Valutazione della funzione e del danno renale filtrato glomerulare, albuminuria proteinuria

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Agenda

- Breve introduzione alle funzioni del rene:
- Filtrato glomerulare (GFR): massa nefronica
- Proteinuria (± ematuria): danno strutturale (max glomeruli)

GLOMERULAR FILTRATION RATE (GFR)

Glomerular filtration rate (GFR) is generally considered the best overall assessment of kidney function.

The normal level of GFR varies according to **age**, **sex**.

The GFR must be judged taking into account of **body size**:
GFR value is reported per 1.73m^2 units of body surface area (i.e. mL/min/1.73m^2)

Invecchiamento fisiologico del rene

- Alla nascita il patrimonio di nefroni (massa nefronica) è di circa 2 milioni di nefroni
- L’organogenesi renale si completa entro la 34° settimana
- Neonati con prematurità e/o patologie in utero hanno una ridotto patrimonio nefronico
- A partire dai 40 anni di età si perde circa 1 ml/min/anno di GFR (invecchiamento fisiologico)

GLOMERULAR FILTRATION RATE (GFR)
PHYSIOLOGICAL AGE-DECLINE IN MALES AND FEMALES

BECAUSE OF PHYSIOLOGICAL AGE-DECLINE "REDUCED GFR" HAVE COMPLETELY DIFFERENT INTEPRETATION IN CKD DISEASE vs AGEING

Iohexol Clearance

Table 4. Predicted percentiles of GFR (ml/min per 1.73 m^2) for healthy women and men according to age group

Age Group (yr)	Women				Men			
	Number of GFR Measurements	Median	2.5th Percentile	97.5th Percentile	Number of GFR Measurements	Median	2.5th Percentile	97.5th Percentile
50–54	226	93.4	73.7	113.1	217	93.0	73.1	113.0
55–59	405	88.8	69.2	108.3	423	89.4	69.6	109.3
60–64	566	84.2	64.7	103.6	521	85.8	66.1	105.5
65–69	296	79.6	60.3	98.9	293	82.2	62.7	101.8
70–74	129	75.0	55.8	94.1	102	78.6	59.2	98.0
75–79	253	70.4	51.4	89.4	225	75.0	55.7	94.3
80–84	164	65.8	46.9	84.7	188	71.4	52.2	90.6
85–89	68	61.2	42.4	79.9	79	67.8	48.8	86.8
≥90	20	56.6	38.0	75.2	34	64.2	45.3	83.1

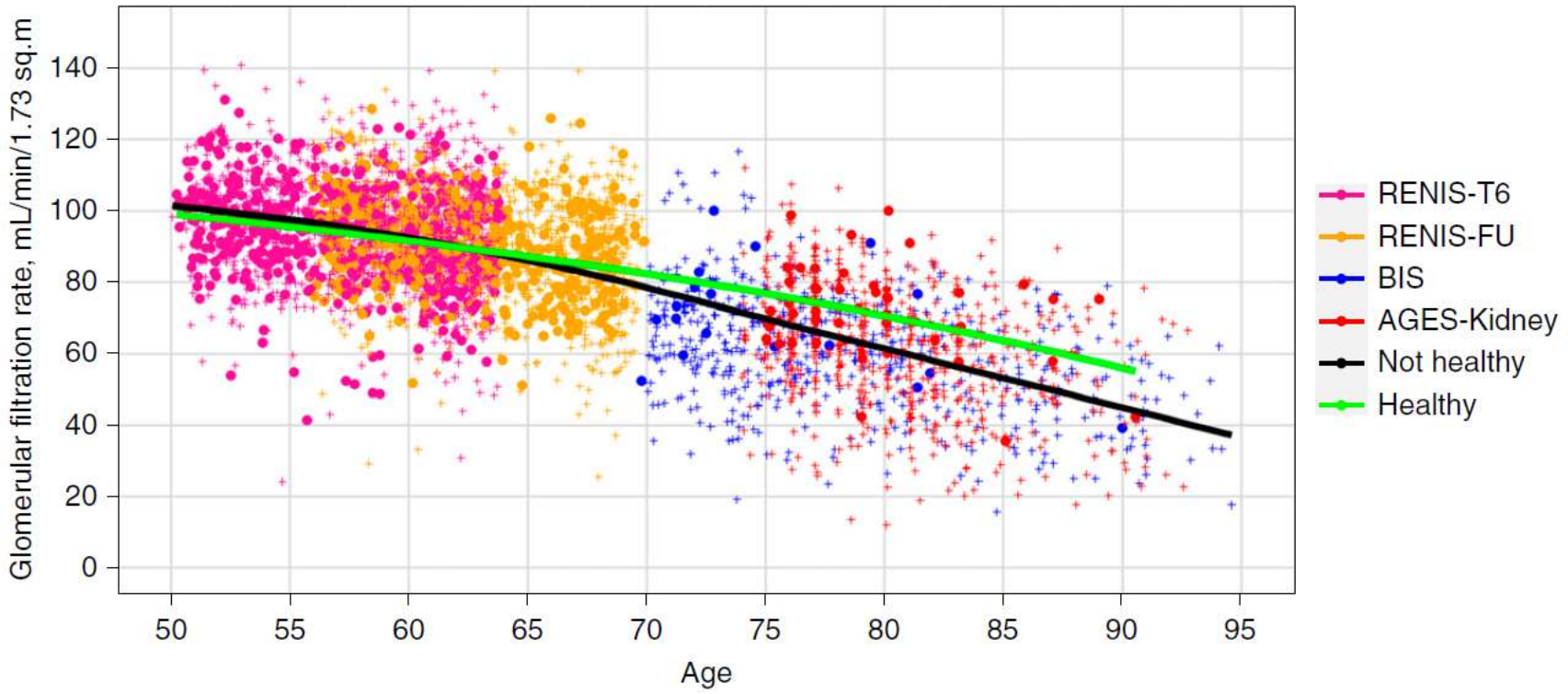
Estimates corresponding to Figure 3.

