Pathophysiology of creatinine

Creatinine is an amino acid derivative with a molecular mass of 113 Da. It is a waste product of creatine and phosphocreatine and is found almost exclusively (90%) in skeletal muscle tissues. The normal muscle concentration of total creatine is about 125 mmol/kg dry mass. About 2% of the body's creatine is converted to creatinine every day, resulting in the daily generation of creatinine at a fairly constant rate (male: 0.18 to 0.22 mmol/kg/day [20 to 25 mg/kg/day], female: 0.13 to 0.18 mmol/kg/day [15 to 20 mg/kg/day]). It is freely filtered through the glomerulus and is also secreted by the proximal tubules (5% to 10% of the excreted creatinine).

Typically, serum creatinine rises 1 to 2 mg/day in acute kidney injury, but it can exceed 5 mg/day in patients with severe rhabdomyolysis, due to massive breakdown of skeletal muscle. In patients with acute and rapidly progressive glomerulonephritis, 90% of renal function can be lost within weeks to months owing to glomerular destruction and this manifests as a 'galloping' rise in serum creatinine.

Laboratory measurement of creatinine

Serum creatinine is commonly measured by alkaline picrate, enzymatic, and high-performance liquid chromatography (HPLC) methods. These different methods of measuring serum creatinine are standardised to the isotope dilution mass spectrometry (IDMS).

- The alkaline picrate (Jaffe) method is subject to interference by glucose, fructose, pyruvate, acetoacetate, uric acid, ascorbic acid, cephalosporins, 5-aminolevulinic acid, bilirubin, and exogenous and endogenous substances and proteins (parenteral nutrition). The assay may overestimate serum creatinine by up to 25%, depending on the severity of renal dysfunction (the difference between creatinine clearance and GFR expands in patients at lower GFR). Assay modifications and the use of IDMS to standardise the measurement have not eliminated this problem. Serum specimens stored at -20°C (-4°F) are adequately stable for the measurement of creatinine for up to 3 months or 10 freeze-thaw cycles within a 3-month period. [1]
- Enzymatic creatinine methods have less interference than the alkaline picrate methods, but they are affected by 5-fluorocytosine, ethamsylate, dopamine, dobutamine, monoclonal IgM, nitromethane, and other substances. In Japanese children, age, gender, and body length appear to effect reference serum creatinine levels determined by enzymatic methods. [2] The enzymatic methods are superior to Jaffe methods. In the compensated Jaffe method, 26.5 micromol/L (0.3 mg/dL) is subtracted from the Jaffe method to match the enzymatic method results. [3]
- IDMS is the diagnostic standard. IDMS is highly specific and offers the most accurate results for serum creatinine, but is available only in selected laboratories. Combining HPLC and IDMS also provides highly accurate results for serum creatinine, but it has limited availability. HPLC methods have better specificity than the conventional methods and are less prone to interference, especially if combined with sample deproteinisation. However, measurement errors can occur owing to systematic bias (a consistent error resulting from calibration differences between measurement procedures), and owing to random measurement errors, including intra-laboratory effects, inter-laboratory random variability in day-to-day calibration, and specimen-specific effects. [4]
- Comparison of the Jaffe versus enzymatic method for creatinine measurement has shown that the Jaffe method is subject to bias due to interfering agents, and that it results in loss of analytical specificity. The risk of miscalculation is highest at the 60mL/minute/1.73m^2

decision limit. However, the risk of miscalculation due to bias is less than the risk of miscalculation due to biological variability. [5]

- Point-of-care testings (POCT) are commonly available in healthcare settings. In critically ill patients, there may be differences in serum creatinine values (8.7%, CI95%: -7.8% to +25.1%) between POCT and central laboratory testing-based measurements (Jaffe method) due to high haemoglobin and lactate levels (higher values with POCT) and high bilirubin, albumin, and calcium levels (lower values with POCT). Despite the negative bias POCT-based serum creatinine measurement appears to be sufficiently accurate for clinical use. [6]
- One innovative method of creatinine measurement, especially for screening chronic kidney disease, is the measurement of creatinine on dry blood spot sample with a sensitivity of 96% and specificity of 55% according to the Modification of Diet in Renal Disease (MDRD) equation. [7]

