Att mäta och estimera glomerular filtrationshastighet (GFR) samt påvisa krympt-por-syndrom

Föreläsning 210331av Anders Grubb

Frågor kan ställas direkt efter föreläsningen
eller per e-mail, anders.grubb@med.lu.se
E-mail besvaras vanligen inom 1 dygn.

SMS-frågor

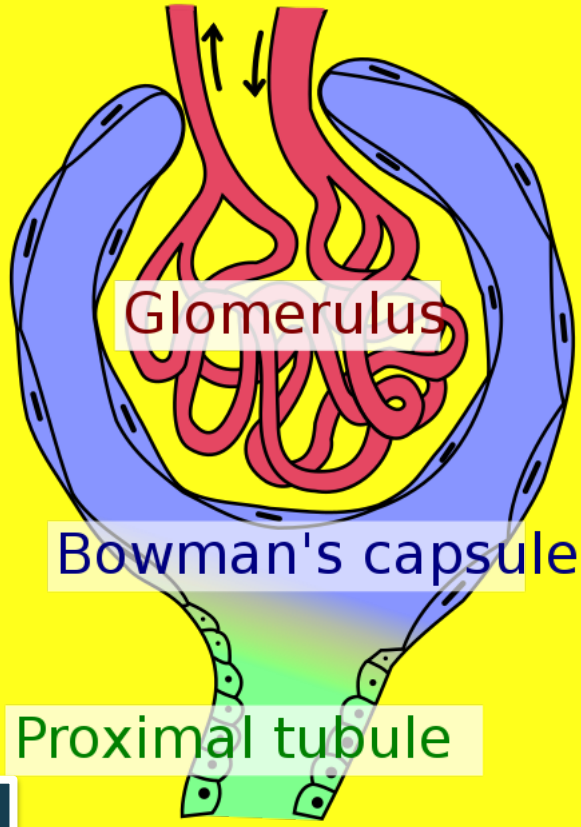
Skicka din fråga till nummer:

070-903 204 15 00

GFR, what is it?

The glomerular filtration rate, GFR, is the volume of primary urine produced per unit of time, correspondning to the volume of plasma filtered during that time.

Production of primary urine in the nephron



Cirka 90% av primärurinen är vatten, några procent salt och några procent peptider/proteiner < 30 kDa.
36% av kroppens extracellulära proteiner kataboliseras huvudsakligen i njurarna.

Can GFR in humans be measured?

No, because it is not feasible to measure the filtration flow in the approximately 800,000 human glomeruli

Vad är sanning?

Absolut sanning finns bara i himlen eller i Platons idévärld.

Vad är då den högsta vetenskapliga sanning som kan uppnås på jorden?

SMS-frågor

Skicka din fråga till nummer:

070-903 204 15 00

Vad är jordisk sanning?

Alla artiklar som publicerats i ämnet samlas in och genomläses av specialister inom sanningsområdet. Därefter väljs de bästa artiklarna ut enligt en kvalitets-skala och specialisterna bedömer om det finns möjlighet att dra slutsatser och graderar slutsatsernas styrka enligt:

Det finns starkt vetenskapligt underlag (⊕⊕⊕⊕) för att ...

Det finns måttligt starkt vetenskapligt underlag (⊕⊕⊕) för att ...

Det finns begränsat vetenskapligt underlag (⊕⊕) för att ...

Det finns otillräckligt vetenskapligt underlag (⊕) för att bedöma om ...