Eriksen J Am Soc Nephrol 2020;31:1602

GLOMERULAR FILTRATION RATE (GFR)
AGE DECLINE DIFFERS IN HEALTHY AND DISEASED SUBJECTS

IT IS DIFFICULT TO DISTINGUISH, BASED ON GLOMERULAR FILTRATION RATE (GFR) ALONE, CKD FROM AGEING

Iohexol Clearance

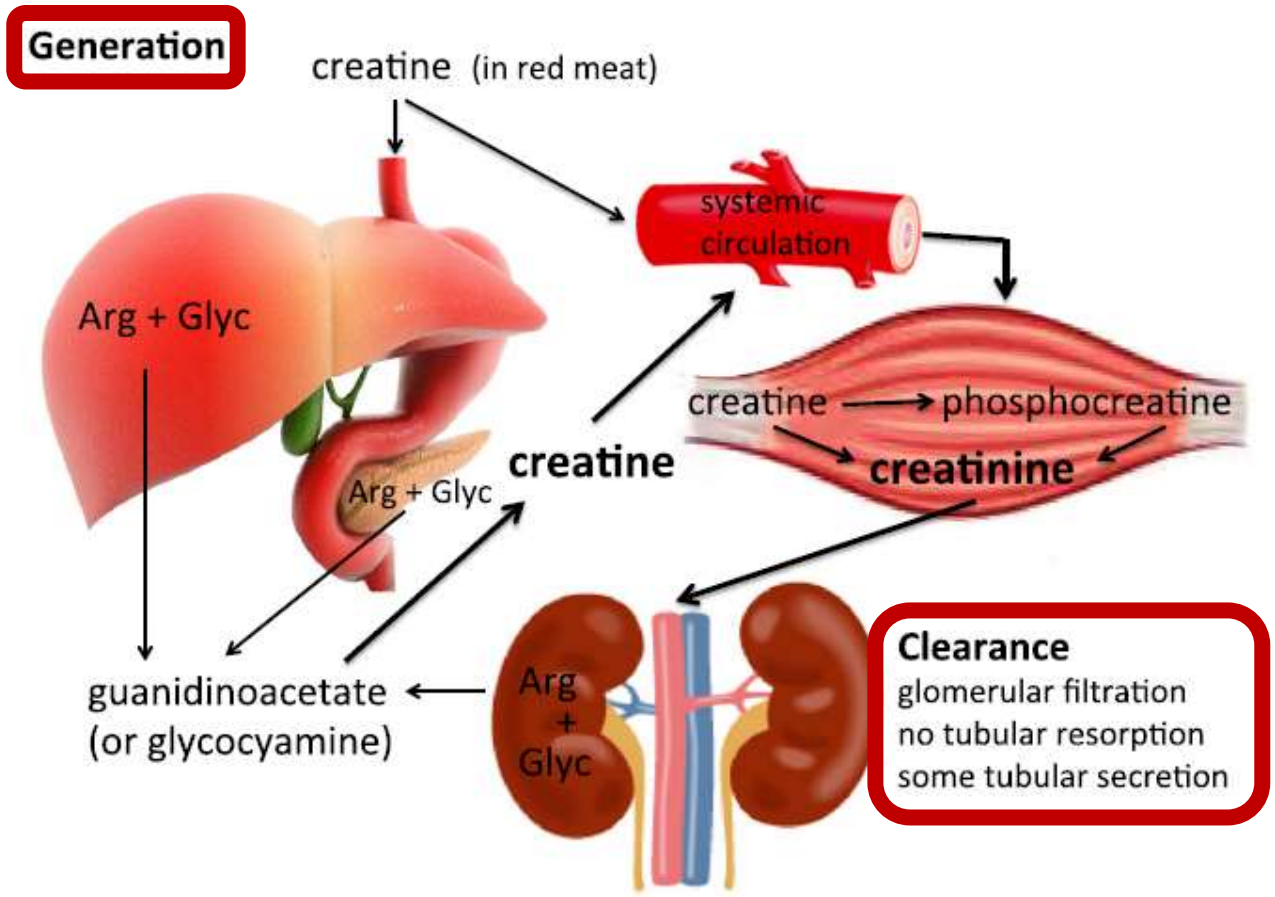


Eriksen J Am Soc Nephrol 2020;31:1602

USO DELLA CREATININA NELLA PRATICA QUOTIDIANA

Nella pratica di tutti i giorni siamo interessati a seguire l’andamento (miglioramento, peggioramento) della funzione renale.
La sola creatinina sierica è sufficiente allo scopo