Interfering chromogens can falsely increase the serum creatinine values by 20% or even more in conditions such as diabetic ketoacidosis. The non-creatinine chromogens do not significantly affect urine creatinine levels, and have a smaller effect on the total reaction in advanced renal dysfunction than in normal renal function. [4]

Another issue is renal function monitoring in patients treated with drugs that interfere with secretion of serum creatinine (e.g., the novel antiretroviral medications). The impact of different creatinine estimation methods are highlighted by the findings that the Jaffe method results in a higher Model for End-Stage Liver Disease (MELD) score than by the enzymatic method. This can lead to a systematic preference in organ allocation in patients requiring liver transplantation. [8]

The recent campaign for standardisation of creatinine measurements has been promoted to allow the widespread use of formulas for estimating GFR. However, studies on trueness verification and measurement interferences still show disappointing inter-assay variation of serum creatinine results. [9] Recent advances in the field are the development of certified reference materials (CRMs) of creatinine in serum. CRMs are prepared with mixtures of creatinine from healthy and chronic kidney disease patients, assigned by liquid chromatography-isotope dilution mass spectrometry, validated by using standard reference material from the National Institute of Standards and Technology, confirmed by an international intercomparison for the determination of creatinine in human serum. These new CRMs of creatinine in human serum pools are apparently totally native without additional creatinine spiked for enrichment. These new CRMs may be useful for validating routine clinical methods for ensuring accuracy, reliability, and comparability of analytical results from different clinical laboratories; instrument validation; development of secondary reference materials; and evaluating the accuracy of high-order clinical methods for the determination of creatinine in human serum. [10]

A unified effort is currently under way to establish measurement traceability to standardise routine serum creatinine measurements. Also, the calculation of the Model for End-Stage Liver Disease (MELD) score, which is used to prioritise patients for liver transplantation, may significantly be influenced by recalibration of creatinine assays.

Estimation of glomerular filtration rate (GFR) and creatinine clearance using serum creatinine

GFR is estimated by measuring the clearance of exogenous filtration markers such as iothalamate, iohexol, and inulin. However, these methods are expensive and require exposure to radiation and compliance with strict regulatory guidelines, and thus have limited use in the routine laboratory settings.

On the other hand, creatinine is freely filtered, has minimal tubular secretion and absorption, is simple and inexpensive to measure from random blood samples, and has relatively good accuracy. It has therefore become a valuable clinical tool for estimating GFR. A rise in serum creatinine is used in clinical practice as a marker of reduced GFR. It varies inversely with GFR, but the relationship is not linear. GFR can be estimated by measuring creatinine clearance using serum creatinine levels and a timed urine specimen.

The use of serum creatinine as an indirect filtration marker is limited by its biological variability, bias and non-specificity affecting creatinine measurement, medication effects, nutrition, and by the alterations in circulating serum creatinine produced by non-renal disease states. The estimation of GFR by serum creatinine differs between healthy people and patients with CKD because of differences in GFR range and creatinine production between these two populations. As a result of these confounding factors, there is a risk of overestimating the GFR, and the magnitude of the overestimation is not predictable. [11]