Bedömningssystemet kallas GRADE

Differences among ”gold standard” methods used to determine ”true” GFR

from the report

Methods to Estimate and Measure Renal Function (GFR)

SBU 2012

SBU = The Swedish Council on Health Technology Assessment

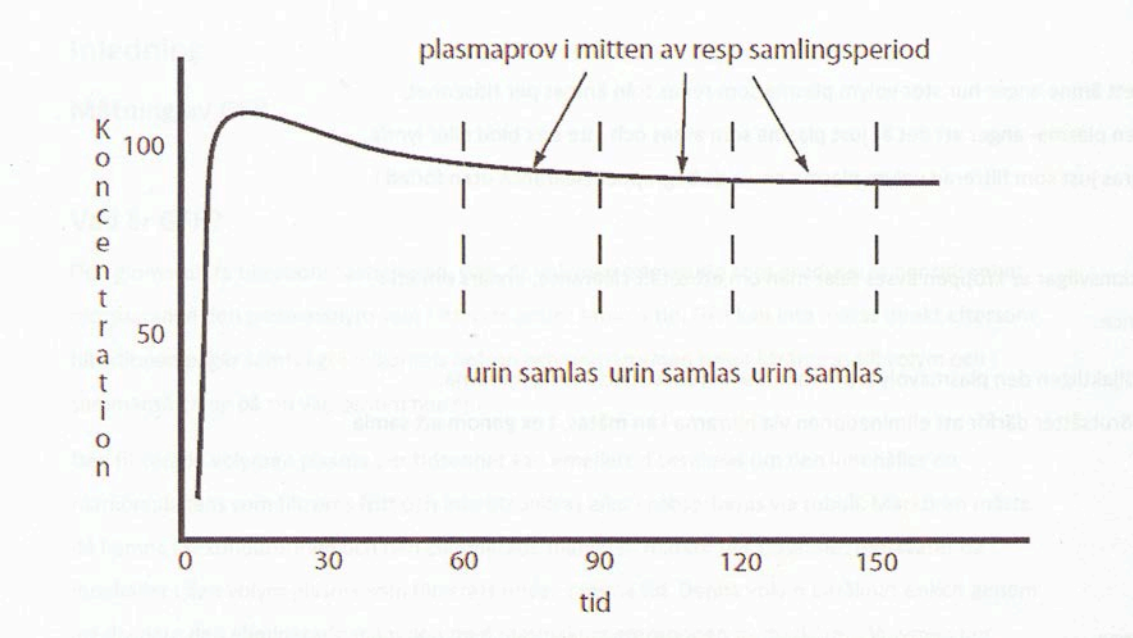
www.sbu.se/en/Published/Yellow/Methods-to-Estimate-and-Measure-Renal-Function-Glomerular-Filtration-Rate

Ultimate reference

- Renal clearance of inulin measured during a continuous infusion
  - Gold standard - universally recognized

- but...
  - cumbersome
  - early analysis methods imprecise
  - expensive

Mätning av renalt inulin-clearance = ”sanningen”
Introducerat/uppfunnet av Homer Smith med de första studierna på 1930-talet



SMS-frågor

Skicka din fråga till nummer:

070-903 204 15 00

Question

Which methods are equally accurate as renal inulin clearance for measuring GFR?

Renal and/or plasma clearance of:

- ^{99m}Tc-DTPA?
- ^{51}Cr-EDTA?
- ^{125}I-Iothalamate?
- Iohexol (non-radioactive)?
- Plasma clearance of inulin?
- Endogeneous creatinine clearance?

Tabell 1. Sammanfattning av resultat och deras evidensstyrka avseende noggrannheten hos olika indexmetoder för att mäta njurfunktion (GFR) jämfört med renalt inulinclearance (gold standard).

Indexmetod	**Tillräcklig noggrannhet***	**Evidensstyrka**
^{51}Cr-EDTA renalt clearance	ja	⊕⊕⊕⊕
Jotalamat renalt clearance		
^{51}Cr-EDTA plasmaclearance	ja	⊕⊕⊕
Johexol plasmaclearance		
DTPA renalt clearance	ja	⊕⊕
Johexol renalt clearance		
Inulin plasmaclearance		
Endogent kreatininclearance	**nej**	⊕⊕⊕⊕
DTPA plasmaclearance	**nej**	⊕⊕
Jotalamat plasmaclearance	**nej**	⊕

*Krav på tillräcklig noggrannhet: P30 ≥80 %. (P30= Den procentuella andelen av resultaten erhållna med indexmetoden som ligger inom ±30 procent av resultaten erhållna med referensmetoden).

