Changing serum creatinine in the detection of acute renal failure and recovery following radiocontrast studies among acutely ill inpatients: Reviewing insights regarding renal functional reserve gained by large-data analysis

Yuri Gorelik a,1, Zaid Abassi b,1, Natalie Bloch-Isenberg a, Mogher Khamaisi a, Samuel N. Heyman c,*

a Department of Medicine D, Rambam Health Care Campus, Israel
b Ruth & Bruce Rappaport Faculty of Medicine, Technion-IIT, Haifa, Israel
c Department of Medicine, Hadassah Hebrew University Hospital, Mt. Scopus and Herzog Hospital, Jerusalem, Israel

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ABSTRACT

A rise in serum creatinine (SCR) is widely used for the detection and definition of evolving acute kidney injury (AKI). Yet, it takes time for SCR to re-adjust in response to changes in glomerular filtration rate (GFR), and subtle transient changes in GFR may remain concealed. Additionally, it cannot differentiate altered glomerular hemodynamics and pre-renal failure from true renal tissue injury, necessitating additional clinical and laboratory diagnostic tools.

While these features limit the usefulness of SCR and subsequently estimated GFR (eGFR) at a single time point for the individual patient, their overall pattern of changes along time in a large cohort of hospitalized patients may provide a powerful perspective regarding the detection and assessment of shifting kidney function in this population. Herein we review our experience running large data analyses, evaluating patterns of day-to-day changes in SCR among inpatients, occurring around the exposure to iodinated radiocontrast agents. These large data evaluations helped substantiating the existence of contrast-induced nephropathy in patients with advanced renal failure, underscoring the impact of predisposing and confounding factors. It also provides novel insights regarding a phenomenon of “acute kidney functional recovery” (AKR), and illustrate that the incidence of AKI and AKR along the scale of baseline kidney function co-associates and is inversely proportional to kidney function. This can be attributed to renal functional reserve, which serves as a buffer for up-and-down changes in GFR, forming the physiologic explanation for concealed subclinical AKI.

Abbreviations: AKI, acute kidney injury (AKI); SCR, Serum creatinine; GFR, glomerular filtration rate; AKR, Acute kidney functional reserve; eGFR, estimated GFR; RFR, Renal functional reserve; CIN, Contrast induced nephropathy; CKD, Chronic kidney disease.

* Corresponding author. Dept. of Medicine, Hadassah Hebrew University Hospital, Mt. Scopus P.O. Box 24035, Jerusalem, 91240, Israel.
E-mail address: Heyman@cc.huji.ac.il (S.N. Heyman).

1 both authors equally contributed to the manuscript.

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1. Introduction

Creatinine is generated from the breakdown of muscle creatine phosphate, and is excreted in the urine by means of passive glomerular filtration with subsequent minimal tubular reabsorption and secretion. The generation of creatinine is quite stable (with the exception of rhabdomyolysis), and as long as glomerular filtration rate (GFR) remains unchanged, a steady-state of its generation and excretion is achieved, reflected by stable levels of serum creatinine (SCr). Thus, SCr is a useful endogenous indicator of GFR, as long as its generation and elimination remain stable. When GFR declines, SCr increases until it reaches a new steady-state, where the continuous daily excretion of creatinine equals its generation, with balance re-established at higher SCr levels [1,2].

Estimated GFR can be calculated by urine collection and concomitant determination in plasma and urine of endogenous biomarkers, such as creatinine, or of exogenously administered compounds such as inulin or iothalamate. Regarding creatinine clearance, a 24-h urine collection period is recommended due to circadian variations of urine creatinine, and since GFR fluctuates along the day, increasing over meals and declining at nighttime. Thus, creatinine clearance roughly represents the mean daily GFR. Several widely used formulas provide an estimate of GFR (eGFR), based on SCr and on anticipated muscle mass (governed by age, gender, weight and race), enabling a close estimate of GFR without the need of urine collection [3–5]. Noteworthy, as some creatinine is actively secreted in the proximal tubule and also lost in the gut, creatinine clearance is generally somewhat higher than the true GFR. On the other hand, medications that inhibit tubular excretion of creatinine, such as cimetidine or trimethoprim, may lead to an underestimation of the true GFR.

