

ORIGINAL ARTICLE

Significant differences when using creatinine, modification of diet in renal disease, or cystatin C for estimating glomerular filtration rate in ICU patients

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Abstract

Background. Renal dysfunction is associated with increased morbidity and mortality in intensive care patients. In most cases the glomerular filtration rate (GFR) is estimated based on serum creatinine and the Modification of Diet in Renal Disease (MDRD) formula, but cystatin C-estimated GFR is being used increasingly. The aim of this study was to compare creatinine and MDRD and cystatin C-estimated GFR in intensive care patients.

Methods. Retrospective observational study was performed, on patients treated within the general intensive care unit (ICU) during 2004–2006, in a Swedish university hospital.

Results. GFR markers are frequently ordered in the ICU; 92% of the patient test results had cystatin C-estimated GFR ($eGFR_{\text{cystatinC}}$) ≤ 80 mL/min/1.73 m², 75% had $eGFR \leq 50$ mL/min/1.73 m², and 30% had $eGFR \leq 20$ mL/min/1.73 m². In contrast, only 46% of the patients had reduced renal function assessed by plasma creatinine alone, and only 47% had $eGFR_{\text{MDRD}} \leq 80$ mL/min/1.73 m². The mean difference between $eGFR_{\text{MDRD}}$ and $eGFR_{\text{cystatinC}}$ was 39 mL/min/1.73 m² for $eGFR_{\text{cystatinC}}$ values ≤ 60 mL/min/1.73 m².

Conclusions. GFR is commonly assessed in the ICU. Cystatin C-estimated GFR yields markedly lower GFR results than plasma creatinine and $eGFR_{\text{MDRD}}$. Many pharmaceuticals are eliminated by the kidney, and their dosage is adjusted for kidney function. Thus, the differences in GFR estimates by the methods used indicate that the GFR method used in the intensive care unit may influence the treatment.

Key words: Cystatin C, glomerular filtration rate, human, intensive care, kidney, MDRD

Introduction

Glomerular filtration rate (GFR) is generally accepted as the best overall indicator of renal function and is therefore an important marker for renal disease. Reduced GFR is one of the most important complications in critically ill patients and is associated with increased morbidity and mortality in the intensive care unit (ICU) population (1–4). Furthermore, reduced GFR influences the clearance of many pharmaceuticals used today. Thus, in many cases the recommended dose of a drug has to be adjusted

depending on the patient's GFR. For instance, the dosage of antibiotics and cytotoxic drugs is usually prescribed according to GFR. Monitoring renal function is thus very important in the management of intensive care patients, and GFR markers are frequently used for this purpose, necessitating convenient and reliable GFR markers. Inulin, iohexol, and ⁵¹Cr-EDTA clearances are considered as 'gold standards' for GFR measurements in Sweden (5–7). The disadvantage with these assays, and creatinine clearance with urine collection, is that they are cumbersome, costly, and associated with long turn-around

times, which may delay initiation and adjustment of treatment. They are thus less suitable for an intensive care unit requiring rapid decisions and actions. Thus, endogenous markers are usually preferred in the intensive care setting. The ideal endogenous marker should have a stable production rate, be unaffected by pathological changes, lack protein binding, be freely filtered through the glomeruli, and lack reabsorption or secretion. To date, no such marker has been identified.

Serum or plasma creatinine is the most commonly used GFR marker (8,9). Creatinine is an inexpensive test widely available in clinical chemistry laboratories, but the assay outcome is hampered by the influence of several extrarenal factors such as age, gender, muscle mass, physical activity, and diet (10,11). It is also insensitive for small decreases in GFR, in the so-called creatinine-blind GFR area, due to the non-linear relationship between plasma concentration and GFR (12).

Cystatin C is an endogenous polypeptide that is more sensitive than serum creatinine for the detection of small decreases in GFR and is reported not to be influenced by inflammation, liver function, age, gender, muscle mass, physical activity, or diet (13). Human cystatin C has a plasma clearance of cystatin C of 94% of the generally used GFR-marker, ⁵¹Cr-EDTA in the rat (14).

Previously, cystatin C assays were hampered by the limited availability of the test, but cystatin C methods have now been developed for clinical chemistry laboratories making the test widely accessible. Cystatin C can thus be analyzed with short turn-round times providing rapid test results for intensive care, at costs comparable to plasma creatinine analysis.