Generazione ed eliminazione della creatinina



La generazione di creatinina è proporzionale alla massa muscolare

Creat 1.3 mg/dL

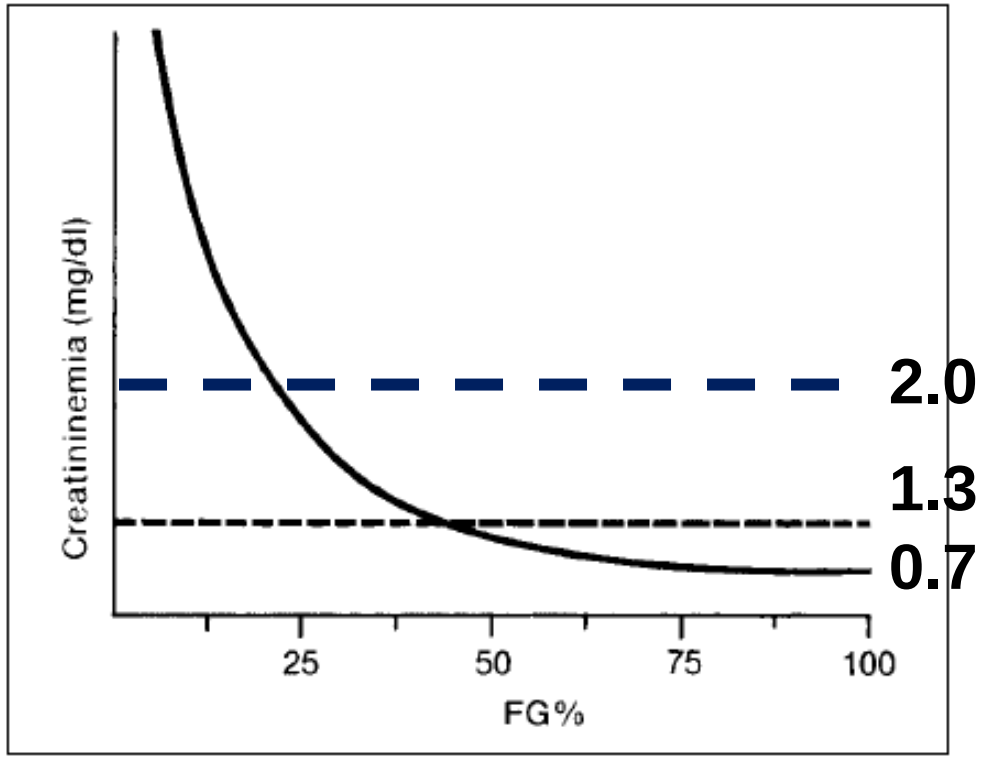
80 anni

GFR 59 ml/min

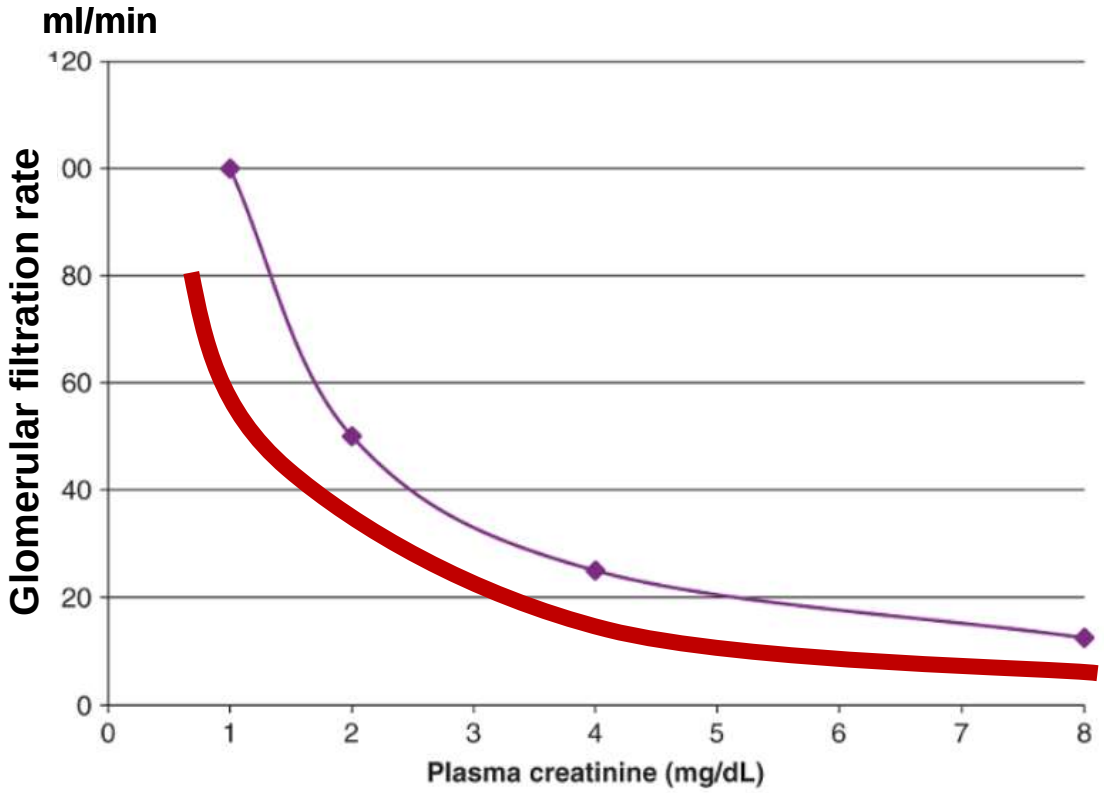
Creat 1.3 mg/dL

30 anni

GFR 120 ml/min


Creatininemia (mg/dl)
25
50
75
100
FG%
2.0 mg/dL
1.3 mg/dL
0.7 mg/dL

Impatto della ridotta massa muscolare (bassa generazione di creatinina) sul rapporto tra creatinina sierica e GFR