Whereas SCr (and reflected eGFR) are quite reliable under steady-state conditions, they are of limited value during abrupt changes in GFR, as it takes time for SCr to stabilize [6]. Another caution regarding the determination of eGFR, based on SCr, is the non-linear association of GFR and SCr. As illustrated in Fig. 1, at the higher range of kidney function a substantial decline in GFR will have a very small impact on SCr, whereas with advanced renal dysfunction, small decrements in GFR will result in a striking rise in SCr. As outlined below, this may reflect to a large extent declining renal functional reserve (the ability to enhance GFR by altering glomerular filtration rate) and declining renal functional mass (A). A scheme showing the exponential rise in SCr as functional renal mass declines along the X axis. Superimposed are the regression lines of baseline- and stress-glomerular filtration rate (GFR), which merge with advanced renal functional impairment, reflecting diminishing renal functional reserve (RFR). In (B) the incidence of both acute renal injury (AKI) and renal functional recovery (AKR) increases as the number of functioning nephrons decline, conceivably due to diminished buffering capacity with the loss of RFR.
hemodynamics), as the mass of functioning nephrons diminishes.

With all these drawbacks in mind regarding the usefulness of SCR and eGFR at a single time-point, day-to-day changes of SCR are useful as indicators of acute kidney failure [5,7]. Herein we review how exploring such day-to-day changes in SCR and calculated eGFR in a large cohort of inpatients, using propensity matching and multivariate regression analyses, provide novel insights regarding the physiology of kidney function during acute illness and convalescence and following a nephrotoxic insult, namely the administration of iodinated radiocontrast medium during computerized tomography.

Notably, propensity matching used in our studies is a novel computerized research tool that enables retrospective optimal data analysis comparing large cohorts of patients. Patients to be compared in the different experimental groups are selected, based on best matching by defined baseline parameters. This is a good and rather cheap substitute to prospective controlled studies, where patients are randomized in a matched pattern according to pre-specified baseline parameters.

2. Contrast-nephropathy and its place within the heterogeneous nature of acute kidney injury (AKI)

AKI, defined as a significant reduction in GFR, with or without reduced urine production, is a heterogeneous phenomenon [7]. It extends from "pre-renal" failure (reduced renal perfusion pressure, principally due to fluid loss and hypotension), through altered glomerular hemodynamics leading to reduced glomerular pressure and GFR (such as sepsis or hepato-renal syndrome), "renal" AKI, reflecting intrinsic renal parenchymal damage (glomerular or tubulointerstitial) or intraluminal tubular obstruction, and "post-renal" failure, generated by urinary outflow obstruction. Post-renal AKI can be easily identified by imaging, and various laboratory parameters and urinalysis help distinguishing between pre-renal and renal AKI. Renal biomarkers facilitate the detection of tubular damage. Yet, AKI in the clinical practice often reflect a combination of pathophysiologies, and the setup of acute-on-chronic renal management of other organ dysfunction. In the setting of renal functional recovery, the detection of renal injury, specifically related to interventions during hospitalization, particularly affecting AKR.

Contrast induced nephropathy (CIN) is a "renal" AKI, caused by the administration of iodinated radiocontrast material during angiographic procedures or computerized tomography (CT). Altered renal medullary microcirculation and transiently enhanced tubular transport activity lead to medullary hypoxia with consequent vicious circle of hypoxic damage and injury related to the formation of oxygen free radicals, while direct tubular toxicity inflicted by the contrast material remains a debate [8,9]. Pre-existing renal disease, diabetes and effective volume depletion are among the leading predisposing factors for CIN, by amplifying microcirculatory alterations, renal parenchymal hypoxia and oxidative stress. Furthermore, vascular interventions and CT are often performed in acutely ill patients with various combinations of hemodynamic instability, inflammation and dysfunction of other organs, leading to renal insults that may directly affect kidney function. Thus, a clear distinction of CIN from other pre-renal, renal and post-renal components of AKI is often impossible.

