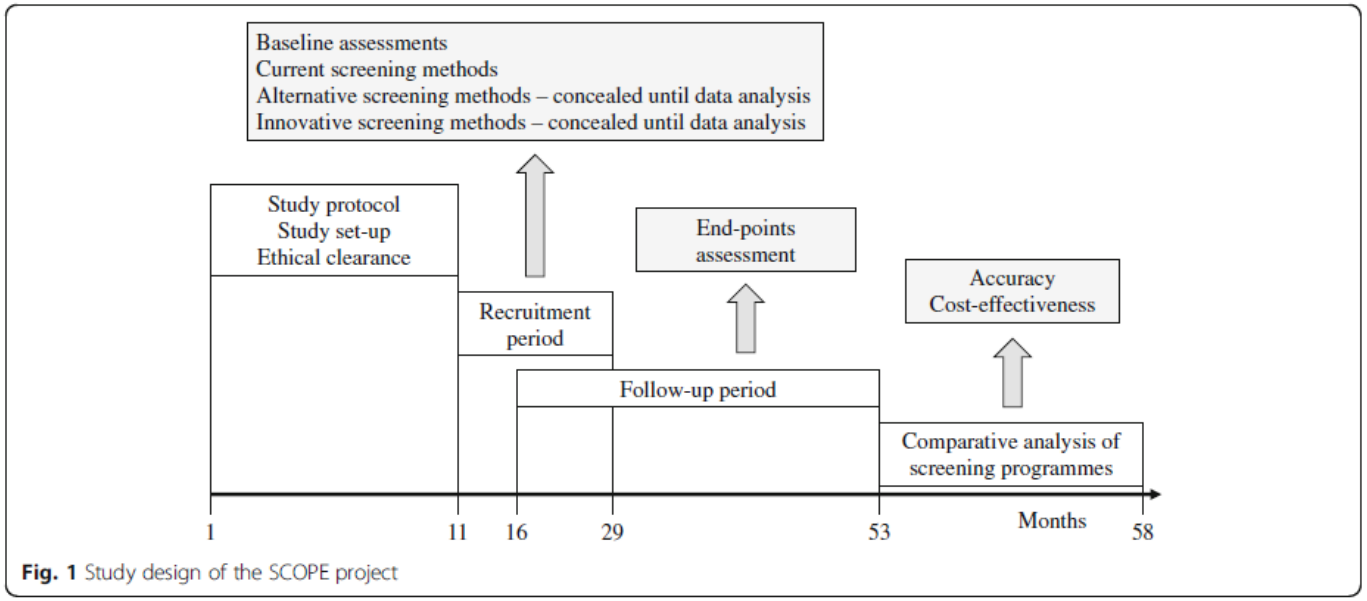


Fig. 1 Study design of the SCOPE project

Table 3 Biomarkers research in the SCOPE project

Current screening methods[a]	Alternative screening methods[b]	Innovative screening methods[b]
Serum creatinine	Serum cystatin C	Serum fibroblast growth factor 23
Creatinine-based eGFR	Serum β-trace protein	Serum and urinary soluble TNF receptor 1
Urinary albumin	Serum β2-microglobulin	Seerum and urinary soluble TNF receptor 2
Albumin-to-creatinine ratio		Serum and urinary osteopontin
		Serum penthraxin 3
		Serum and urinary endostatin
		Serum and urinary TIM-1 (KIM-1)
		Serum TRAIL R2
		Serum and urinary endostatin

[a]current screening measures will be assessed at local laboratories and are immediately available after enrollment and follow-up visits;
[b]alternative and innovative screening measures will be centrally assessed and will be concealed until data analysis