The equations for estimation of GFR are mainly used for the systematic staging of CKD and should not be used in the setting of acute serum creatinine increases. Comparative study of estimated creatinine clearance in critically-ill patients by Cockcroft-Gault's Simplified MDRD and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations within the first 24 hours after ICU admission showed a high degree of variability. Therefore, these equations cannot be recommended in ICU settings. [12] GFR is estimated mostly from the MDRD GFR equation. It performs well in populations with a low range of GFR and often out-performs the Cockcroft-Gault equation. This equation has several limitations, including age, disease state, and considerable variations in the standardisation of the serum creatinine assays. The MDRD GFR formula generally offers reliable data for the calculation of drug doses. In peritoneal dialysis patients, creatinine clearance estimated from the MDRD equations may accurately approximate measured 24-hour urine and dialysate creatinine clearance; it should not be used to assess small-solute removal or adequacy in individual patients or to predict outcome in any cohort of patients over narrow ranges of limited clearance. [13]

$$\text{MDRD GFR (mL/min/1.73m}^2\text{)} = 30849 \times [\text{standardised SCr (micromol/L)}]^{-1.154} \times [\text{age(years)}]^{-0.203} \times 1.212 \text{ (if black)} \times 0.742 \text{ (if female)}$$

The 4-variable MDRD formulaFrom: Levey AS, Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardised serum creatinine values. Clin Chem. 2007;53:766-772. Used with permission

The original MDRD equation was developed using the alkaline picrate method and is subject to error if serum creatinine measurements obtained by other methods are used. For this reason, the abbreviated MDRD equation has been revised to produce the IDMS-traceable abbreviated MDRD equation. This equation can be used with different creatinine measurement methods once the measurements have been recalibrated and standardised to IDMS. It is currently recommended that those clinical laboratories that have not yet been recalibrated should continue to use the original MDRD equation, while recalibrated laboratories should use the IDMS-traceable abbreviated MDRD equation. [4]

$$\text{GFR (mL/min/1.73m}^2) = 175 \times [\text{standardised SCr (micromol/L)}]^{-1.154} \times [\text{age(years)}]^{-0.203} \times 1.212 \text{ (if black)} \times 0.742 \text{ (if female)}$$

This equation can also be expressed as:

$$\text{GFR (mL/min/1.73m}^2) = e^{(5.165 - 1.154 \times \ln[\text{pCr}/88.4] - 0.203 \times \ln[\text{age(years)}] - 0.299 [\text{if female}] + 0.192 [\text{if black}])}$$

This equation can be rewritten in a form that facilitates comparison with the Lund-Malmö (LM) equations:

$$\text{GFR (mL/min/1.73m}^2) = e^{(X - 0.203 \times \ln[\text{age(years)}] - 0.299 [\text{if female}] + 0.192 [\text{if black}])}$$

Where $X = 10.337 - 1.154 \times \ln(\text{pCr})$

IDMS-traceable 4-variable MDRD equation (MDRD-IDMS)From: Stevens LA, Coresh J, Greene T, et al. Assessing kidney function: measured and estimated glomerular filtration rate. N Engl J Med. 2006;354:2473-2483. Bjork J, Back SE, Sterner G, et al. Prediction of relative glomerular filtration rate in adults: new improved equations based on Swedish caucasians and standardized plasma-creatinine assays. Scand J Clin Lab Invest. 2007;67:678-695. Used with permission

One study has shown that the CKD-EPI equation is more accurate than the MDRD equation for estimating GFR, especially for values >60 mL/minute/1.73 m^2. [14] However, elderly people and black people with higher levels of GFR and ethnic minorities other than black people were not well represented in the study. In one meta-analysis of data from 1.1 million adults comparing the CKD-EPI with the MDRD equation, 24.4% and 0.6% of participants from general population cohorts were reclassified to a higher and lower estimated GFR category, respectively, by the CKD-EPI equation. [15] The prevalence of CKD stages 3 to 5 (estimated GFR <60 mL/minute/1.73 m^2) was reduced from 8.7% to 6.3%. Thus, the CKD-EPI equation classified fewer individuals as having CKD compared with the MDRD equation. [15]

141 × min (Scr /κ, 1)α × max(Scr /κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black]

where Scr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr /κ or 1, and max indicates the maximum of Scr /κ or 1.