Radiocontrast agents have been considered as leading iatrogenic causes of AKI among inpatients [10], but the incidence of CIN...
following CT has likely diminished with the use of safer low- or iso-osmolar contrast media and especially since small volumes of contrast material are currently needed for CT with the introduction of advanced imaging equipment. Patients’ selection and hydration protocols also diminish the incidence of CIN, while the value of antioxidants, vasoactive compounds and other interventions currently remains speculative [8,11].

Altogether, the likely declining incidence of CIN following CT led to the wide-spreading belief that CIN should be considered as a myth [12], with large retrospective studies indicating renal safety following contrast-enhanced CT in ambulatory and acute medical settings [13–17]. These studies are based on post-imaging changes in SCr, with varied definition of CIN, usually a rise by over 25%–50%, relative to baseline values, or an absolute rise in SCr levels of 0.25–0.50 mg/dL, as compared with baseline values within 48–72 h following imaging.

3. Large data analysis with propensity matching assessing the risk of CIN following contrast-enhanced CT

The confounding factors detailed above illustrate the difficulties in the detection and assessment of CIN in clinical practice. As outlined in Table 1, we conducted a series of large-data analyses over the last several years, aimed to assess the risk and true incidence of post-CT CIN among inpatients, based on changes in SCr following imaging [18–20]. We used a huge data base encompassing numerous clinical and laboratory parameters of all inpatients in a large tertiary-care medical center, looking at those with repeated measurements of SCr before and following imaging. The protocols of administered radiocontrast material (iohexol) were unchanged throughout the study period. The large numbers of patients in our series enabled the conduction of compensatory matching, designed to control for numerous possible confounders. We used the KDIGO criteria for the definition and staging of AKI [7].

We first compared 8133 patients undergoing contrast-enhanced CT with 742 individuals that underwent gadolinium-based enhanced magnetic resonance imaging (MRI). This study showed that a comparison of well-matched groups following compensatory matching revealed a comparable likelihood to develop AKI following the two types of imaging, suggesting that the risk of CIN is negligible following contrast-enhanced CT [18]. Yet, importantly, this deduction likely does not apply for angiographic procedures using large volume of iodinated contrast media [21]. Furthermore, importantly, we could not comment upon the risk of CIN in patients with advanced chronic kidney disease (CKD), the most important risk factor for CIN. Unfortunately for this analysis, very few such patients (with eGFR<30 ml/kg/1.73 m²) underwent gadolinium-based imaging, with caution regarding the risk of developing nephrogenic systemic fibrosis. This precluded adequate compensatory matching specifically for this important subgroup of patients. Indeed, non-matched comparisons of 28 and 366 patients undergoing gadolinium- and iodinated radiocontrast-enhanced imaging, respectively, suggested a 3-fold increase in the risk of developing AKI following iodine-based contrast imaging.

This led us to the second study [19], where we further compared 403 patients with eGFR<30 ml/kg/1.73 m² undergoing contrast-enhanced CT with two compensatory matched groups: one with a comparable degree of CKD following non-enhanced CT, and the other – patients with eGFR>30 ml/kg/1.73 m² that underwent contrast-enhanced CT. These two comparisons unequivocally revealed that contrast-enhanced CT is associated with a 55% increase in the likelihood to develop post-imaging AKI in patients with advanced renal failure.

4. Acute renal functional recovery (AKR) following radiocontrast studies

Running the two studies discussed above, we noticed that SCr declined in a substantial fraction of patients following imaging. This is not surprising since in many patients imaging took place shortly following hospitalization with an acute deterioration. Restoration of kidney function in these patients likely reflects the successful management of the acute illness, likely irrespective to the imaging procedure, and perhaps to hydration prior to the administration of contrast medium.