A parità di valori creatininemia, il GFR sarà più basso nei soggetti con massa muscolare più ridotta (malnutrizione, anziani)

malnutriti

REASONS FOR ESTIMATING RENAL FUNCTION (eGFR)

1. PLANNING CKD FOLLOW-UP AND RENAL REPLACEMENT THERAPY IN
   (e.g., PATIENTS WITH ADVANCED CKD; THE «30-20-10» eGFR RULE OF THUMB)
2. DOSING ADJUSTMENT FOR DRUGS WITH RENAL EXCRETION
3. SOME DRUGS MAY NOT BE USED FOR eGFR < CERTAIN THRESHOLDS
4. EVALUATION OF LIVING DONOR CANDIDATES

FOR PURPOSES 1. 2. 3. eGFR (AS OPPOSED TO mGFR) IS SUFFICIENT IN MOST IF NOT ALL CIRCUNMSTANCES

eGFR LEVEL AND UREMIC SYMPTOMS

- inability to control volume status or BP
- acid-base or electrolyte abnormalities
- a progressive deterioration in nutritional status refractory to dietary intervention
- pruritus
- cognitive impairment
- serositis

…This often but not invariably occurs in the GFR range between 5 and 10 ml/min per 1.73m^2. (2B)

KDIGO CKD Work Group *Kidney Int Suppl* 2013; 3:1

THE «30-20-10» eGFR RULE OF THUMB

GFR (mL/min/1.73m^2)	Action
< 30	Nephrologist referral
<20	Choice of kidney replacement modality
<10	Ready for start RRT[#]

[#]The decision to start of RRT may also dependent on

1. Symptoms (anorexia /vomiting, weakness, malaise, cognitive impairment, pruritus)
2. Signs (edema, hypertension, nutritional status, frailty)
3. Lab examinations (anemia, acidosis, hyperphosphatemia, iperkalemia)
4. Rate of decline of eGFR

RRT, Renal Replacement Therapy (Dialysis or Transplantation)

EXPLENATION OF ACRONYMS

MDRD, **M**odification of **D**iet in **R**enal **D**isease Study (US)
CKD-EPI, **C**hronic **K**idney **D**isease **Epi**demiology Collaboration (US)
EKFC **E**uropean **K**idney **F**unction **C**onsortium Equation (EU)

-cr, based on serum creatinine
-cys, based on serum cystatin

eGFR: CREATININE-BASED EQUATIONS

MDRD – cr : kidney disease, age, sex, race

↓

CKD-EPI 2009 -cr : normal population

↓

CKD-EPI 2009 -cr and/or -cys : based on Cystatin C

↓

CKD-EPI 2021 -cr and/or -cys : does not require race

↓

EKFC 2021 -cr :European, does not require race

↓

EKFC 2023 –cr : does not require race
EKFC 2023 -cys : not even sex is required

Note: race may be difficult to classify and it is often not available in health electronic records («sistemi informativi»)

eGFR Calculator

Glomerular filtration rate (GFR) is the best overall index of kidney function. Normal GFR varies according to age, sex, and body size, and declines with age. The National Kidney Foundation recommends using the CKD-EPI Creatinine Equation (2021) to estimate GFR. More information regarding this recommendation may be found here.

NKF and the American Society of Nephrology have convened a Task Force to focus on the use of race to estimate GFR. *Read more about the task force here.*

Serum Creatinine:		◉ mg/dL ○ µmol/L
Serum Cystatin C:		mg/L
Age:		Years
Gender:		◉ Male ○ Female
Standardized Assays:		◉ Yes ○ No ○ Not Sure
Adjust for body surface area:		○ Yes ◉ No ○ Not Sure

Calculate

Calculators

Use our GFR calculators to estimate GFR for adults or children.

- eGFR Calculator
- Pediatric GFR Calculator
- Cockcroft-Gault formula *(use for drug research only)*
- Pediatric Chronic Kidney Disease Risk Calculator *(used by nephrologists and other healthcare providers only)*
- Kidney Failure Risk Equation
- eGFR Calculator App for iPhone/iPad
- FAQs About GFR Estimates

https://www.kidney.org/professionals/kdoqi/gfr_calculator

NKF and the American Society of Nephrology have convened a Task Force to focus on the use of race to estimate GFR. *Read more about the task force here.*

Serum Creatinine:	1.0	◉ mg/dL ○ µmol/L
Serum Cystatin C:		mg/L
Age:	55	Years
Gender:	◉ Male ○ Female	
Standardized Assays:	○ Yes ○ No ◉ Not Sure	

These equations are valid only with standardized creatinine and cystatin methods. To learn more, click **here**.