Sedan 2014 vet världen sanningen!

AJKD

Original Investigation

Measuring GFR: A Systematic Review

*Inga Soveri, MD, PhD,[1] Ulla B. Berg, MD, PhD,[2] Jonas Björk, PhD,[3] Carl-Gustaf Elinder, MD, PhD,[4] Anders Grubb, MD, PhD,[5] Ingegerd Mejare, PhD,[6] Gunnar Sterner, MD, PhD,[7] and Sten-Erik Bäck, MSc, PhD,[5] on behalf of the SBU GFR Review Group**

Background: No comprehensive systematic review of the accuracy of glomerular filtration rate (GFR) measurement methods using renal inulin clearance as reference has been published.

Study Design: Systematic review with meta-analysis of cross-sectional diagnostic studies.

Setting & Population: Published original studies and systematic reviews in any population.

Selection Criteria for Studies: Index and reference measurements conducted within 48 hours; at least 15 participants studied; GFR markers measured in plasma or urine; plasma clearance calculation algorithm verified in another study; tubular secretion of creatinine had not been blocked by medicines.

Index Tests: Endogenous creatinine clearance; renal or plasma clearance of chromium 51–labeled ethylenediaminetetraacetic acid (^{51}Cr-EDTA), diethylenetriaminepentaacetic acid (DTPA), iohexol, and iothalamate; and plasma clearance of inulin.

Reference Test: Renal inulin clearance measured under continuous inulin infusion and urine collection.

Results: Mean bias < 10%, median bias < 5%, the proportion of errors in the index measurements that did not exceed 30% (P_{30}) ≥ 80%, and P_{10} ≥ 50% were set as requirements for sufficient accuracy. Based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, the quality of evidence across studies was rated for each index method. Renal clearance of iothalamate measured GFR with sufficient accuracy (strong evidence). Renal and plasma clearance of ^{51}Cr-EDTA and plasma clearance of iohexol were sufficiently accurate to measure GFR (moderately strong evidence). Renal clearance of DTPA, renal clearance of iohexol, and plasma clearance of inulin had sufficient accuracy (limited evidence). Endogenous creatinine clearance was an inaccurate method (strong evidence), as was plasma clearance of DTPA (limited evidence). The evidence to determine the accuracy of plasma iothalamate clearance was insufficient. With the exception of plasma clearance of inulin only, renal clearance methods had P_{30} > 90%.

Limitations: The included studies were few and most were old and small, which may limit generalizability. Requirements for sufficient accuracy may depend on clinical setting.

Conclusions: At least moderately strong evidence suggests that renal clearance of ^{51}Cr-EDTA or iothalamate and plasma clearance of ^{51}Cr-EDTA or iohexol are sufficiently accurate methods to measure GFR.

Am J Kidney Dis. ■(■):■-■.

Since GFR cannot be measured in all patients on all occasions, we must rely on estimations of GFR. Many potential markers for GFR are available, but only creatinine and cystatin C have been extensively evaluated.

Observera skillnaden mellan relativt GFR och absolut GFR!

Relativt GFR, *alias* kroppsytenormaliserat GFR, mäts i ml/min/1,73 m^2 kroppsyta och används för att estimera och följa GFR eftersom då storleken på en individ inte påverkar referensområdet (”normalvärdet”). 1,73 m^2 är numera medelvärdet av den vuxna svenska kvinnans kroppsyta.