Our third complementary study was, therefor, aimed at the evaluation of acute kidney functional recovery (AKR) following imaging [20]. We used the same data base and methodology of compensatory matching, defining and grading AKR by changes in SCr along time, but reciprocal to those used for AKI, i.e. declining, rather than increasing SCr levels. This study revealed that AKR is much more common than AKI, and possibly conceal to some extent the adverse outcome caused by contrast media, leading to an underestimation regarding the true incidence of CIN. In line with this assumption, we found that at baseline eGFR <30 ml/min/1.73 m², the likelihood for AKI was higher while that of AKR was lower following contrast-enhanced CT, as compared with patients undergoing non-enhanced imaging. Most importantly, we found that likelihood of AKI and AKR were closely associated along the scale of baseline SCr and were inversely correlated with kidney function, reaching 30% and 70% of patients with the most advanced renal dysfunction (Fig. 1). This observation provided a novel insight regarding a shared mechanism for AKI and AKR, namely reduced renal functional reserve [22], as outlined below.

5. Renal functional reserve and its impact on AKI and AKR

Normal kidneys are able to acutely and transiently enhance single-nephron GFR (SNGFR) and overall GFR may increase by about 20 ml/min in response to various stimuli, such as a protein load. SNGFR also abruptly increases in response to acute reduction in nephron mass, for instance following unilateral nephrectomy. These dynamic increments in SNGFR are likely mediated by relaxation of mesangial cells with increasing filtration coefficient and by glomerular hemodynamic changes leading to increased trans-glomerular pressure. Thus, as shown in Fig. 1, basal GFR can transform into a higher stress GFR, and the difference between these values is termed renal functional reserve (RFR). RFR can be determined by monitoring GFR at baseline and following an acute stress, such as the administration of amino-acids [23,24]. In addition to these dynamic and transient adaptations, prolonged loss of nephrons leads to
gradual adaptive structural changes in the form of hypertrophied remnant nephrons, characterized by an increase in glomerular size and filtration area, with enhanced SNGFR.

Unfortunately, both the dynamic functional changes in SNGFR and the adaptive nephron hypertrophy in response to acute or chronic reduction in the number of functioning nephrons, respectively, is associated with reduced RFR, as remnant nephrons are already hyper-functioning with maximal SNGFR.

Thus, as illustrated in Fig. 1, with normal kidneys and preserved RFR, SCr may remain unchanged or only modestly rise despite evidence for renal parenchymal injury, a condition that may be termed “subclinical AKI” [25,26]. By contrast, SCr will rise even with modest acute renal insult in the presence of an already advanced loss of nephron units, with diminished RFR, if the acute reduction in functioning nephron mass goes beyond the diminishing buffering capacity of functional reserve in remnant nephrons. In other words, RFR can be considered as a “shock absorber” mechanism that can compensate for a transient functional loss of a fraction of all nephrons, by enhanced SNGFR in remnant nephrons. However, the capacity of this buffering RFR mechanism diminishes as renal functional mass declines, leading to a gradual rise in SCr in CKD, and to an overt uncovered rise in SCr even following a minute renal injury [22]. Importantly protracted enhancement of SNGFR in remnant nephrons is regarded as maladjustment on the long run, with a wear-and-tear progressively leading to glomerular sclerosis and hyalinosis with progressing CKD [27].

This scheme may explain the absence of overt rise in SCr following contrast-enhanced CT in the majority of patients with relatively preserved GFR and intact RFR, possibly with a fraction of them with subclinical AKI, whereas the likelihood to develop unconcealed AKI increases with diminished nephron mass and RFR [28]. The co-association of AKR and AKI, proportional to the degree of diminishing kidney function also fits well with this scenario, as AKR among inpatients represents recovery from an already acutely compromised renal function. Thus, as described in depth elsewhere [22], AKR and AKI following contrast-enhanced imaging among inpatients may both serve as indicators for diminished RFR, with a potential predictive value regarding the likelihood to develop repeated bouts of AKI and progressive CKD. This possibility is well established (so far for AKI, only) by former clinical studies [29,30].