Adjust for body surface area: ○ Yes ○ No ◉ Not Sure

Choosing "No" will calculate an indexed eGFR value, standardized to a body surface area of 1.73m^2 (units: mL/min/1.73m^2)

- Assessment for CKD staging and CKD progression should generally be assessed using the indexed eGFR value.

Choosing "Yes" will bring up fields to input height and weight. A non-indexed eGFR value (i.e. adjusted for the patient's body surface area) will be calculated (units: mL/min).

- Drug dosing decisions should generally be based on non-indexed eGFR value.
- Exception: Using non-indexed eGFR in morbidly obese patients can result in a large overestimate of measured GFR and potential for overdosing.

https://www.kidney.org/professionals/kdoqi/gfr_calculator

How to Classify CKD

- Identify cause of CKD (C)
- Assign GFR category (G)
- Assign albuminuria category (A)

Collectively referred to as "CGA Staging"

Nota: CKD Chronic Kidney Disease si traduce Con «Malattia Renale Cronica» non con «Insufficienza Renale Cronica!

Assign GFR category as follows:

GFR categories in CKD

Category	GFR ml/min/1.73 m^2	Terms
G1	≥90	Normal or high
G2	60-89	Mildly decreased*
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Relative to young adult level.
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

https://www.kidney.org/professionals/kdoqi/gfr_calculator

Assign Albuminuria category as follows:

Albuminuria categories in CKD

Category	ACR (mg/g)	Terms
A1	<30	Normal to mildly increased
A2	30-300	Moderately increased*
A3	>300	Severely increased**

Abbreviations: ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease.
*Relative to young adult level.
**Including nephrotic syndrome (albumin excretion ACR >2220 mg/g)

***Collectively referred to as "CGA Staging"*

https://www.kidney.org/professionals/kdoqi/gfr_calculator

Is it CKD?

Either of the following must be present for ≥3 months to be CKD:

- GFR less than 60 ≥3 months
- ACR ≥30 mg/g or other markers of kidney damage

Click to learn more.

Equation used to estimate GFR?

- (●) CKD-EPI Creatinine (2021)
- ( ) CKD-EPI Creatinine-Cystatin C (2021)
- ( ) CKD-EPI Cystatin C (2012)

What is the patient's ACR?†

( ) <30 mg/g	( ) <3 mg/mmol
( ) 30-300 mg/g	( ) 3-30 mg/mmol
(●) >300 mg/g	( ) >30 mg/mmol

Based on the information supplied:

GFR category is:‡	G2
ACR category is:**	A3
CKD classification is:	G2/A3
Risk of progression is:	Moderate
Frequency of monitoring should be:	2 times per year
Referral to a nephrologist is:	Recommended

† Neither the category of GFR nor the category of albuminuria alone can fully capture prognosis of CKD. Persistent and increased albuminuria has been shown to be an independent risk factor for CKD progression.

‡In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

**ACR 30-300 mg/g for > 3 months indicates CKD.

Creatinine 1.0 mg/dL, Male aged 50 → CKD-EPI eGFR = 92 ml/min/1.73m^2

https://www.kidney.org/professionals/kdoqi/gfr_calculator

Clearance della creatinina misurata

- Cosa serve per calcolarla: creatininemia (Cr_P, mg/dL), creatininuria (Cr_U, mg/dL), volume di diuresi (V), o arco, di tempo in minuti in cui è stato raccolto (t = 1440 munuti se l'arco di tempo è 24 ore). Nota che si potrebbere adottare anche periodi di durata minore, ad es. 4-12 ore)

- **<u>La formula</u>: $[(Cr_U \times V_u) \div t] / Cr_P$**
- Ad es, se creatin è 0.9 mg/dL, creatininuria 80 mg/dL, diuresi 24 ore 1800 ml, t = 1440; allora cl creat sarà: (80*1800)÷1440÷0.9 = 111 ml/min

- Esiste una correlazione inversa tra creatininemia e clearance della creatinina (funzione renale)
- E' essenziale che la raccolta delle urine sia completa nel periodo stabilito
- Classicamente si fa su campione delle 24 ore, ma può essere fatta anche su periodi di raccolta più brevi (ad es. in terapia intensiva 2-4-6 ore con catetere vescicale)

Clearance della creatinina stimata (eCL)

Cockcroft-Gault equation

$$\frac{(140\text{-Età}) * \text{Peso}}{Cr_P * 72}$$

Generata per evitare la raccolta urinaria, derivando una formula per predirre la escreta di creatinina nelle 24 ore negli uomini sulla base di età e peso, e poi inserendola nella formula della Clearance della Creatinina misurata, e riarrangiandone i termini.

