UNIVERSITÄTS KLINIKUM ulm

Kreatinin, Cystatin C und GFR zur Diagnostik bei akuter Nierenschädigung

Frieder Keller

AWMF Leitliniengruppe:

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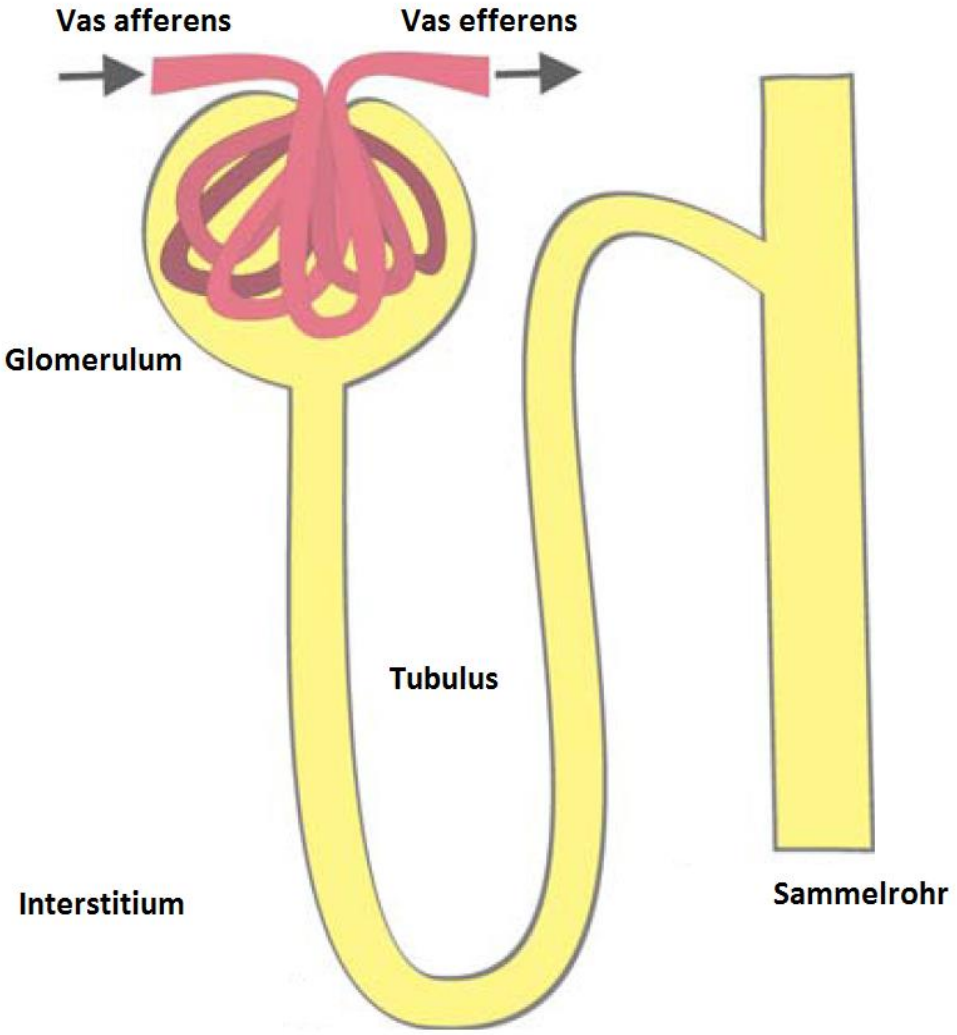
Offenlegung: Reise + Übernachtung event lab. GmbH

Netzplan

- Crea
- GFR
- Cystatin C
- AKI
- CKD

Nephron


Vas afferens
Vas efferens
Glomerulum
Tubulus
Interstitium
Sammelrohr

Crea = Kreatinin

Glücksfall <= Geschenk der Natur

- Crea Blutspiegel unabhängig von Körpergrösse und -gewicht !
- Stadien AKI = Crea basiert
- Stadien CKD = eGFR basiert, aber eGFR = Crea basiert
- uCrea = 1,0 gr pro Tag = const.
- uCrea Referenz für Urinausscheidung (uPCR uACR uNaCR)

Rehberg PB.

Studies on Kidney Function: The Rate of Filtration and Reabsorption in the Human Kidney.

Biochem J. 1926; 20: 447-60.

The calculation of the amount of filtrate is possible if we have a substance filtered out through the glomeruli none of which is reabsorbed during passage through the tubules. Suppose A to be a substance of this kind and F to be the amount of filtrate formed in the capsules, U the amount of urine, A_P % the percentage of the substance A present in the plasma in a diffusible state, and A_U % the percentage in the urine; then

$$\frac{F \times A_P\,\%}{100} = \frac{U \times A_U\,\%}{100}.$$

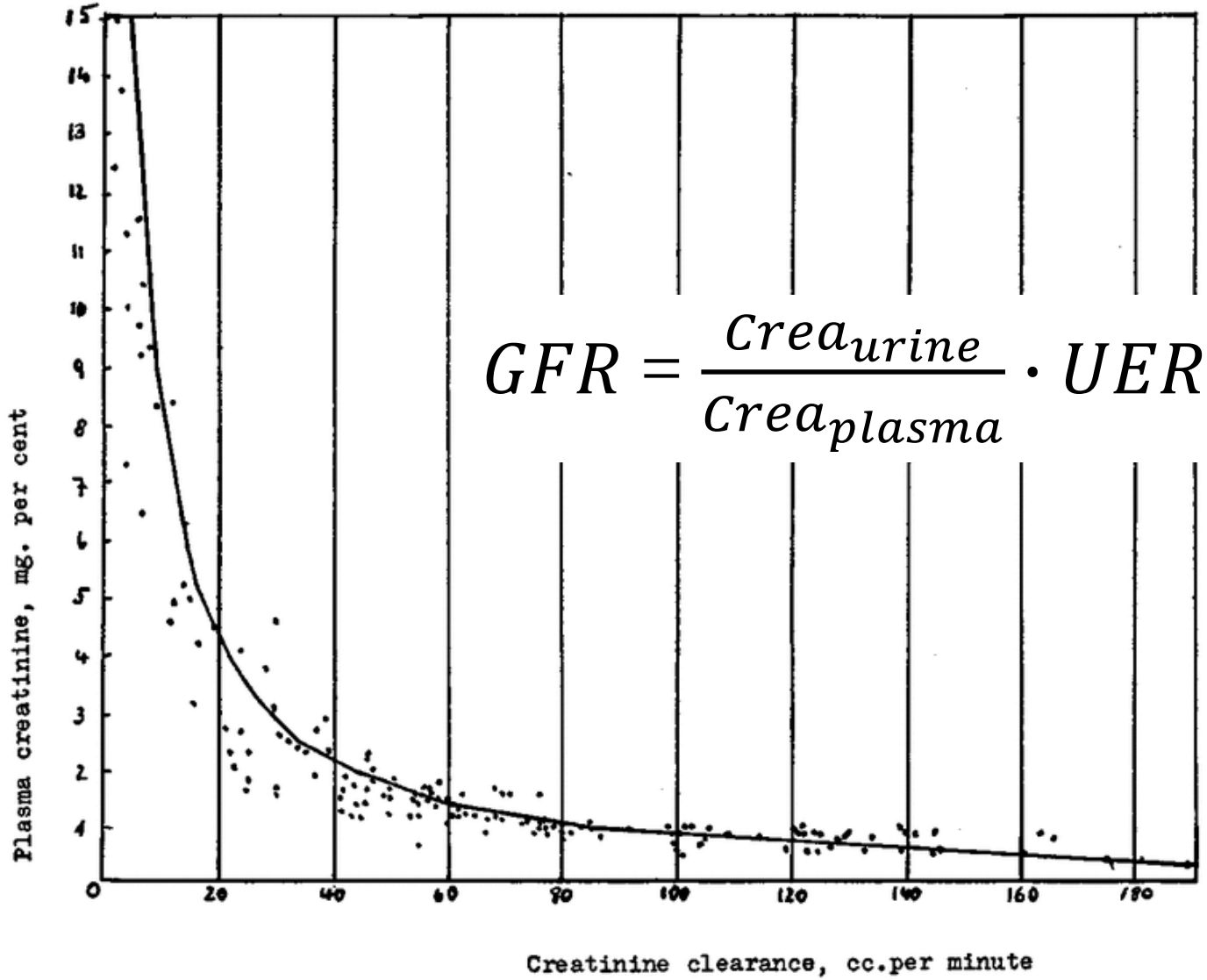
F (Glomerular Filtration Rate) = U (Urinary Excretion Rate)

A_{P+U} => Urea => Crea

Steinitz K, Türkand H.