CKD-EPI GFR expressed as a single equationFrom: Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604-612. Used with permission CKD-EPI performs better at GFR >60 mL/minute/1.73m^2.

The Cockcroft-Gault equation is an alternative equation that estimates creatinine clearance, but has the limitation that the serum measurements on which it was based were not standardised using IDMS.

CrCl (mL/s) = [(140-age {years}) x weight (kg) x 0.85 (if female)] / [48816 x SCr (micromol/L)]

Where SCr (mg/dL) = Scr (mmol/L) x 11.3

The Cockcroft-Gault formula, measuring creatinine clearance (CrCl) in mL/s (SI units)From: Jones

GRD, Lim E. The National Kidney Foundation guideline on estimation of the glomerular filtration rate. Clin Biochem Rev. 2003;24:95-98. Used with permission

CrCl (mL/minute) = [(140 – age {years}) x weight (kg) x 0.85 (if female)] / [72 x SCr (mg/dL)]

The Cockcroft-Gault formula, measuring creatinine clearance (CrCl) in mL/minuteFrom: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41. Used with permission

Pitfalls in the use of estimated GFR values

Estimated GFRs, commonly referred as eGFRs, are less accurate in both high and low GFR states. They overestimate GFRs in low GFR states due to increased tubular secretion of creatinine, and are inaccurate at high GFR states due to the lack of actual eGFR values above 60 mL/minute/1.73 m^2. A review of the literature suggests that Cockroft-Gault and MDRD formulas correctly assigned overall only 64% and 62%, respectively, of the subjects to their actual CKD classification's GFR groups as determined by measured GFR. This suggests that approximately 10 million (38%) subjects may have been misclassified, on the basis of estimated CKD prevalence of 26.3 million adults in the US. [16] The predictive value of serum creatinine versus eGFR may not be equivalent in all clinical situations. In contrast media-induced nephropathy, an increase in serum creatinine, but not eGFR, was predictive for long-term mortality, with a threshold of 44.2 micromol/L (0.5 mg/dL) or more indicating worse prognosis. [17] Similarly, haemodilution associated with cardiopulmonary bypass procedures overestimates GFR based on serum markers. [18] The controversy regarding the optimal method to estimate GFR for disease detection and monitoring may be addressed by an ongoing study. [19]

Kinetic estimated GFR (KeGFR)

Estimated GFR (eGFR) is based on the assumption of a steady state creatinine concentration. However, acute kidney injury is a non-steady state and eGFR in this situation is unreliable. Retooling the fundamental creatinine clearance equation has now provided the power and versatility to estimate renal function under non-steady conditions. Kinetic estimated GFR (KeGFR) is derived from the initial creatinine content, volume of distribution, creatinine production rate, and the quantitative difference between consecutive plasma creatinines over a given time. For that period, the deciphered creatinine excretion then yields the creatinine clearance rate. [20]

KeGFR = (Steady state plasma creatinine x Creatinine clearance / Mean plasma creatinine) x (1 – (24Dplasma creatinine / DTime (h) x max Dplasma creatinine/day)). Serum creatinine level (SCr) reflects adjusted SCr throughout the manuscript. KeGFR can be calculated by accessing a demonstration calculator. [KeGFR calculator] (external link)

Another method for calculating KeGFR is through the Jelliffe Creatinine clearance (Cr Cl):

- Cr Cl, Male: (98 - (0.8 * (age - 20))) / SCr in (mg/dL) x Patient's BSA/1.73m^2; and
- Cr Cl, Female: multiply the above result by 0.9. [21]

KeGFR has been shown to improve prediction of dialysis and recovery after renal transplant. [22]