Absolut GFR mäts i ml/min och används för att dosera läkemedel vars omsättning är njurfunktionsberoende (dvs GFR-beroende). Vanligen, och i Region Skåne alltid, ger laboratorierna svar på cystatin C- och kreatinin-estimerat GFR som relativt GFR (ml/min/1,73 m^2). Därav kan man lätt räkna ut absolut GFR (ml/min) om patientens längd och vikt är känd med hjälp av olika formler t. ex. DuBois och DuBois formel:

Kroppsyta i m^2 = 0,007184 x (vikt i kg)^{0,425} x (längd i cm)^{0,725}.

Hjälpmedel finns på www.egfr.se

Vid invasiv bestämning av GFR ges svar på både relativt och absolut GFR.

P-Cystatin C and P-Creatinine

are recommended as markers of GFR by both

“The international society of nephrology in the KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease”

and by

SBU (Swedish Council on Health Technology Assessment) in their recommendation of 2013

”Methods to Estimate and Measure Renal Function (GFR)”

Cystatin C- and Creatinine (+sex,race age)-based estimating equations for GFR should always be used and never ”naked” cystatin C and creatinine values in order to get the best and most reproducible results.

At least 100 different equations are suggested. Which ones should be used?

Suggested cystatin C-based $eGFR_{cystatinC}$ equation: CAPA

Because

1. it is based upon 7 of the most widely used assays, all calibrated against the international cystatin C calibrator and
2. a large general Caucasian-Asian-Pediatric-Adult population
3. It works from 1year of age for all races and sexes (no race- or sex-factors are required)

Generation of a new cystatin C-based estimating equation for glomerular filtration rate using seven assays standardized to the international calibrator.

Clin Chem 2014; 60: 974 – 986.

Suggested creatinine(+sex,race,age)-based $eGFR_{creatinine}$ equation: LM-rev

Because

1 it is based upon enzymatic creatinine assays calibrated against an international creatinine calibrator and works for children and adults

and

2 has been shown to perform better than the CKD-EPI and MDRD-equations in a large Scandinavian population

The revised Lund-Malmö GFR estimating equation outperforms MDRD and CKD-EPI across GFR, age and BMI intervals in a large Swedish population. Clin Chem Lab Med 2014; 52: 815-824.

Diagnosing kidney disease 2021

To measure relative and absolute glomerular filtration rate (GFR)
Iohexol- or ^{51}Cr-EDTA-clearance (Invasive procedures)

To estimate relative glomerular filtration rate (GFR)
Pt-eGFR$_{\text{Cystatin C}}$ or Pt-eGFR$_{\text{Creatinine}}$, unit: mL/min/1.73m^2 body surface area.
Best estimation is the mean of Pt-eGFR$_{\text{Cystatin C}}$ and Pt-eGFR$_{\text{Creatinine}}$
Internet-tool to do it: www.egfr.se

To estimate absolute GFR for dosage of drugs excreted by the kidneys; unit: mL/min
Pt-eGFR$_{\text{Cystatin C}}$ or/and Pt-eGFR$_{\text{Creatinine}}$ + weight + height using internet calculators *e.g.* www.egfr.se

To calculate risk for end-stage renal disease (hemodialysis), myocardial infarction, hospitalization and death at reduced GFR
Pt-eGFR$_{\text{Cystatin C}}$ Unit: mL/min/1.73m^2 body surface area
Even stronger risk in "**Shrunken Pore Syndrome**" i.e. when Pt-eGFR$_{\text{Cystatin C}}$ < 0.7 x Pt-eGFR$_{\text{Creatinine}}$

Remiss
rutin / akut 1
Klinisk kemi

Helsingborg
Kristianstad
Lund
Malmö

Kundkod beställaretikett eller beställaradress.