THE DETERMINATION OF THE GLOMERULAR FILTRATION BY THE ENDOGENOUS CREATININE CLEARANCE.

J Clin Invest. 1940; 19: 285-98.



$$GFR = \frac{Crea_{urine}}{Crea_{plasma}} \cdot UER = CL_{crea}$$

GFR und Crea

Ursache => Wirkung

- GFR ↓ => Crea ↑

$$Crea \cong \frac{1}{GFR}$$

aber

$$GFR \cong \frac{1}{Crea}$$

- primär gemessen = Crea
- sekundär berechnet = GFR

$$GFR \cong Crea^{-1.0}$$

Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS;

CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C.

N Engl J Med. 2012 Jul 5;367(1):20-9.

Basis of Equation and Sex	Serum Creatinine†	Equation for Estimating GFR
	mg/dl	
CKD-EPI creatinine equation‡		
Female	>0.7	$144 \times (Scr/0.7)^{-1.209} \times 0.993^{Age}$ [× 1.159 if black]
Male	>0.9	$141 \times (Scr/0.9)^{-1.209} \times 0.993^{Age}$ [× 1.159 if black]

Der grosse Unterschied

- Akutes Nierenversagen (= AKI): reversibel wenn Ursache beseitigt
- Chronische Nierenkrankheit (= CKD): progredient, zwar therapierbar aber nicht heilbar

Akutes Nierenversagen (AKI): 3 Stadien

Chronische Niereninsuffizienz (CKD): 5 Stadien

AKI			CKD			
	Δ Creatinine within < 7 days	Diuresis for 6 – 12 h		GFR ml/min per 1.73 sqm		uACR mg/g
			Stage G1	GFR > 90	A1	< 30
Stage 1	1.5 fold	< 90 ml/h	Stage G2	GFR > 60	A2	< 300
Stage 2	2 fold	< 60 ml/h	Stage G3	GFR > 30	A3a	< 2000
Stage 3	> 3 fold	< 30 ml/h	Stage G4	GFR > 15	A3b NS	> 2000
			Stage G5	GFR < 15		

Chawla LS, Davison DL, Brasha-Mitchell E, Koyner JL, Arthur JM, Shaw AD, Tumlin JA, Trevino SA, Kimmel PL, Seneff MG.

Development and standardization of a furosemide stress test to predict the severity of acute kidney injury.

Crit Care. 2013; 17: R207.

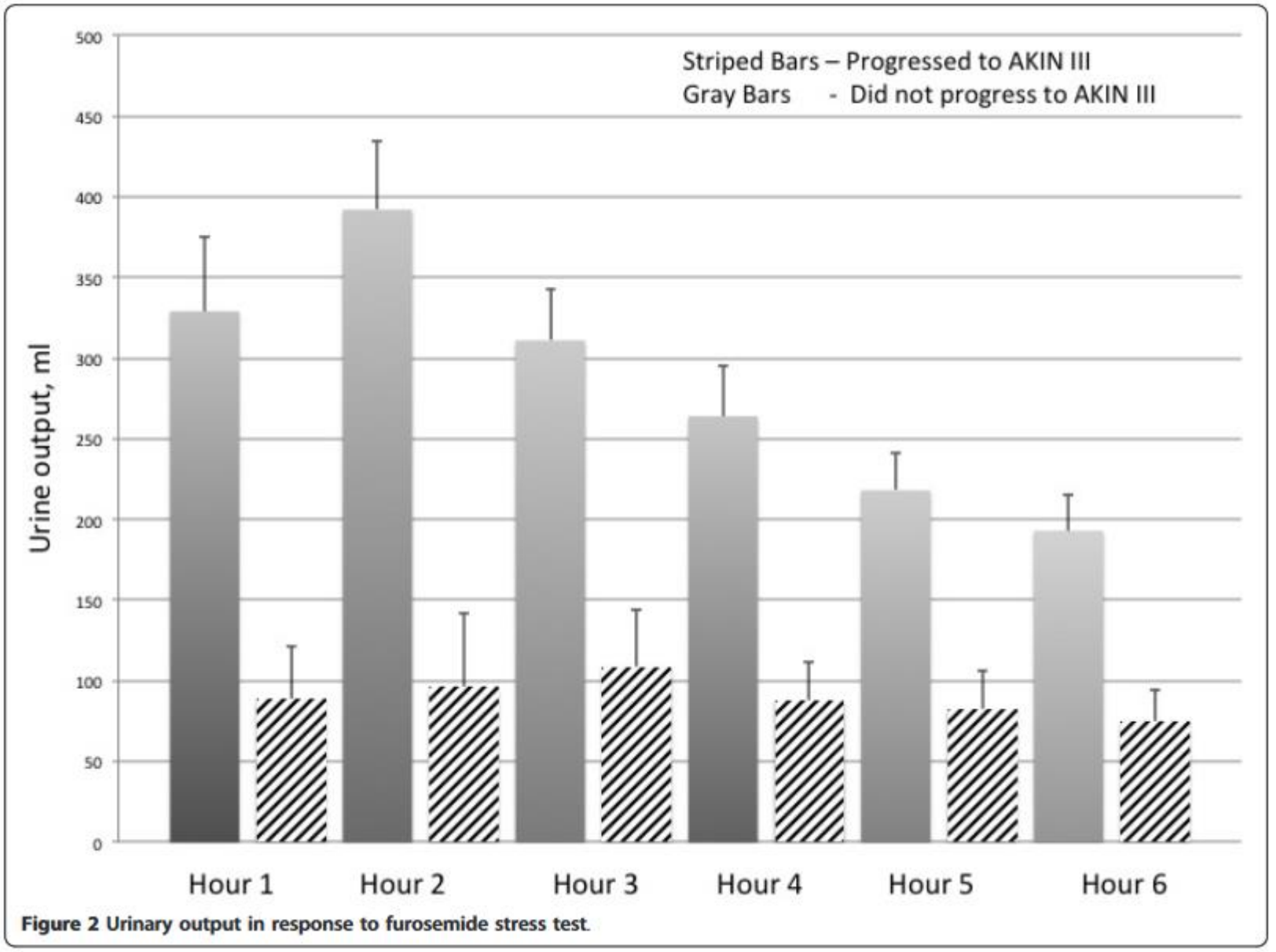
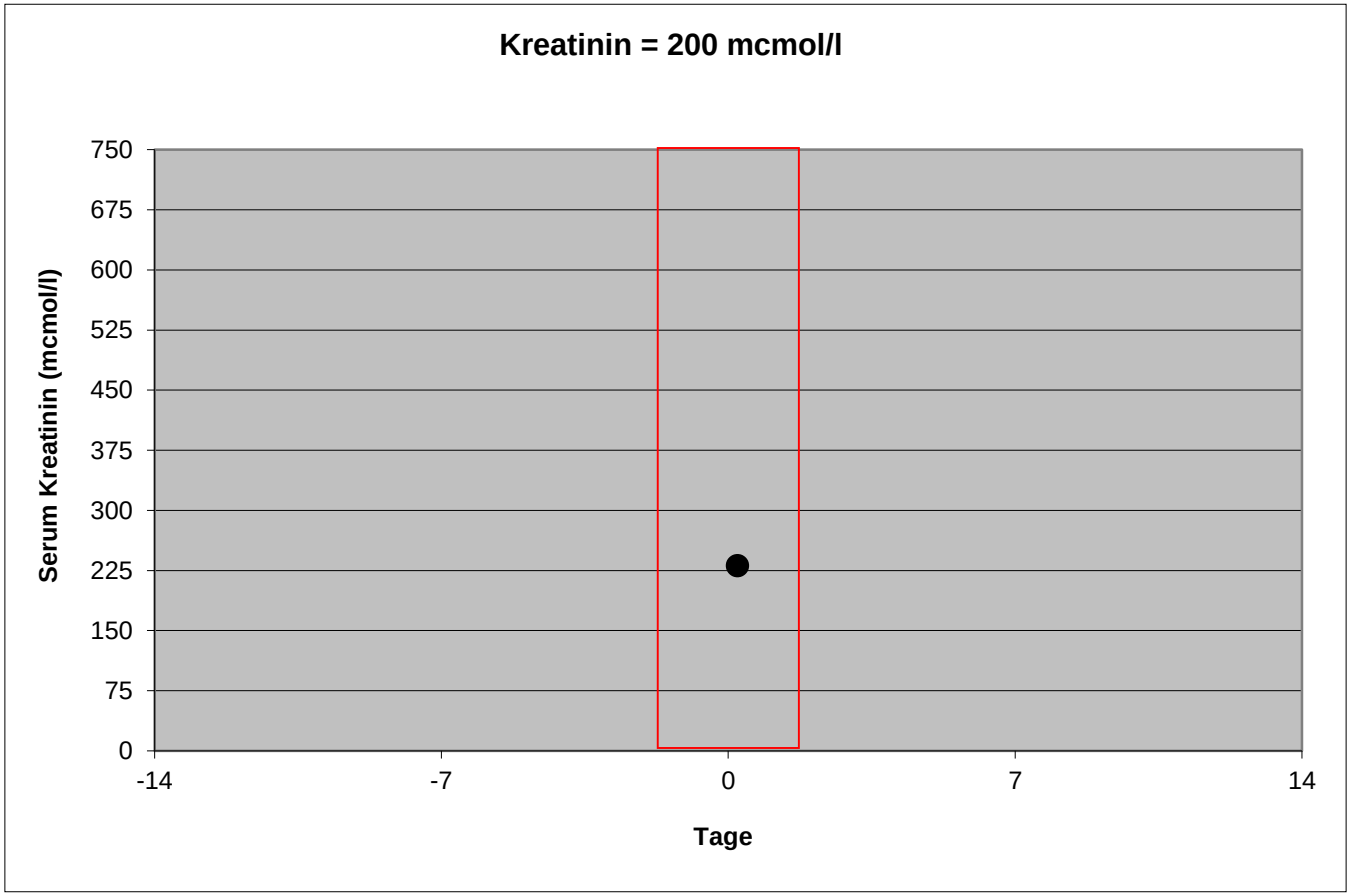