6. Limitations of our studies using eGFR as an estimate of AKI and AKR

Our data assessment does not address few parameters, such as the hydration status and the amount of fluids administered around the imaging procedure. Likely, patients given radiocontrast material were over-hydrated, as compared with those undergoing MRI or non-enhanced CT. This could lead to an underestimation of the risk of AKI with tubular damage and would increase the likelihood to develop AKI, particularly in patients with advanced CKD. On the other hand, our definition of AKI, based on KDIGO criteria could lead to over-estimation of AKI in this population. With the non-linear association of plasma creatinine and the decline in GFR, shown in Fig. 1, with a sharp rise in SCr at the lower range or renal function, our estimates regarding AKI and AKR, based on KDIGO criteria, might be somewhat skewed, amplifying projected changes in eGFR at the range of advanced renal dysfunction. Noteworthy, a new AACC Academy definition of AKI [31], based on biological variability data with strong clinical outcomes, states that a change of 20% should be more appropriate for the definition of AKI/AKR at SCr levels ≥1 mg/dL, whereas a change of ≥0.2 mg/dL should be used when SCr is < 1 mg/dL. This could prevent a substantial overestimation of AKI/AKR in patients with advanced CKD [32], questioning our conclusions regarding the 1.55 folds increase in the risk to develop AKI following radiocontrast-enhanced CT among patients with eGFR < 30 ml/min/1.73 m². Still, we believe that the true important parameter in CIN is structural tubular damage, and that changes in eGFR are only surrogate indicators that might be markedly affected by other factors [8,9]. Thus, with confounders such as hydration status and volume replacement and the absence of available data for all patients that could serve as a clear-cut evidence for true tubular damage, the significance of the formulas used for the determination of AKI/AKR will remain debatable for the time being.

7. Conclusions and future directives

The studies detailed in Table 1 underscore the power of large data analysis with propensity matching in resolving disputes raised in retrospective comparisons of non-matched groups, and illustrate that with all its limitations, repeated measurements of SCr can provide substantial insight regarding changing renal function during an acute illness. We clearly showed that CIN remains a significant issue following contrast-enhanced CT in patients with advanced renal functional impairment. Our data also provide a close look at an unstudied aspect of renal functional changes during hospitalization, namely AKR. We found that the odds to develop AKR by-and-large surpasses that of AKI, proposing that AKR may interfere with assessing the true incidence of AKI. Additional clinical and laboratory tools, such as biomarkers of tubular injury might need to be assessed the true incidence of renal damage. Moreover, our data, based on changes in SCr in acutely ill hospitalized patients, indicate that the incidence of AKI and AKR along the scale of baseline kidney function co-associates and is inversely proportional to kidney function. This can be attributed to RFR, which serves as a buffer for up-and-down changes in GFR. Diminished RFR with advanced CKD forms the physiologic explanation for concealed subclinical AKI in patients with preserved renal integrity and the propensity to develop CIN in patients with advanced CKD.

Some 70% of imaging procedures took place upon admission to the hospital, explaining the frequent restoration of kidney function that can be attributed to interventions such as the restoration of euvoema and hemodynamic stability, or the successful management of infection and organ dysfunction. Our post-imaging findings showing direct association of AKI and AKR, both inversely proportional to baseline kidney function, were recently reported also among inpatients immediately following hospitalization and irrespective to imaging [33]. Future studies are required to validate our hypothesis regarding diminishing RFR manifested as increasing likelihood to develop AKI and AKR. Prospective studies of such patients should monitor the subsequent incidence of repeated bouts of AKI and the rate of progressive CKD on the long run.