Serum creatinine vs. alternate markers for the assessment of kidney function

The clinical use of cystatin as an alternate marker for estimating GFR is still limited despite considerable evidence that it could provide a reliable support for clinical practice. Reasons include a general diffidence among clinicians, the absence of definitive cut-off values, conflicting results in clinical studies, no clear evidence on when and how to request the test, the poor commutability of results, and no accurate examination of costs and of its routine use in a stat laboratory. In a study investigating kidney function estimating equations in patients with chronic kidney disease, serum cystatin C-based equations were reliable markers of GFR comparable to creatinine-based formulas. [23] Cystatin may be useful in those cases where creatinine measurement is not appropriate: for instance, in those who have liver cirrhosis, are very obese, are malnourished, or have a reduced muscle mass. Cystatin C is produced at a constant rate in all cells of the body and is excreted by glomerular filtration followed by catabolisation in the tubular cells. Because production rate of cystatin C is proportional to body cell mass (BCM), recent studies have suggested that estimated GFR (mL/min) may be proportional to BCM/cystatin C. [24] In comparison with 7 well-established GFR prediction methods, the inclusion of BCM was reported to increase the efficacy of GFR estimation in the paediatric population. [25] In this study, GFR was estimated by using two prediction models (where SCysC is serum cystatin C level, BSA is body surface area, and SCr is serum creatinine level):

- BCM model: GFR (mL/min) = 0.542 × (BCM/SCysC)(0.40) × (height × BSA/SCr)(0.65) and
- Weight model: GFR (mL/min) = 0.426 × (weight/SCysC)(0.39) × (height × BSA/SCr)(0.64).

Despite the lack of independent validation cohort, the BCM and weight models were comparable and predicted 98% within ±30% of reference GFR and 66% within ±10%, and 97.5% within ±30% of reference GFR and 62% within ±10%, respectively. The advantage of the weight model is that it does not require knowledge of BCM. Although both models predict GFR with higher accuracy than referent models, endogenous methods are still not sufficiently accurate to replace exogenous markers when GFR must be determined with high accuracy.

Acute kidney injury (AKI)

Definition

- AKI is associated with renal vasoconstriction, reduced GFR, decreased urine output, and increased serum creatinine. There is considerable debate regarding the magnitude of serum creatinine increase that constitutes AKI. More than 22 different definitions have been used. Consensus defines AKI as an abrupt (within 48 hours) reduction in kidney function defined as an absolute increase in serum creatinine of ≥26.5 micromol/L (≥0.3 mg/dL), an increase in serum creatinine to 1.5-fold from baseline, which is known or presumed to have occurred within the prior 7 days, or a reduction in urine output (documented oliguria of <0.5 mL/kg/hour for >6 hours). [26] [27] [28] [29] Stage 1 is defined as an increase in serum creatinine >26.5 micromol/L (>0.3 mg/dL) or 150% to 200% of baseline values. Stage 2 is defined as a 200% to 300% (2- to 3-fold) and stage 3 as a more than 300% (3-fold) increase in serum creatinine from baseline.
- The utility of serum creatinine to detect and assess the severity of AKI is limited. Serum levels are influenced by a multiplicity of factors, so the absolute level does not reflect the

severity of the underlying kidney damage. Rises in serum creatinine after marked injury take 12 to 24 hours to occur and do not detect early-stage damage. In addition, creatinine kinetic studies have shown that the time to reach a 50% increase in serum creatinine is directly related to baseline kidney function and ranges from 4 hours (normal kidney function) to 27 hours (in stage 4 chronic renal failure). An alternative definition of AKI that incorporates absolute changes in serum creatinine over a 24- to 48-hour period has been proposed. [30] Adding to this complexity is the new concept of acute kidney disease (AKD), characterised by renal biopsy findings of diffuse, acute abnormalities. Not all AKD patients have AKI. In fact, Chu reported that only two-thirds of patients with AKD were diagnosed with the clinical presentation of AKI. [31]