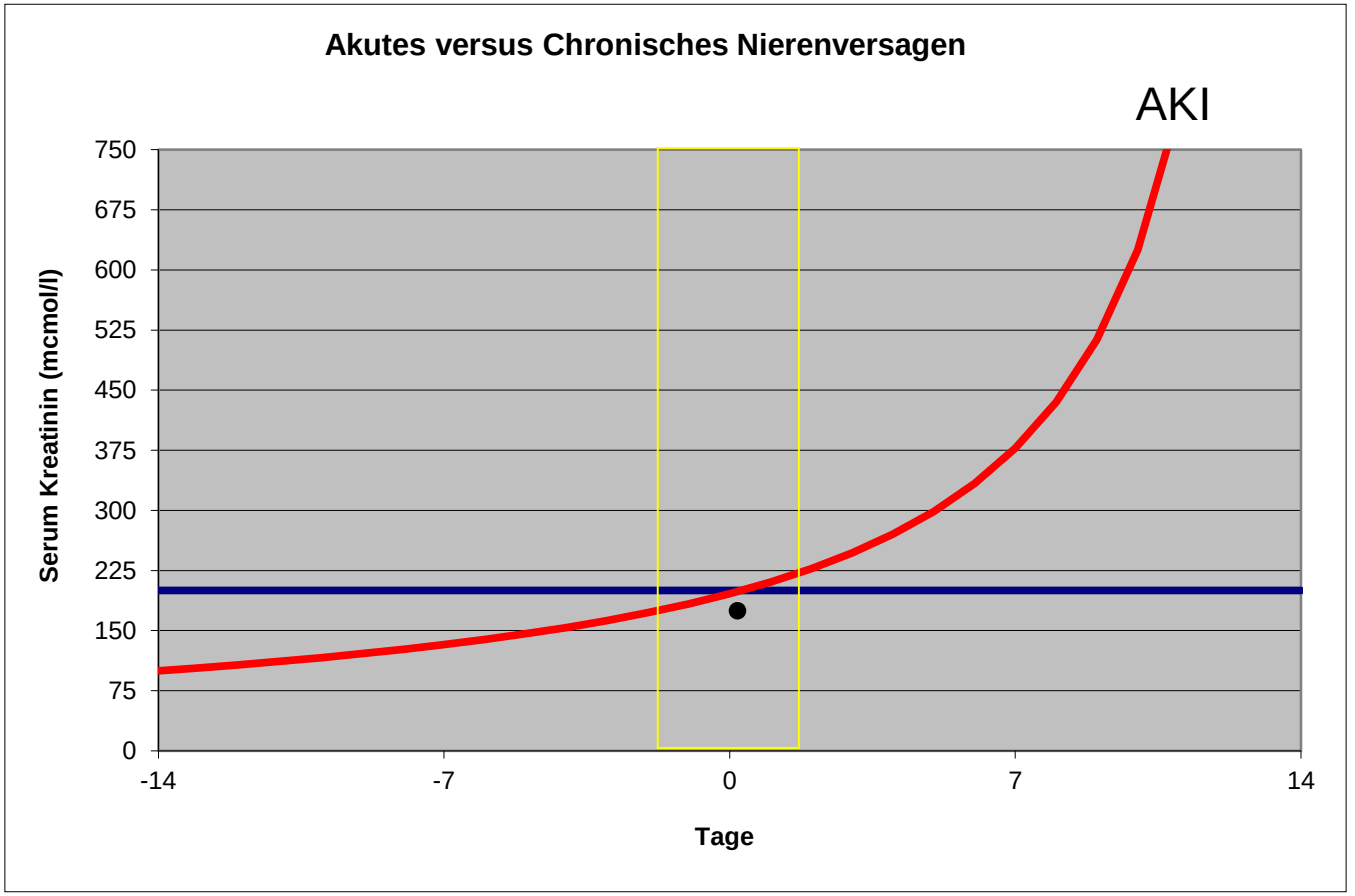
Figure 2 Urinary output in response to furosemide stress test.

< 100 ml/h
=> AKI

AKI oder CKD


Kreatinin = 200 mcmol/l
Serum Kreatinin (mcmol/l)
750
675
600
525
450
375
300
225
150
75
0
-14
-7
0
7
14
Tage

AKI oder CKD


Akutes versus Chronisches Nierenversagen
AKI
CKD
Serum Kreatinin (mcmol/l)
750
675
600
525
450
375
300
225
150
75
0
-14
-7
0
7
14
Tage

Fall 1

27 jähriger Patient mit
schwerem Verkehrsunfall
Geschätzter Blutverlust 2 L
RR 70 / 30 mmHg, Puls 120 /min

Kreatinin bei Aufnahme 87 µmol/L

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schwerem Verkehrsunfall
Geschätzter Blutverlust 2 L
RR 70 / 30 mmHg, Puls 120 /min