Läkarid / ert ordernummer

Patientetikett / alternativt patientdata (Personnummer, namn)

*Se speciella anvisningar i Analysportalen
www.skane.se/labmedicin

Provtagarens id

Meddelande till laboratoriet / provtagarens telefonnummer

AKUT-etikett

AA 77 101

Laboratoriets anteckningar

Ys Si Lu La He Än Kr Hä Ma Tr Sl Ba

AKUT-svar markera i rutan

Provtagningstid Kapillärt Ej fastande Hälsovård Patientid ej styrkt

Dag 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31

Tim 00 01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19 20 21 22 23

Min 00 10 20 30 40 50

Koagulation *
- P-PK (INR)
- P-APTt
- P-D-dimer
- P-Fibrinogen
- P-Antitrombin

Läkemedel/Allmän-/Immunokemi
- P-Digoxin
- P-Fenytoin
- P-Karbamazepin
- P-Teofyllin
- P-Paracetamol
- P-Salicylat
- P-Tobramycin
- P-TSH
- P-T4, fritt
- P-T3, fritt
- P-PTH
- P-PSA
- P-hCG + beta
- P-Kortisol
- P-Prokalcitonin (Ej Helsingborg)
- P-CRP
- P-Natrium
- P-Kalium *
- P-Kreatinin
- Pt-eGFR medel
- P-Albumin
- P-Calcium *
- P-Urea
- P-Fosfat
- P-Urat
- P-Magnesium
- P-Klorid
- P-CKMB (Ej Helsingborg)
- P-Troponin T
- P-Myoglobin
- P-CK
- P-NT-proBNP
- P-ASAT
- P-ALAT
- P-GT
- P-ALP
- P-Bilirubin
- P-Bil, konj
- P-Pankr. amylas
- P-Kolesterol
- P-TG *
- P-HDL, LDL
- P-Apo A1, Apo B, kvot
- P-Järn,* P-TIBC
- P-Homocystein*
- P-Folat
- P-Kobalaminer (B12)
- P-Ferritin

- S-LD *
- S-Ca-jon *
- S-Litium
- S-Vankomycin

ENDAST Malmö och Helsingborg
- S-TPO-ak

- aB-Blodgas *
- P-Laktat *
- Ecv-Basöverskott*
- P-Etanol
- U-Alb/Krea kvot
- B-HbA1c
- P-Glukos *

Hematologi
- B-Hb
- B-Lkc
- B-Trc
- Trc-MPV
- B-Erc
- B-EVF
- Erc-MCV
- Erc-MCH
- B-Rtc
- Rtc-MCH
- B-Neu
- B-Diff
- Anemiutredning
- B-SR (ENDAST Kristianstad)
- B-SR

3137188539

Labmedicin Skåne
En del av Region Skåne

Art nr: 23024 2013 apr

In addition to supplying the best way to estimate GFR, *i.e.* $eGFR_{mean}$,use of the $eGFR_{cystatinC}$ and $eGFR_{creatinine}$ equations allows an internal quality check of the estimation.

Procedure: To compare the results and reject too big differences

Improved estimation of GFR by comparison of $eGFR_{cystatinC}$ and $eGFR_{creatinine}$

Scand J Clin Lab Invest 2012; 72: 73-77.

A tool to produce the best estimate of GFR can be found at

www.egfr.se

Bakgrund | Relativt GFR | Absolut GFR

Verktyg för beräkning av

PÅLITLIGT CYSTATIN C- OCH KREATININ-BASERAT ESTIMAT AV RELATIVT GFR

och av

ABSOLUT GFR FRÅN RELATIVT GFR

samt för diagnostik av

KRYMPT-POR-SYNDROM

LUND UNIVERSITY

Bakgrund | Relativt GFR | Absolut GFR

Beräkning av pålitligt estimat av relativt GFR

Använd decimalpunkt

Cystatin C (mg/L)

Kreatinin (μmol/L)

Ålder (år)

(•) Okänt ( ) Man ( ) Kvinna

Relativt GFR (mL/min/1.73 m^2)

CAPA, $eGFR_{cystatin\ C}$

LM-Rev, $eGFR_{kreatinin}$

Medel, $(eGFR_{cystatin\ C} + eGFR_{kreatinin})/2$

CAPA/LM-Rev-kvot

CAPA/LM-Rev-kvot <0,70 betyder krympt-por-syndrom

Shrunken Pore Syndrome and mortality (CAPA ≤ 0.6 x LMrev)