Per le donne si usa un fattore di correzione (generalmente = 0.85)

Caduta in disuso con l'avvento dell'eGFR, ma è ancora il riferimento su cui poggiano le tavole per l'aggiustamento posologico dei farmaci ad eliminazione renale

COCKROFT GAULT EQUATION MUST BE ABANDONED

RIEPILOGO DEI METODI PER MISURARE OPPURE PREDIRRE I VALORI DEL GFR

	Method of GFR Mesurements (mGFR, mCrCL)	Formula for estimating w/o measuring (eGFR, eCrCL)	Parameters used in the estimatinng formula
«True» GFR (exogenous substance)	Iohexol Plasma Clearance Iothalamate (US)	CKD-EPI (2021) EKFC (2021)	Creatinine age, sex (sex not for EKFC-cys)
Creatinine Clearance	24hr Urinary Clearance (timed urine collection)	Cockcroft-Gault formula	age, **weight**, creatinine (sex: correction factor)

MDRD formula for estimating GFR is equivale to CKD-EPI in patients with CKD, but may substantially Underestimate GFR in healthy subjects

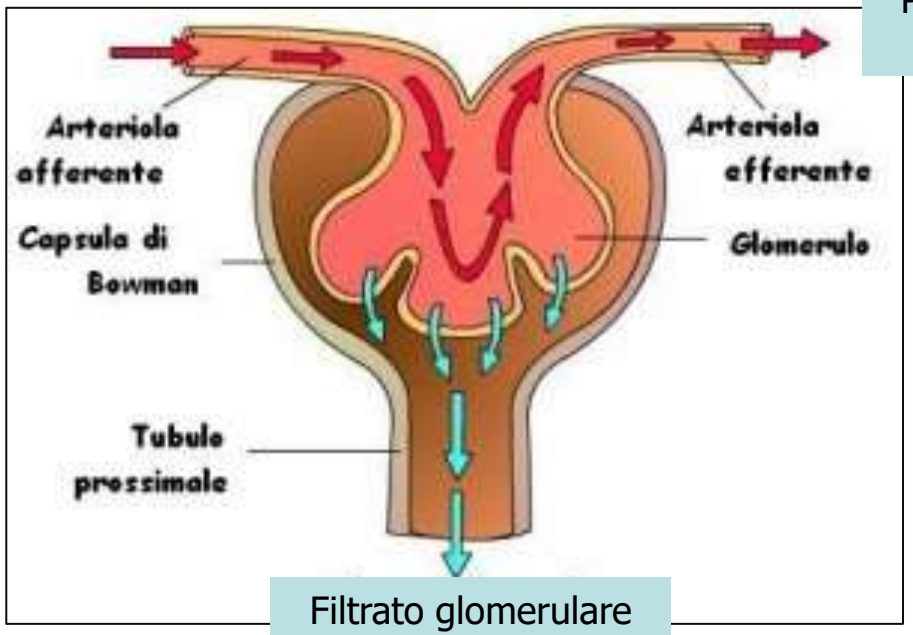
RIASSUNTO RACCOMANDAZIONE SULLE FORMULE FONDATE SULLA CREATININA

Performance of creatinine-based equations to estimate glomerular filtration rate in White and Black populations in Europe, Brazil and Africa

Pierre Delanaye[1,2,*], Emmanuelle Vidal-Petiot[3,*], Jonas Björk[4,5], Natalie Ebert[6], Björn O. Eriksen[7], Laurence Dubourg[8], Anders Grubb[9], Magnus Hansson[10], Karin Littmann[11], Christophe Mariat[12], Toralf Melsom[7], Elke Schaeffner[6], Per-Ola Sundin[13], Arend Bökenkamp[14], Ulla B. Berg[15], Kajsa Åsling-Monemi[15], Anna Åkesson[4,5], Anders Larsson[16], Etienne Cavalier[17], R. Neil Dalton[18], Marie Courbebaisse[19], Lionel Couzi[20], Francois Gaillard[21], Cyril Garrouste[22], Lola Jacquemont[23], Nassim Kamar[24], Christophe Legendre[25], Lionel Rostaing[26], Thomas Stehlé[27,28], Jean-Philippe Haymann[29], Luciano da Silva Selistre[30], Jorge P. Strogoff-de-Matos[31], Justine B. Bukabau[32], Ernest K. Sumaili[32], Eric Yayo[33], Dagui Monnet[33], Ulf Nyman[34], Hans Pottel[35,†] and Martin Flamant[36,†]

Cockroft-Gault (eCrCL): no
MDRD: no
CKD-EPI 2009: OK USARLO METTENDO SEMPRE RAZZA: NON AA
CKD-EPI 2021: non richiede razza ma ha maggior bias
EKFC: OK