Kreatinin bei Aufnahme 87 µmol/L
Kreatinin am nächsten Tag 198 µmol/L

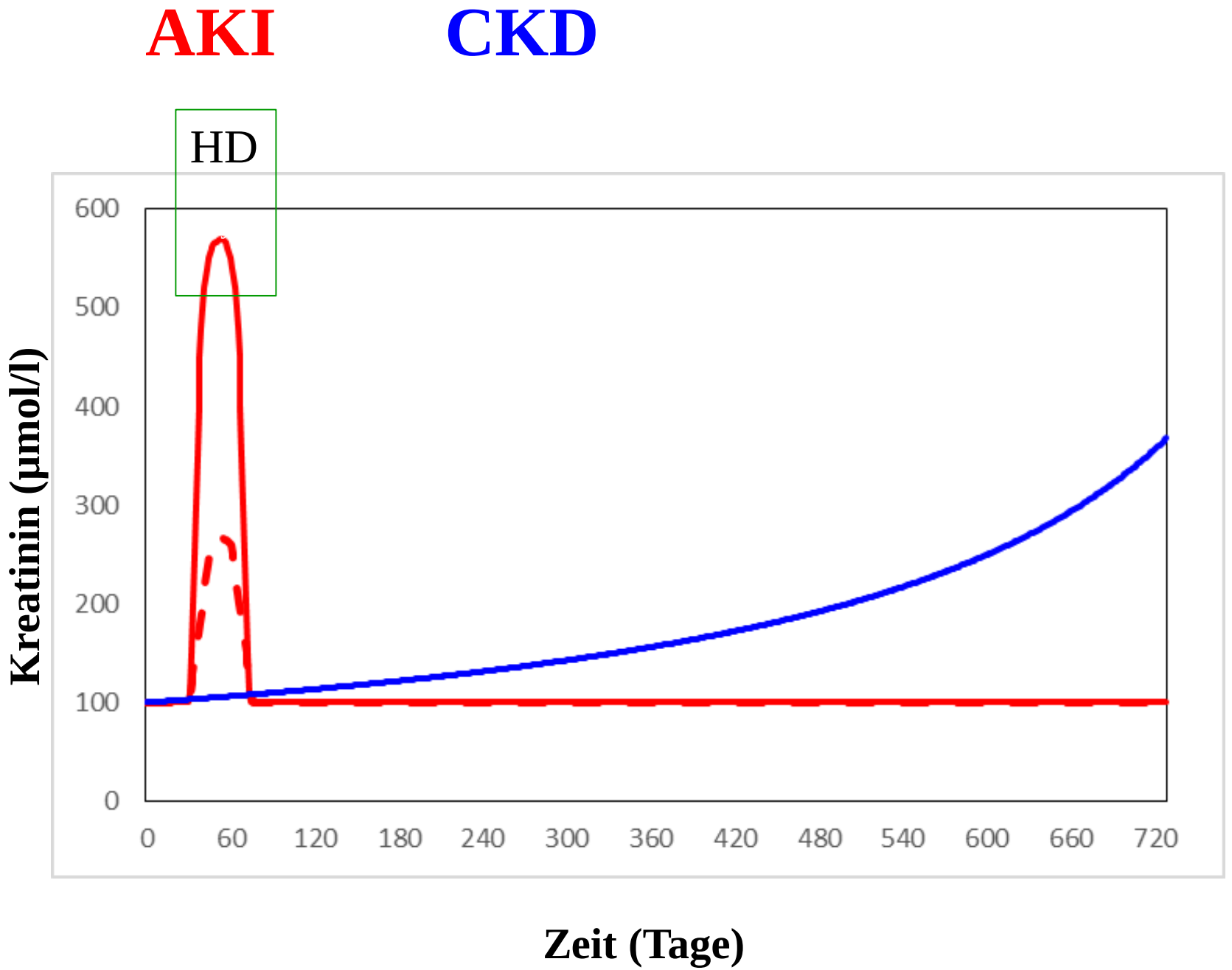
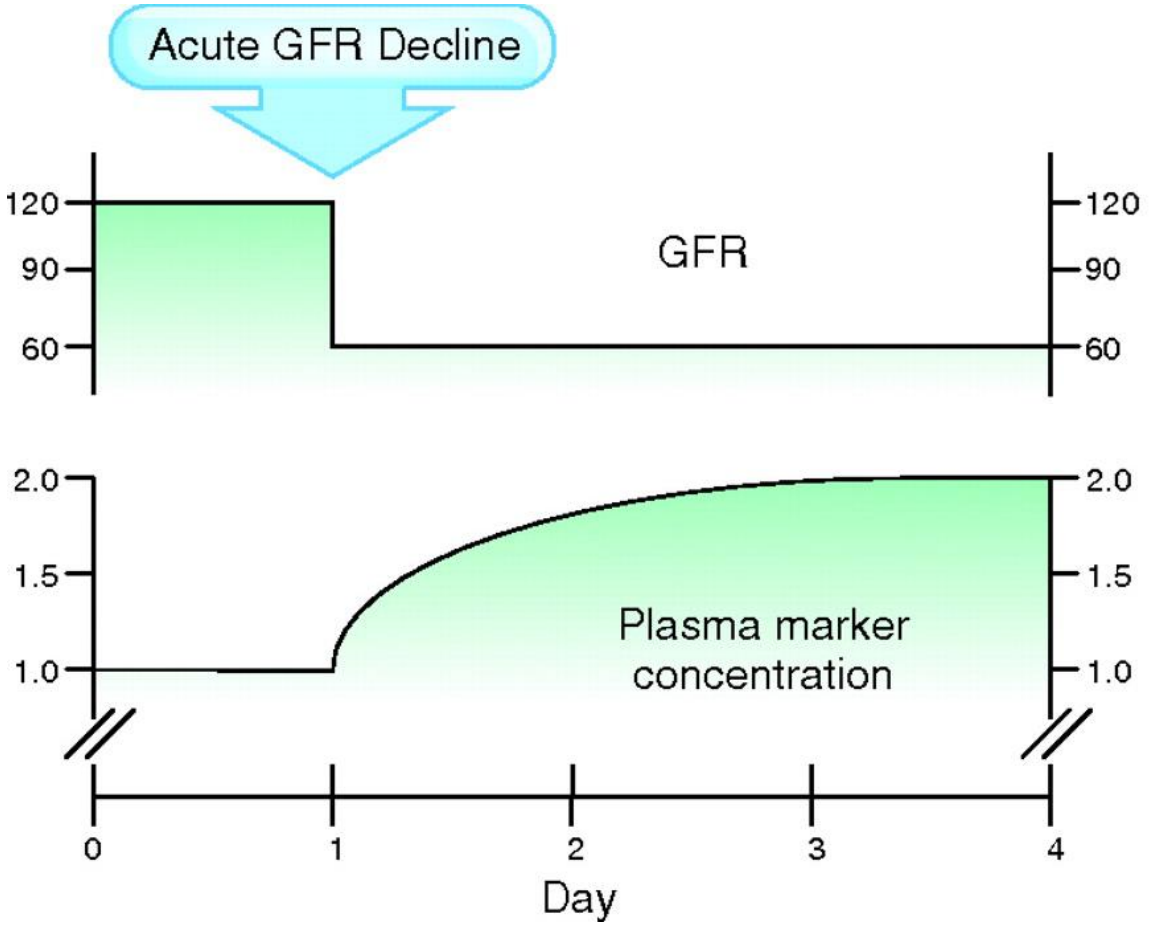
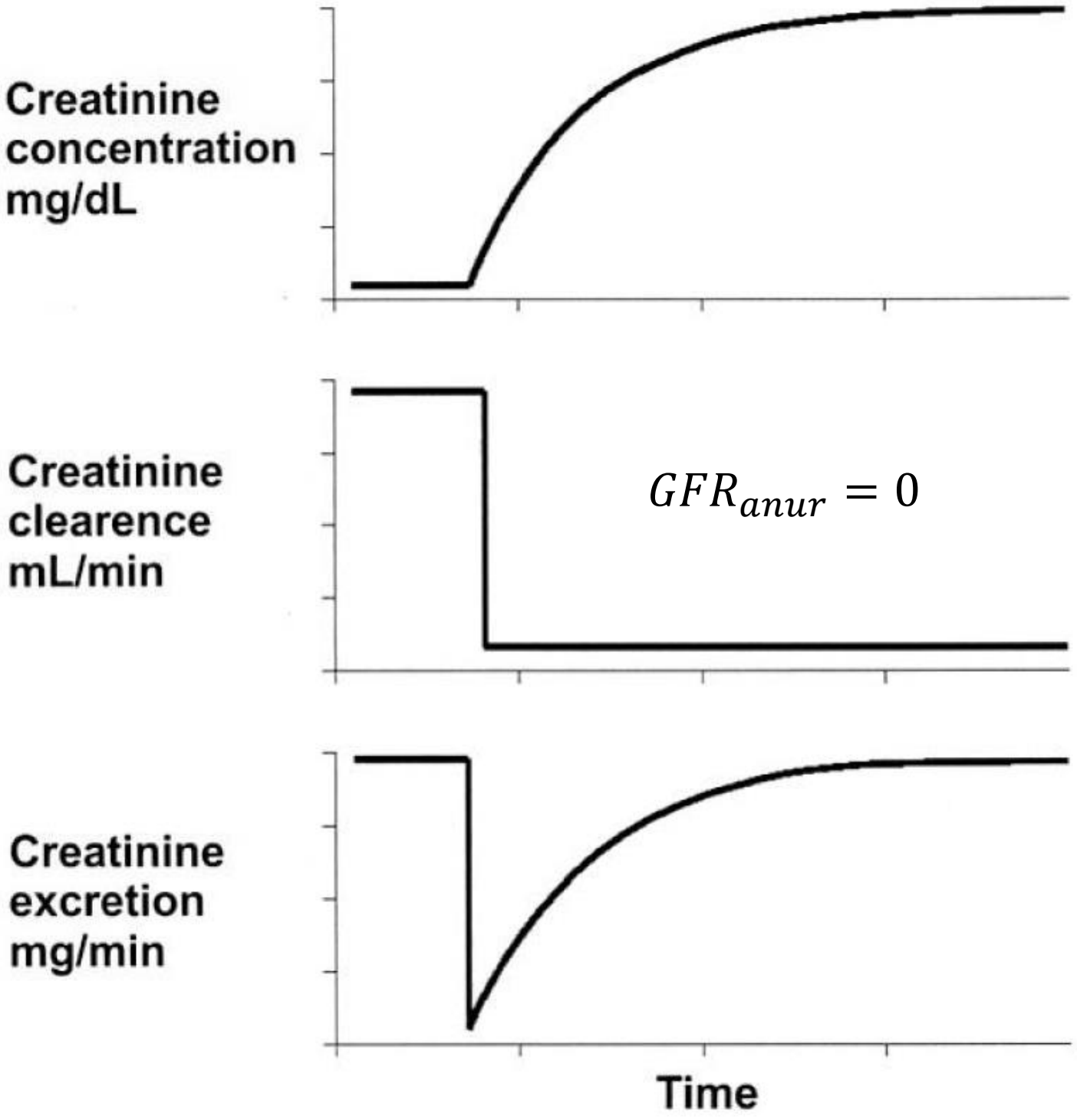