- Serum creatinine is a useful prognostic indicator. Mild increases in in-hospital serum creatinine have been associated with short-term mortality, progression to CKD, and accelerated progression to end-stage renal disease (ESRD), and they present a higher long-term mortality risk, especially in those with partial renal recovery. [32] [33] [34] They may also have prognostic significance for estimating the risk of death in many disease states: for example, an increase of only urea levels and a combination of increased urea and creatinine levels, but not isolated elevated creatinine, were independent risk factors of death from acute coronary syndromes. [35]
- The RIFLE (Risks, Injury, Failure, Loss of function and End-stage renal disease) classification of AKI was published in 2004 by the Acute Dialysis Quality Initiative (ADQI) Group with the aim to standardise the definition and stratification of AKI based on changes in serum creatinine and urine output. It has 3 severity classes of AKI (risks, injury, and failure) and 2 outcomes (loss of function and end-stage renal disease). Limitations of RIFLE include the need for serum creatinine values, inferior prognostic performance to other methods, and influence of creatinine kinetics, diuretics, and renal replacement therapies. [36] A modified version of RIFLE, known as the AKIN criteria, was published in 2007. [26] Baseline serum creatinine is not required, but at least two values of serum creatinine within a period of 48 hours is required.

Incidence

- Data on the incidence of AKI vary, depending on the cutoff serum creatinine values, the period of observation, and the population studied. In patients undergoing general surgery, and defining AKI as an increase in serum creatinine of at least 177 micromol/L (2 mg/dL) or requiring dialysis, the incidence of AKI was 1% over a 30-day period, [37] whereas the incidence was 64.4% in patients with septic shock using the RIFLE criteria, [38] 3.1% in older Medicare patients using ICD-9-CM codes 584.x as definition of AKI, [39] 5% to 10% in patients undergoing cardiac surgery, [40] [41] [42] 1% of hospital admissions in the USA, [43] and 5.7% in the intensive-care setting. [44]

Chronic kidney disease (CKD)

Definition

- CKD is defined by two independent criteria: [45] [46] [47] [48] [49] [50]
    - Kidney damage for ≥3 months as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by pathological abnormalities, markers of kidney damage (including abnormalities in the composition of the blood or urine), or abnormalities in imaging tests
    - GFR <60 mL/minute/1.73 m^2 for ≥3 months, with or without kidney damage.

- The presence of CKD is an important prognostic factor for patients admitted to hospital, due to the associated increased risk of in-hospital AKI. [51]
- The definitions rely on the estimation of GFR from serum creatinine to classify CKD according to severity of disease and guide treatment. However, there is controversy over whether estimation of GFR adds useful information to the serum creatinine measurement in this setting. An increasing portion of serum creatinine is excreted by tubular secretion rather than by glomerular filtration in advanced CKD, contributing to gross overestimation of GFR. Extra-renal secretion of serum creatinine is also increased, so the uptake of creatine generated by bacterial breakdown of creatinine in the gut, normally a negligible source of creatine, becomes significant.
- Creatinine is secreted through organic cation pathways located in the basolateral side of the proximal tubules. The secretion of creatinine is not constant, and substantial intra- and inter-individual variations are present. The proportion of tubular creatinine secretion increases with worsening renal function, while urine creatinine excretion decreases, and extra-renal secretion of creatinine increases. Serum creatinine can therefore overestimate GFR in advanced renal dysfunction.

Prevalence

- According to the US National Health and Nutrition Examination Surveys (NHANES 1988-1994 and NHANES 1999-2004), a nationally representative sample of non-institutionalised adults aged ≥20 years in 1988-1994 (15,488 people) and 1999-2004 (13,233 people), 26.3 million Americans have CKD, and the numbers are increasing, owing to the increasing prevalence of diabetes and hypertension, and the limited precision of creatinine used for the estimation of GFR. [52] [53] A study on the estimation of the age-dependent decline of glomerular filtration rate, from formulae, based on creatinine and cystatin C in the Swedish general elderly population, highlights the controversy regarding the true epidemiology of CKD. In Sweden, age-associated decline of renal function was common in the elderly and increased immensely after 80 years of age. More than 25% of the oldest participants demonstrated estimated GFR <30 mL/minute/1.73 m^2. Cockroft-Gault and estimated GFR-cystatin C yielded the highest prevalence of decline, and MDRD the lowest. [54]