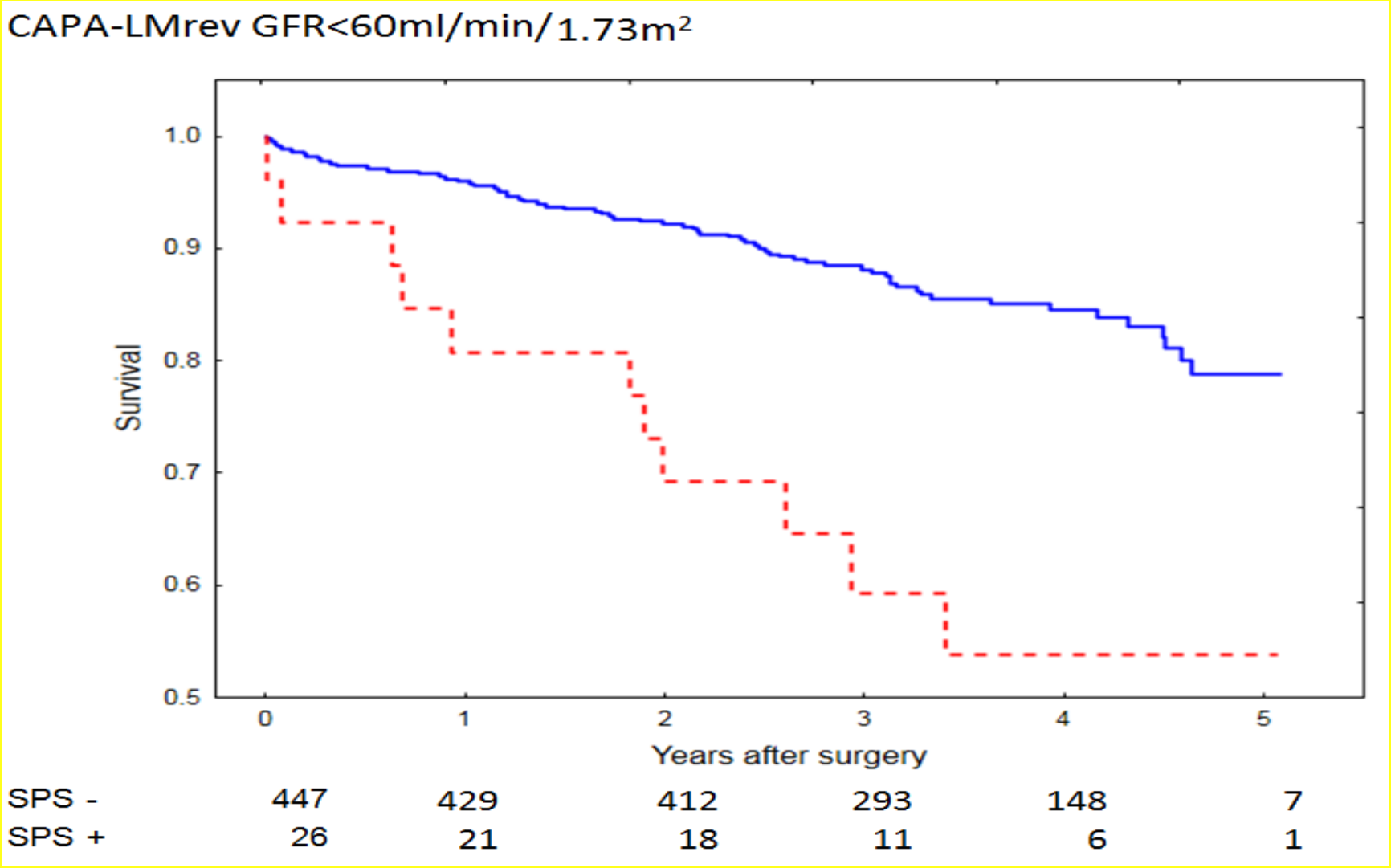
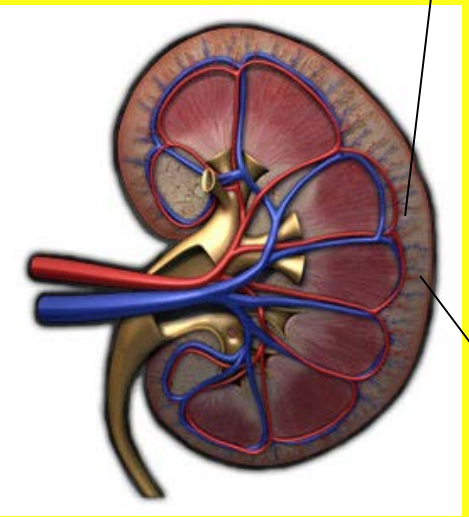