AKI
CKD
HD
600
500
400
300
200
100
0
Kreatinin (µmol/l)
0
60
120
180
240
300
360
420
480
540
600
660
720
Zeit (Tage)

Figure 2. Effect of an acute GFR decline on serum level of endogenous filtration markers



Stevens LA. J Am Soc Nephrol. 2009; 20: 2305-13



Verzögerter Anstieg

Diagnostische Lücke

Unmittelbar im Urin messbar

Mellas. Clin Nephrol. 2017

73 Jähriger => Klebsiellen Pneumonie nach TAVI

Meropenem infus 3 x 1000 mg/d + Linezolid 3 x 600 mg/d

		31.08.2017	=>	01.09.2017
Krea S	(69-104)	275 µmol/l		???

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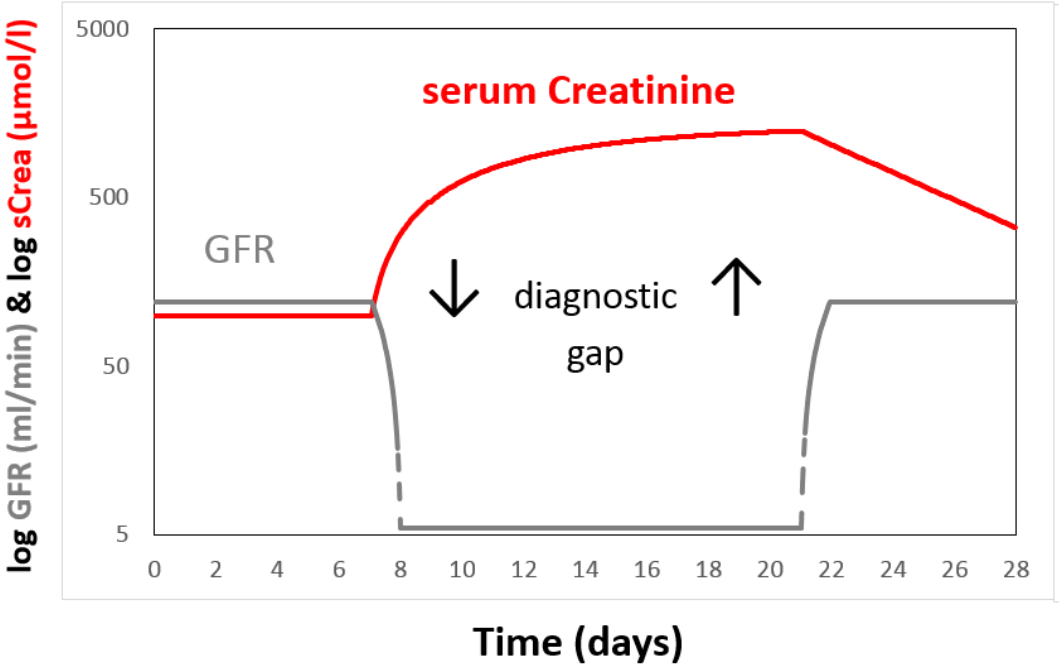
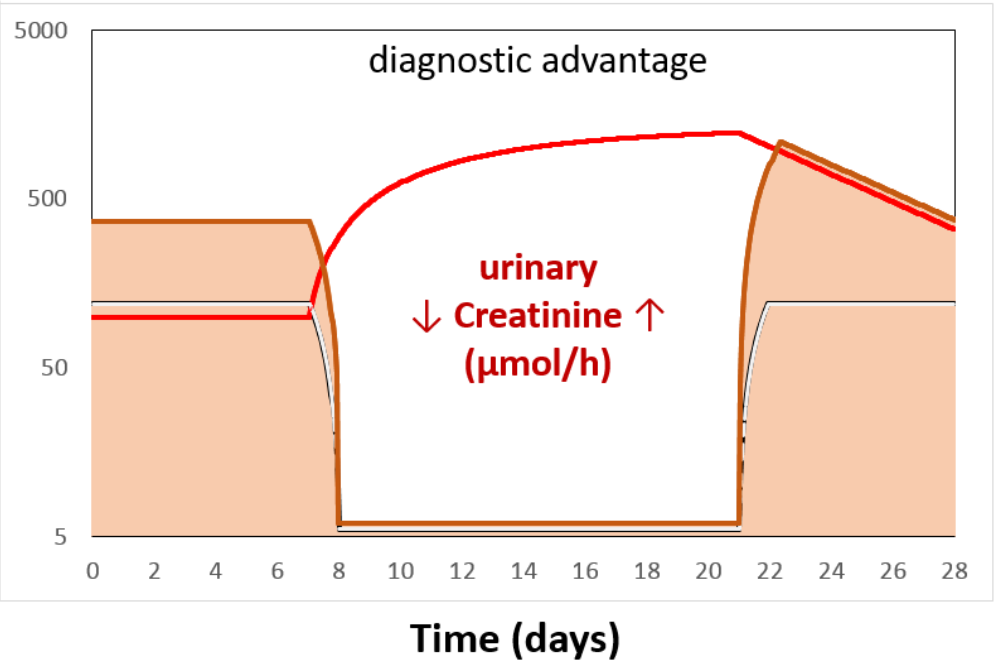
Krea S	(69-104)	275 µmol/l		???
Krea U	**(1.9-2.9)**	**6.1 mmol/l**		

Krea U = 555 µmol/h
(norm 120 – 200 µmol/h)

Crea Ausscheidung im Urin

Acute Kidney Injury





73 Jähriger => Klebsiellen Pneumonie nach TAVI

Meropenem infus 3 x 1000 mg/d + Linezolid 3 x 600 mg/d

		31.08.2017	=>	01.09.2017
Krea S	(69-104)	275 µmol/l		247 µmol/l ↓
Krea U	**(1.9-2.9)**	**6.1 mmol/l**		

Krea U = 555 µmol/h
(norm 120 – 200 µmol/h)