Delanaye Nephrol Dial Transplant 2023; 38:106

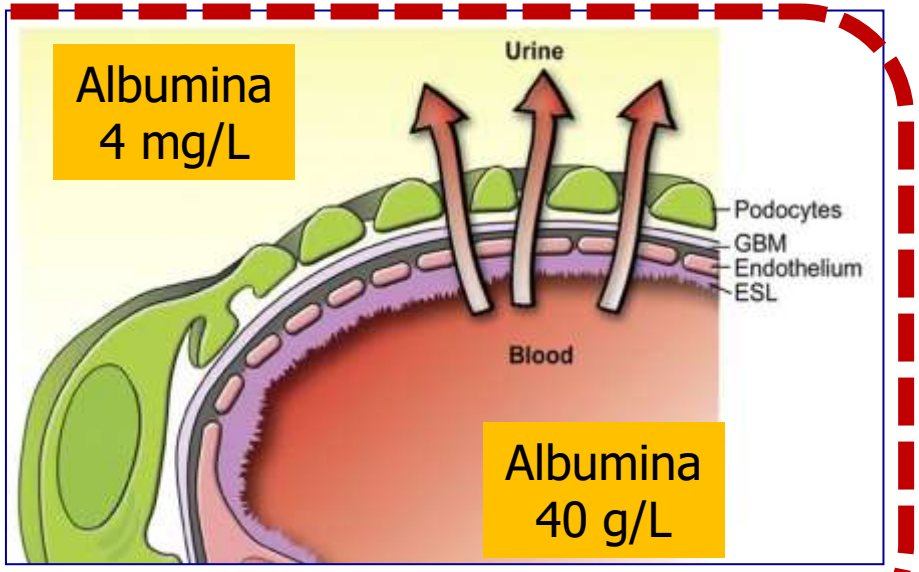


Portata renale ematica
1.2 L/min

Filtrato glomerulare
120 ml/min

Filtrazione glomerulare → GFR (glomerular filtration rate)

Selettività barriera glomerulare (danno) → albuminuria e proteinuria



Proteinuria

- L’albuminuria è una delle componenti della proteinuria, che normalmente è fino a 150 mg/24 ore (fino a 30 mg sono albuminuria, il resto sono proteine tubulari, prevalentemente uromodulina)

- Per valori superiori a 3.5 g/24hr si parla di proteinuria in range nefrosico. La sindrome nefrosica è data dalla concomitante presenza di ipoalbuminemia (<3.5g/dL), iperlipemia (colesterolo totale), ed edema. La sindrome nefrosica indica la presenza di una glomerulopatia con danno diffuso a tutti i capillari glomerulari

Tipi di Proteinuria

Glomerular proteinuria. Albuminuria typically exceeds 400 mg/day.

Tubular proteinuria. **Unlikely to be identified by the traditional urine dipstick** that detects intact albumin. Tubular proteinuria occurs at a **level of 200 to 2000 mg/day with albuminuria at less than 400 mg/day**, but larger amounts of albuminuria can be seen with coexisting glomerular disease.

Overflow proteinuria occurs when overproduction and excessive filtration of low-molecular-weight proteins exceeds the reabsorptive capacity of the tubule. This can result in the appearance in the urine of immunoglobulin light chains (with multiple myeloma). **Not detected by dipstick**.

Proteinuria can occur with damage to the collecting system, often referred to as ***postrenal proteinuria***.

MISURAZIONE: METODI SEMIQUANTITATIVI (DIPSTICK URINARIO)

Trace	15–30 mg/dL
1+	30–100 mg/dL
2+	100–300 mg/dL
3+	300–1000 mg/dL
4+	>1000 mg/dL

The urine dipstick uses pads impregnated with indicator dyes that undergo a colorimetric reaction with **albumin** in the urine. The common dyes, tetrabromophenol blue and bromocresol green, are very specific but lack sensitivity in the setting of dilute urine or nonalbumin proteins such as immunoglobulin light chains. Interpretation must **account for urinary concentration** (often estimated by the specific gravity). **Scores of 2+ and greater are highly suggestive of significant proteinuria**. False negatives are seen in dilute Urine. In addition to urine concentration, the sensitivity and specificity of the urine dipstick is affected by the presence of other chemicals. False positives are seen with alkaline urine (pH >8), drugs, and iodinated radiocontrast agents.