Table 3. Total all-cause mortality (%), prevalence (%) of SPS in four different cohorts using different $eGFR_{CYS}/eGFR_{CR}$-ratios for the diagnosis and corresponding hazard ratios (HR) for all-cause mortality.

$CAPA_{CYS}$ / LMR_{CR} ratio	Total cohort (n= 2 781)		Sub-cohort 1 Diagnose-free (n= 1 049)		Sub-cohort 2 Normal measured GFR (≥60 mL/min/1.73m^2;n= 1 300).		Sub-cohort 3 Normal measured GFR and diagnose-free (n= 567)	
	%	HR (95 % CI)	%	HR (95 % CI)	%	HR (95 % CI)	%	HR (95 % CI)
<0.70	23.1	2.97 (2.37 - 3.72)[a]	17.1	3.69 (2.25 - 6.05)[b]	17.0	4.08 (2.57 - 6.48)[b]	11.5	7.30 (2.29 - 23.22)[b]
<0.60	11.1	3.33 (2.48 - 4.47)[c]	8.2	4.41 (2.29 – 8.52)[c]	7.4	5.32 (2.77 – 10.24)[c]	5.3	14.25 (2.38 – 85.16)[c]
Total all-cause mortality, %		37.7		21.0		30.2		11.8

[a] Fully-adjusted model presented in Table 2.
[b] Fully-adjusted model presented in Supplementary Table 4.
[c] Adjusted for the same variables as in a and b, respectively, full model not presented.