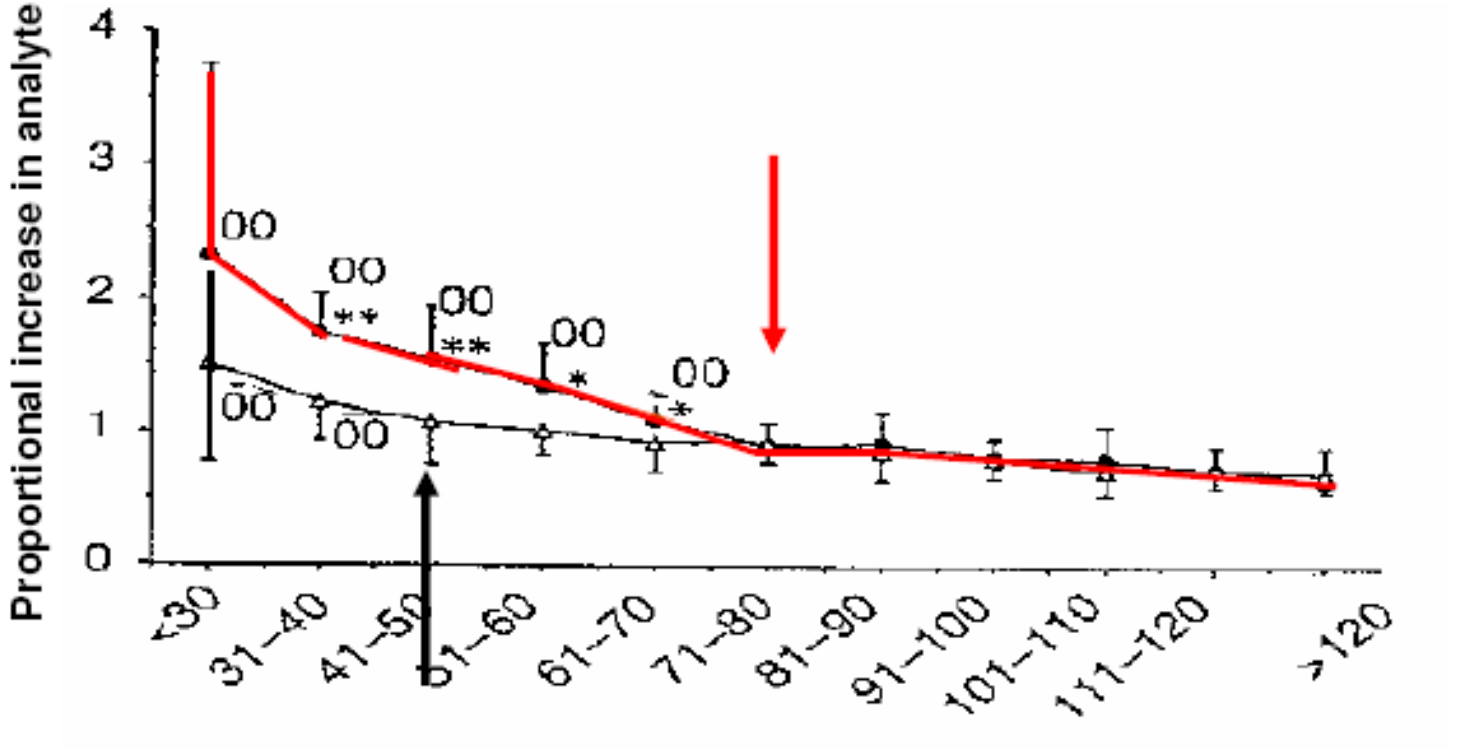
Fraktionelle Natrium Exkretion

$$FE_{Na} = \frac{Na_{urine} \cdot Crea_{serum}}{Crea_{urine} \cdot Na_{serum}}$$

$$uNaCR = \frac{Na_{urine}}{Crea_{urine}}$$

niedrig = praerenales ANV
hoch = intrarenales ANV

Cystatin C versus Creatinine



Newman DJ, Kidney Int 1995

Cyst C norm < 0,95 mg/l

Fehlbestimmungen

Crea

- Falsch hoch:
  körperliche Aktivität, Rhabdomyolyse, IgM Paraproteine, Cotrim, Statine, Paracetamol
- Falsch niedrig:
  tubuläre + intestinale Sekretion, Vegetarier, Sarkopenie, Leberversagen, Bilirubinämie

Cyst C

- Falsch hoch:
  Hyperthyreose, Leukozytose, Lymphom, Schwangerschaft, Pubertät, Sepsis, Nierentransplantat, Steroidmedikation
- Falsch niedrig:
  Obesitas, Alter, CKD G5

Qiu X, Liu C, Ye Y, Li H, Chen Y, Fu Y, Liu Z, Huang X, Zhang Y, Liao X, Liu H, Zhao W, Liu X.
The diagnostic value of serum creatinine and cystatin c in evaluating glomerular filtration rate in patients with chronic kidney disease: a systematic literature review and meta-analysis.
Oncotarget. 2017 Aug 16;8(42):72985-72999.

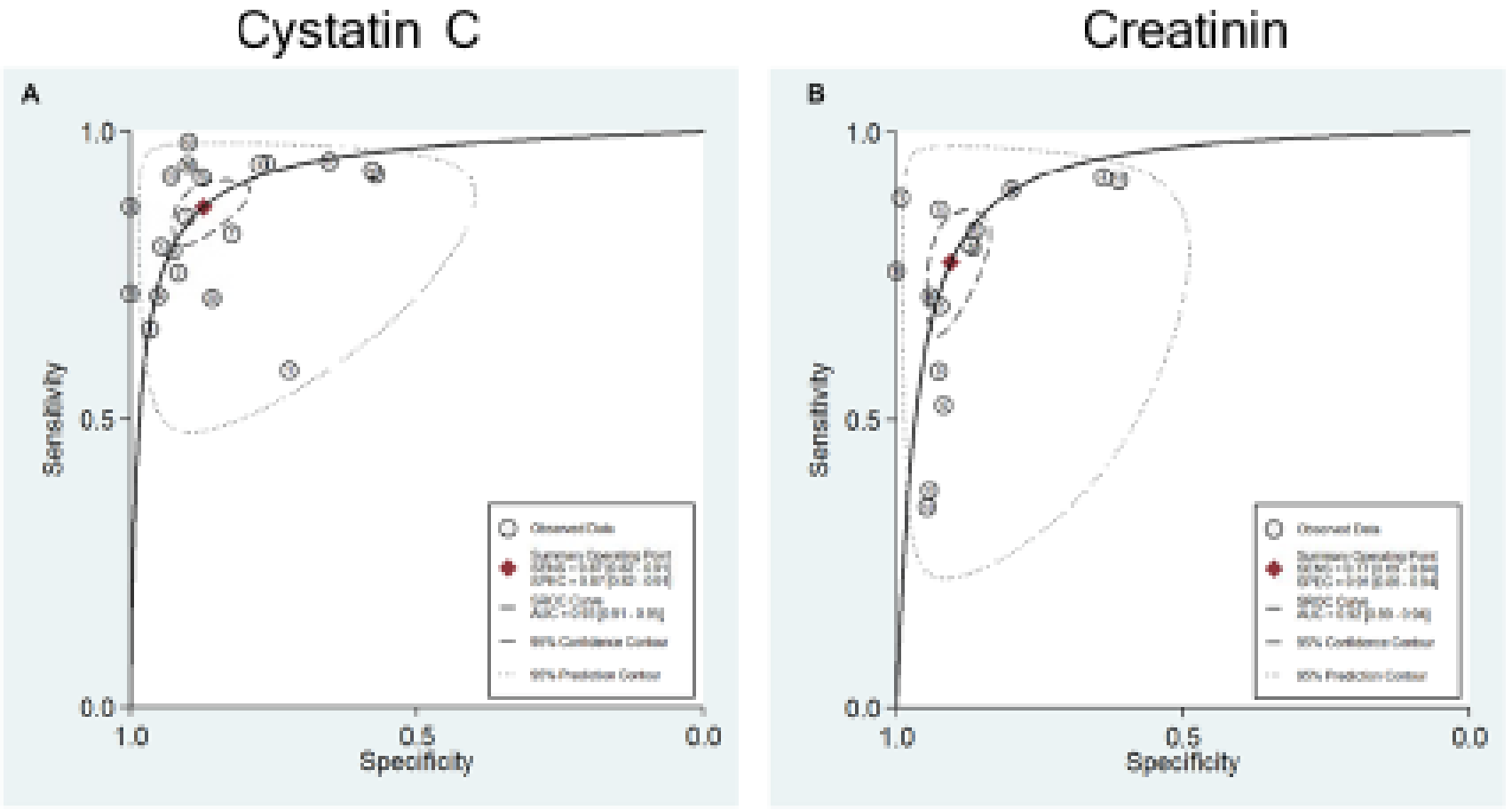


Figure 9: (A) ROC curve of the diagnostic value of GFR via SCysC. (B) ROC curve of the diagnostic value of GFR via SCr.