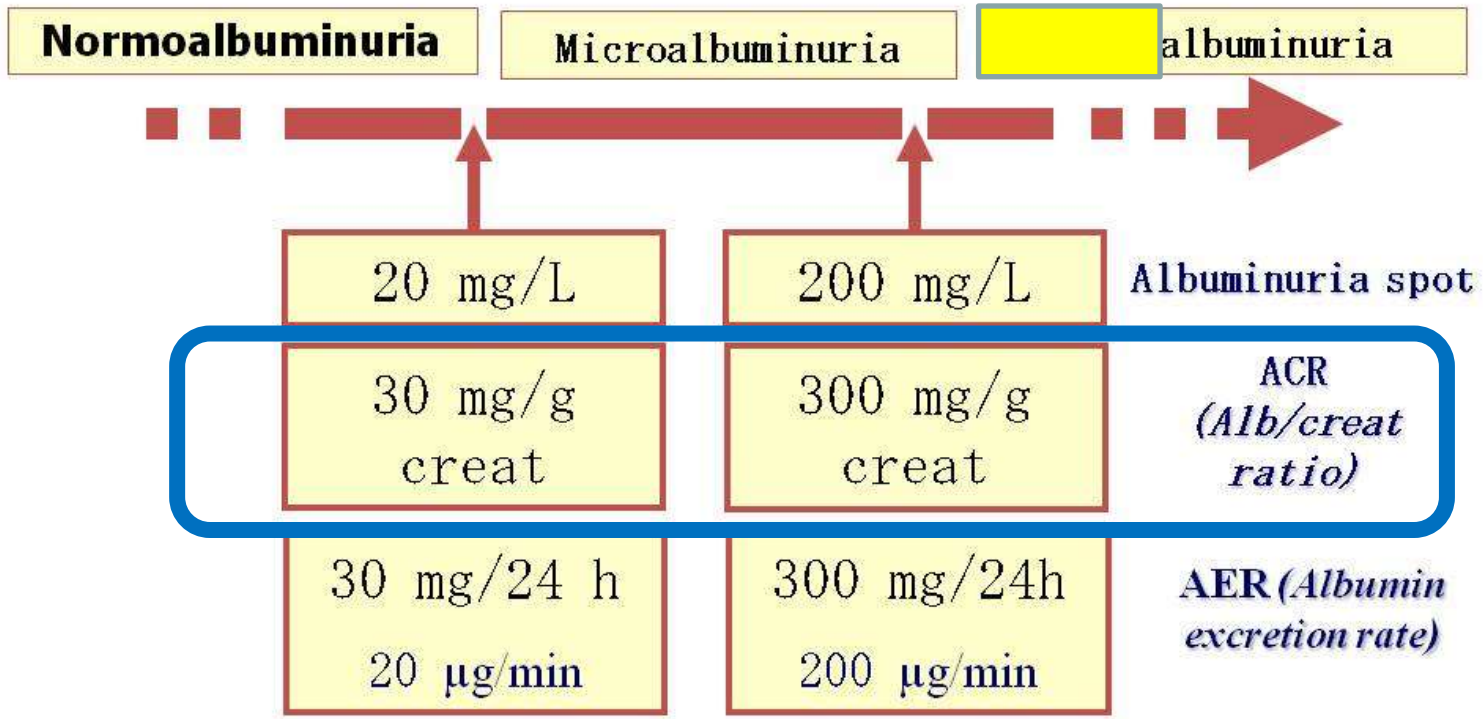
RACCOLTA URINE E MISURAZIONE: METODI QUANTITATIVI

The standard for measuring proteinuria is a timed, usually **24-hour, urine collection**. These collections are cumbersome to collect, difficult to transport, and often inaccurate because of improper or incomplete collection. Timed collections are particularly challenging for individuals with persistent proteinuria who require frequent measurements. Collections of shorter duration (6 or 12 hours) suffer from wider variability. The completeness of a collection can be assessed by assuming **women below the age of 50 excrete 15 to 20 mg creatinine per kilogram lean body mass per day, while men excrete 20 to 25 mg creatinine per kilogram** lean body mass. Creatinine excretion declines with advancing age.

An alternative is the measurement in a spot urine collection of the ratio of protein or albumin to creatinine. The urine **protein-to-creatinine ratio (UPCR)** and urine **albumin-to-creatinine ratio (UACR)** corrects the protein and albumin measurements (in mg/dL) for urinary concentration or dilution by standardizing for 1 g of daily creatinine excretion.
This is expressed in **units of mg/g** and correlates closely with the daily protein and albumin excretion

NUMERICAMENTE, IL DATO DELLE 24 ORE E QUELLO DATO DAL RAPPORTO CON LA CREATININURIA SONO VIRTUALMENTE IDENTICI

Albumina urinaria: valori normali e patologici



20 µg/min = 0.2 mg/min
1440 min = 24 hr
0.2mg/min*1440 ≈ 30 mg/ 24 hr

Per convertire da ACR in mg/mmol a mg/g, multiplicare per 8.84 (approx. cut-point for mg/mmol: 3 and 30)

PROTEINURIA CHE RAPPRESENTA INDICAZIONE DIRETTA ALLA BIOPSIA RENALE

Proteinuria associated with a **declining GFR**

Proteinuria in the **nephrotic range** (greater than 3500 mg/day)

Significant proteinuria (eg >0.5-1g/day) with features of a **glomerular disease** (acanthocytes, RBC casts) or **tubular disease** (low-molecular-weight proteins)

Persistent proteinuria greater than 500 mg/day in a patient with systemic lupus erythematosus (SLE) or other rheumatologic condition

Assign Albuminuria category as follows:

Albuminuria categories in CKD

Category	ACR (mg/g)	Terms
A1	<30	Normal to mildly increased
A2	30-300	Moderately increased*
A3	>300	Severely increased**

Abbreviations: ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease.
*Relative to young adult level.
**Including nephrotic syndrome (albumin excretion ACR >2220 mg/g)

***Collectively referred to as "CGA Staging"*

https://www.kidney.org/professionals/kdoqi/gfr_calculator

Prognosis of CKD by GFR and Albuminuria Categories

GFR categories (ml/min/1.73 m²) Description and range				Albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	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.
KDIGO 2012

CKD is classified based on: · Cause (C) · GFR (G) · Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (ml/min/1.73m^2) Description and range	G1	Normal or high	≥90	1 if CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Figure 1 Risk of chronic kidney disease progression, frequency of visits, and referral to nephrology according to estimated glomerular filtration rate (eGFR) and albuminuria. The GFR and albuminuria grid depict the risk of progression, morbidity, and mortality by color, from best to worst (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of visits (number of times per year). Green can reflect CKD with normal eGFR and albumin-to-creatinine ratio (ACR) only in the presence of other markers of kidney damage, such as imaging showing polycystic kidney disease or kidney biopsy abnormalities, with follow-up measurements annually; yellow requires caution and measurements at least once per year; orange requires measurements twice per year; red requires measurements at 3 and deep red 4 times per year. These are general parameters only, based on expert opinion and must take into account underlying comorbid conditions and disease state, as well as the likelihood of impacting a change in management for any individual patient. "Refer" indicates nephrology services are recommended. *Referring clinicians may wish to discuss with their nephrology service, depending on local arrangements regarding treating or referring. This figure is adapted with permission from reference 4.