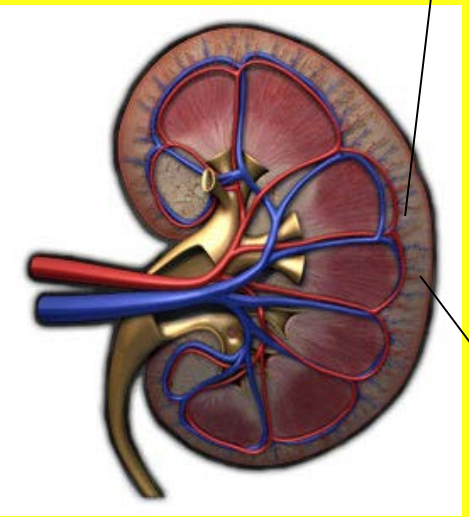


40 Å

L2
L1
N
β3
β2
β1
β4
β5
α1
C
α2
AS

30 Å

5 Å



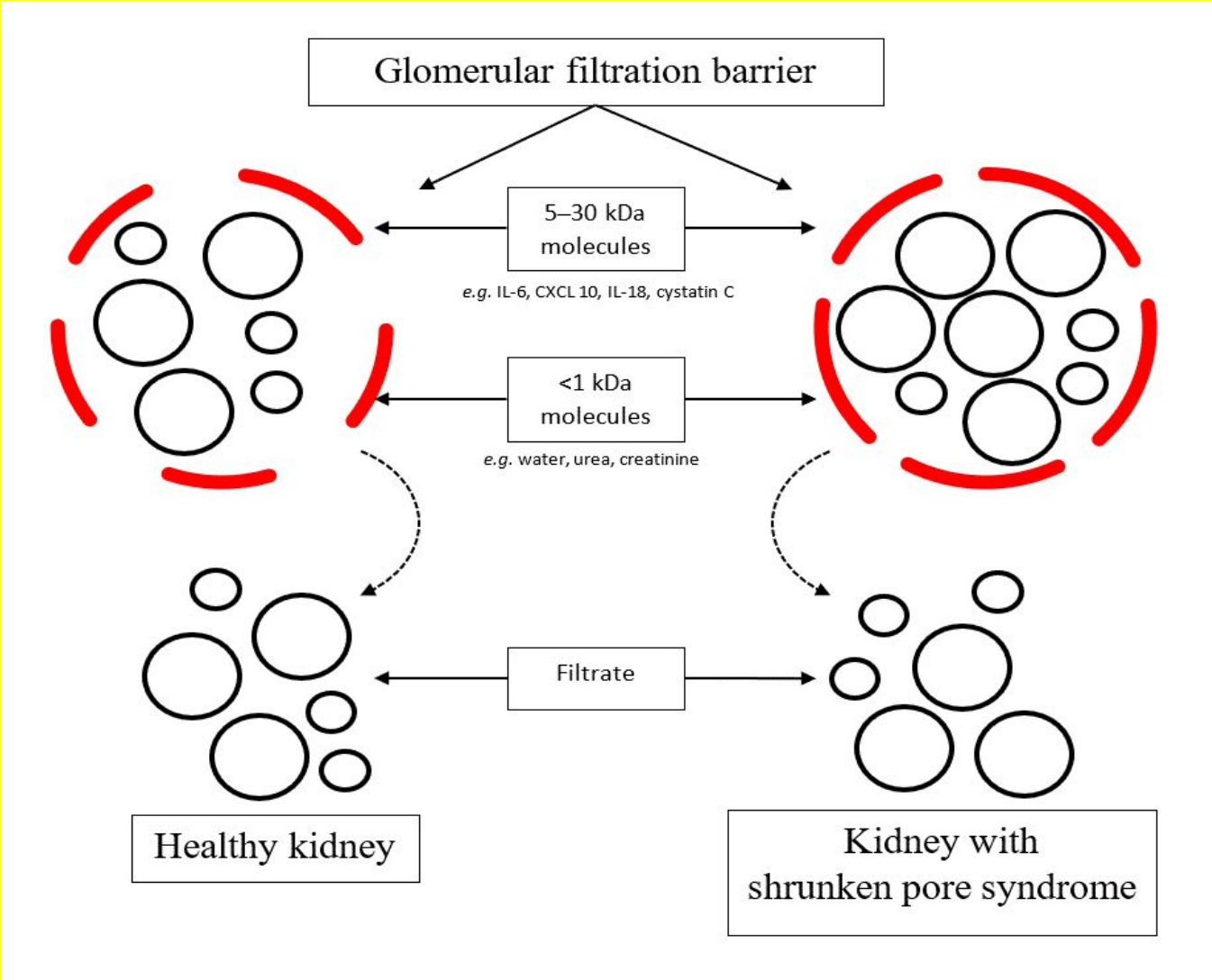
No passage

L2
L1
N
β3
β2
β1
β4
β5
α1
C
α2
AS

NH
NH
N
CH3

Passage

A model for the pathophysiology of shrunken pore syndrome



Implications of all the available evidence

As a significant part of patients with SPS cannot be identified by using the diagnostic procedures recommended in KDIGO 2012, these recommendations have to be adjusted to identify this syndrome associated with a very high mortality. It can easily be done by adding a determination of cystatin C to the recommendations.