Meta-analysis: 21 articles involving 3112 study subjects (n.s.)

AUC = 0.93 [0.91-0.94] AUC = 0.92 [0.89-0.93]

Dosisanpassung = GFR basiert

Table 3 | Stepwise approach to adjust drug dosage regimens for patients with CKD and AKI

Step 1	Obtain history and relevant demographic/clinical information	Assess demographic information, past medical history including history of renal disease, and current clinical and laboratory information, including DNA polymorphisms to ascertain drug therapy needs
Step 2	Estimate GFR	Use most appropriate tool to assess eGFR or CL_{cr} for the patient based on age, body size, ethnicity, and concomitant disease states
Step 3	Review current medications	Identify drugs for which individualization of the treatment regimen will be necessary
Step 4	Calculate individualized treatment regimen	Determine treatment goals (see text); calculate dosage regimen based on pharmacokinetic characteristics of the drug and the patient's volume status and eGFR or CL_{cr}
Step 5	Monitor	Monitor parameters of drug response and toxicity; monitor drug levels if available/applicable
Step 6	Revise regimen	Adjust regimen based on drug response or change in patient status (including renal function) as warranted

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; CL_{cr}, creatinine clearance; eGFR, estimated GFR; GFR, glomerular filtration rate.

AKI + ICU + CRRT

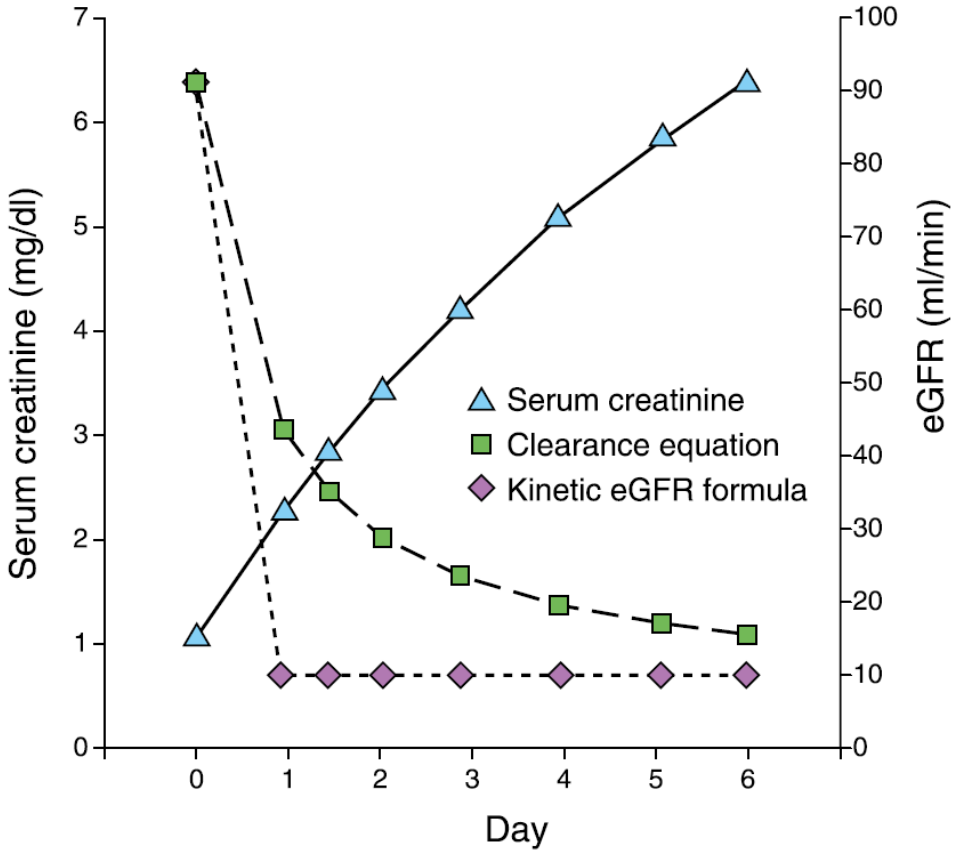
CL_{crea} = C&G GFR

Chen S.

Retooling the Creatinine Clearance Equation to Estimate Kinetic GFR when the Plasma Creatinine Is Changing Acutely.

J Am Soc Nephrol. 2013; 24: 877-88.

$$KeGFR = \frac{SSP_{crea} \cdot Cl_{crea}}{meanP_{crea}} \cdot \left(1 - \frac{24 \cdot \Delta P_{crea}}{\frac{\Delta Time(h)}{day} \cdot \max \Delta P_{crea}} \right)$$