Prognostic value of elevated creatinine

Serum creatinine may be regarded as the window into the state of the function and structure of the kidney. An elevated serum creatinine signifies kidney injury. Studies indicate that elevated serum creatinine during hospitalisation is an independent risk factor for mortality, progression to CKD, end-stage renal disease, and reduced long-term survival. Patients with chronically elevated serum creatinine (i.e., impaired baseline renal function) have a higher risk for acute kidney injury during hospital stays and are more often dialysis-dependent at hospital discharge than those without. [33] [34] [55] [56] [57] [58] [59] Elevated serum creatinine after endovascular aneurysm repair has been reported to be a significant and strong predictor of post-operative mortality and complications. [60] Even minimal changes of serum creatinine predict prognosis, as demonstrated in one prospective cohort study of 4118 patients undergoing cardiac and thoracic aortic surgery wherein a change in serum creatinine >0.5mg/dL within 48 hours post-operatively was associated with a 32.5% increase in 30-day mortality. [61] Chronically elevated serum creatinine signifies decreased GFR and has been linked to progression of CKD, increased mortality, and post-operative complications following cardiac surgery. Additionally, mild elevations in serum creatinine increase the risk for short- and long-term complications; worse patient survival; and progression to CKD regardless of complete, partial, or non-recovery to baseline levels during hospital stay. [59]

Prognostic value of serum creatinine versus cystatin C

In one study in high-risk adult patients undergoing cardiac surgery, measuring levels of cystatin C was found to be less sensitive than serum creatinine for the detection of acute kidney injury. [62] However, in patients with normal or mildly decreased renal function (eGFR >60 mL/minute/1.73 m^2) and coronary artery disease, elevated (upper quartile) cystatin C was associated with a 2-fold higher risk for cardiovascular death. [63] Serum creatinine did not show any association with mortality. [63] Investigation of kidney function and mortality in octogenarians in the Cardiovascular Health Study revealed a U-shaped association between GFR estimated by serum creatinine and all-cause mortality, whereas the association was linear between those with GFR <60 mL/minute/1.73 m^2 estimated by the cystatin C one-variable equation and all-cause mortality. [64] In renal transplantation, serum cystatin C outperformed serum creatinine in predicting early graft function following deceased donor renal transplantation. [65] Cystatin C and serum creatinine were found to be equally reliable for the estimation of residual renal function in peritoneal dialysis patients, without the need for 24-hour urine collection. [66] In adult patients with acute kidney injury, both serum creatinine and cystatin C were comparable in predicting need for dialysis or in-hospital mortality. [67] Since cystatin C is not affected by dietary protein intake, cystatin C-based GFR estimates may be more accurate than creatinine-based GFR estimates in patients with reduced protein intake. [68]

Differential diagnosis

Sort by: common/uncommon or category
Common

- Glomerulonephritis
- Diabetic nephropathy
- Systemic vasculitis
- Nephrotoxic medications/fenofibrate-associated creatinine increase
- Radiocontrast-induced nephropathy (RCIN)
- ACE inhibitors and angiotensin II receptor blockers
- Inhibitors of tubular creatinine secretion
- Shock
- Volume depletion
- Hypertension
- Congestive heart failure
- Renal vein thrombosis
- Pre-eclampsia
- Acute interstitial nephritis
- Acute tubular necrosis
- Cardiac surgery
- Nephrectomy
- Renal transplant rejection
- Biological serum creatinine variation

Uncommon

- Radiotherapy
- Endogenous nephrotoxins
- Renal artery stenosis
- Traumatic renal infarction
- Multiple cholesterol emboli syndrome
- Obstructive uropathy
- Creatine supplementation
- Heredofamilial kidney disease
- Methodological variations of measurement of creatinine
- Assay-interfering substances