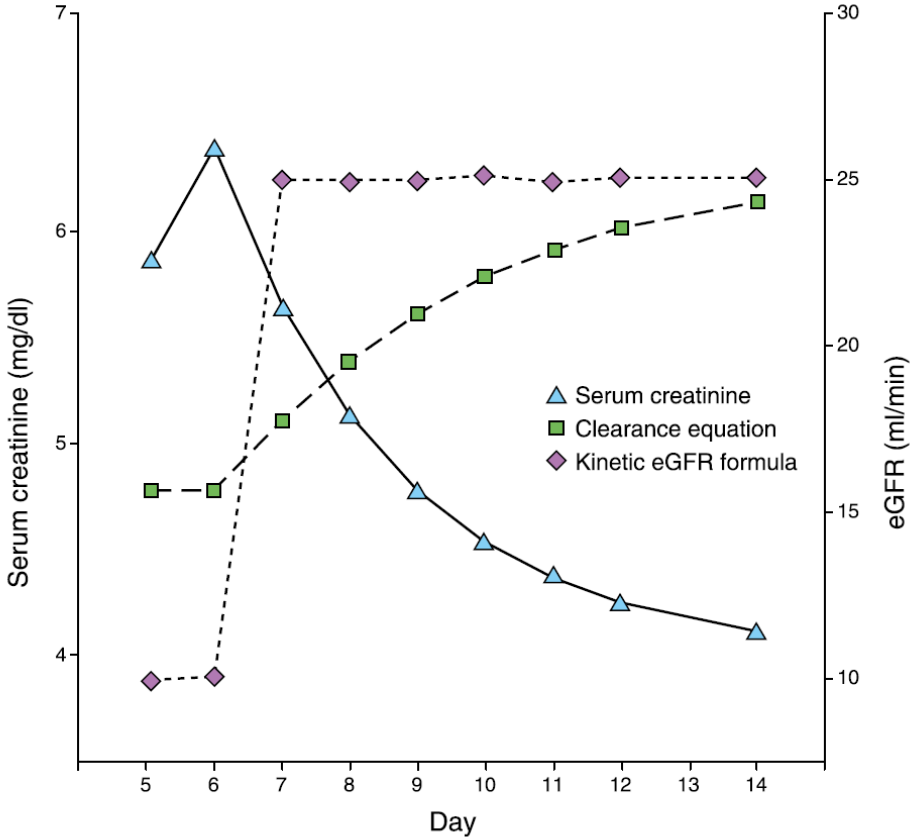
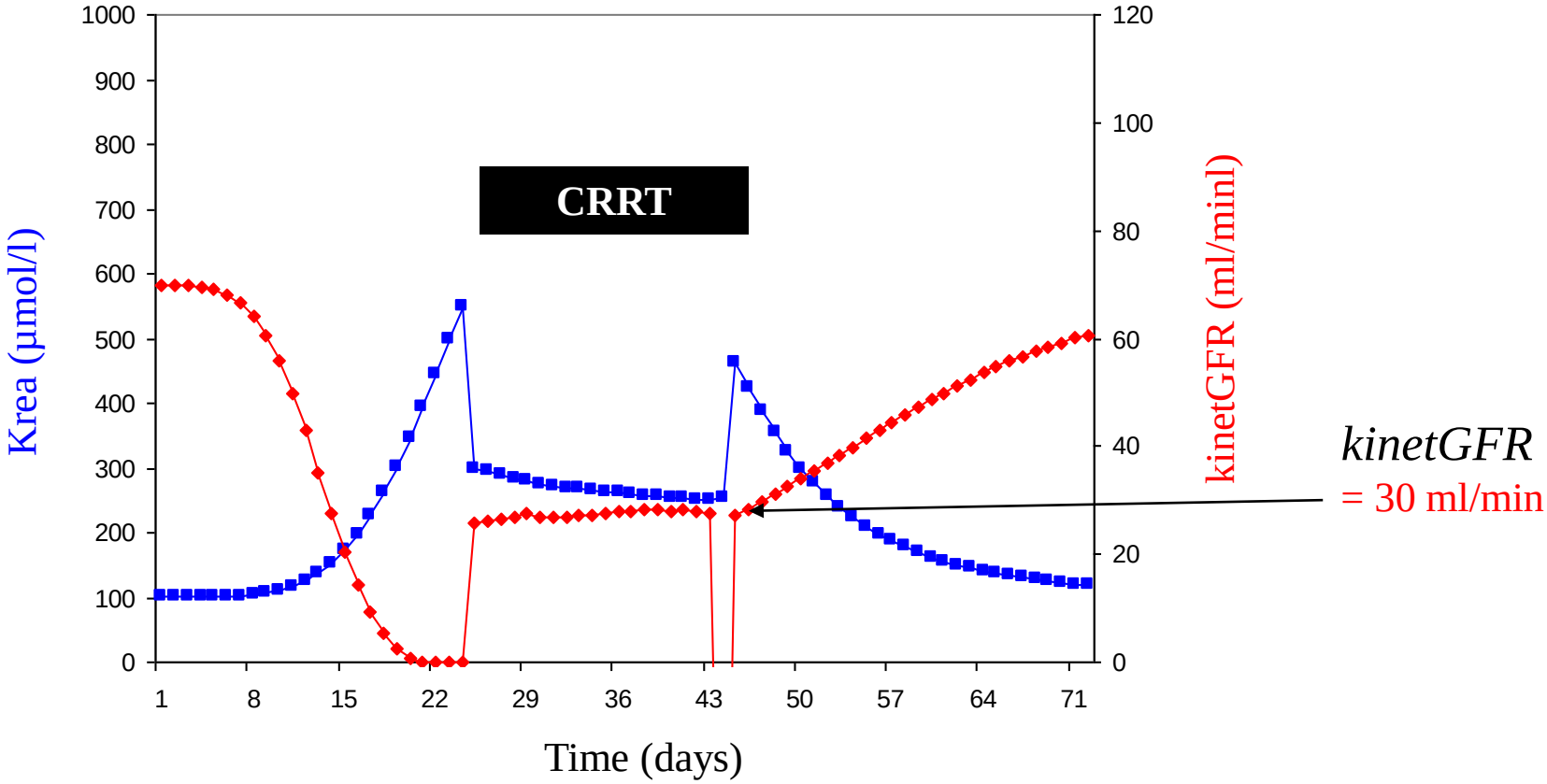


Figure 5. Graph of clearance function being provided by CVVH. In the midst of AKI

Chen S.

Continuous Renal Replacement Therapy CRRT

J Am Soc Nephrol. 2013; 24: 877-88.

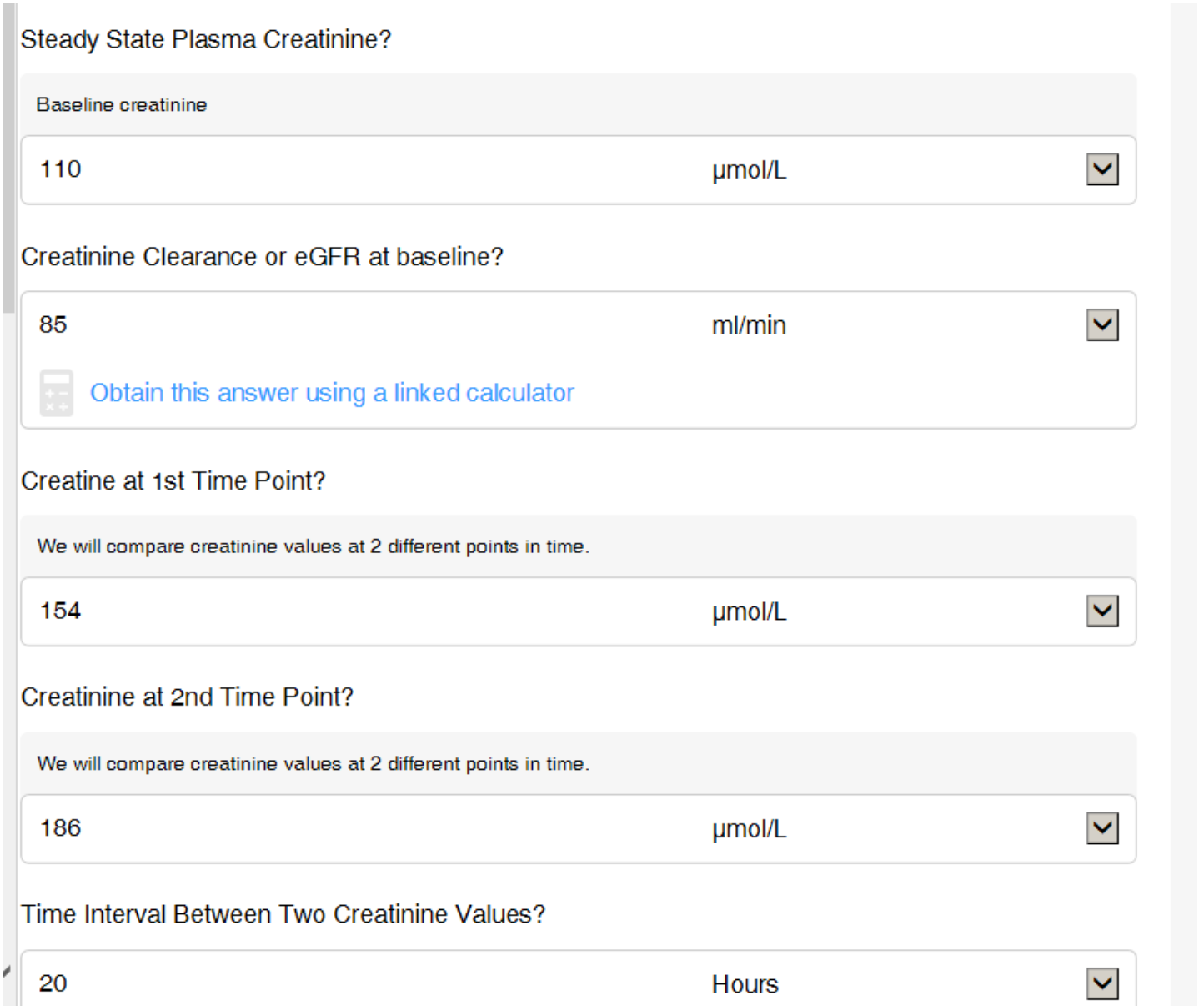


$$kinetGFR = eGFR_2 - 30 \cdot \frac{Crea_2 - Crea_1}{Crea_2 + Crea_1}$$

Kinetic eGFR (KeGFR)

Estimate GFR when creatinine is changing acutely (either rising or falling)

[https://qxmd.com/calculate/calculator_367/kinetic-egfr-kegfr]



kinetGFR
zur Cefepime Dosisanpassung

- in 20 Stunden Kreatinin 154 => 186 µmol/l => kinetGFR = 39 ml/min
- Kreatinin 186 µmol/l => CKD-EPI eGFR = 50 ml/min.
- Cefepime

  kinetGFR 39 ml/min => 2000 mg alle 12 Stunden

  eGFR 50 ml/min => 2000 mg alle 8 Stunden = überdosiert !

Albert Einstein * 1879 in Ulm

Martina Geiselhard

„Politik ist für die Gegenwart, Gleichungen sind für die Ewigkeit“