A recent meta-analysis has shown that cystatin C is superior to plasma creatinine as a marker of renal function (15). Another study has suggested that cystatin C is superior to creatinine as a GFR marker in critically ill patients (16).

The aim of this study was to assess the prevalence of reduced GFR in this patient group using creatinine and Modification of Diet in Renal Disease (MDRD) and cystatin C-estimated GFR, as several pharmaceuticals are prescribed according to renal function, and to investigate the request frequency of laboratory markers in an ICU, with special reference to GFR markers.

Materials and methods

Study population

This study included all patients treated within the general intensive care unit, Uppsala University

Hospital, during the time period 1 January 2004 to 1 September 2006. The total number of tests per year, presented in Table I, was based on all requests during the same time period. The Table thus also includes requests for patients below 16 years of age and requests without a valid test result (e.g. samples that could not be analyzed due to insufficient sample volumes). For comparison between cystatin C and creatinine results, only valid test results from patients older than 16 years of age were included. Blood samples for cystatin C analyses were usually collected early in the morning and not more than once a day.

Intensive care unit (ICU)

The study was conducted in a ten-bed general intensive care unit admitting patients from medical and surgical specialties in a university hospital. Approximately 1,200–1,500 patients are treated in this unit each year, with a mean admittance time of 2.5 days. The unit has an ABL 725 (Radiometer, Copenhagen, Denmark) blood gas instrument for point of care testing in the ward.

Sample collection

The samples for creatinine and cystatin C analyses were collected in gel tubes with lithium-heparin (LH PST™ II, BD Vacutainer Systems, Plymouth, UK).

Table I. GFR markers, drug levels in plasma among the most frequently ordered tests during the study period 2004–2006 (mean number of tests per year).

Test	<i>n</i>
1. Blood gases (ABL 725)	50725
2. Creatinine	3089
3. Blood cell counts	3070
4. C-reactive protein	3063
5. Activated partial thromboplastin time	2883
6. Prothrombin complex	2797
7. Bilirubin, direct method	1972
8. Alanine aminotransferase (ALT)	1972
17. Pt-GFR (CystC-calculated)	875
25. Vancomycin	182
28. Tobramycin	120
31. Digoxin	84
36. Gentamycin	56

Pt-GFR, Patient-Glomerular filtration rate.

Plasma cystatin C and cystatin C-estimated GFR (eGFR)

Plasma cystatin C measurements were performed by latex-enhanced reagent (N Latex cystatin C, Dade Behring, Deerfield, IL, USA) using a Behring BN ProSpec analyzer (Dade Behring). The total analytical imprecision of the method was 4.8% at 0.56 mg/L and 3.7% at 2.85 mg/L. The cystatin C results are reported as a cystatin C-estimated GFR (eGFR) in mL/min/1.73 m² (17). GFR in mL/min/1.73 m² was calculated from cystatin C results in mg/mL by the equation $y = 77.24 \times (\text{Cystatin C result})^{-1.2623}$ (17). The reference value for cystatin C-estimated GFR (eGFR) was ≥ 80 mL/min/1.73 m².

Plasma creatinine and Modification of Diet in Renal Disease (MDRD) formula-estimated GFR (eGFR)

Plasma creatinine was analyzed with a modified kinetic Jaffé reaction on an Architect Ci8200[®] analyzer (Abbott, Abbott Park, IL, USA) and reported as SI units ($\mu\text{mol/L}$). The method is isotope dilution mass spectrometry (IDMS)-calibrated in collaboration with the Swedish external quality assurance organization (Equalis, Uppsala, Sweden). The total analytical imprecision of the creatinine method was 4.8% at both 94 and 337 $\mu\text{mol/L}$. The reference interval for creatinine concentration in adult males was 60–100 $\mu\text{mol/L}$. The reference interval for creatinine concentration in adult females was 50–90 $\mu\text{mol/L}$. eGFR_{MDRD} was calculated from creatinine using the MDRD formula: $\text{eGFR} = 175 \times (\text{creatinine } (\mu\text{mol/L}) / 88.4)^{-1.154} \times \text{age (years)}^{-0.203} \times 0.742$ (if female) (18). The factor for African Americans was not used.

Statistical calculations

All calculations were performed with the statistical software package Statistica 7.0 (StatSoft, Tulsa, OK, USA). Associations between continuous variables were tested with Spearman's rank correlation analysis (*R*). *P* values < 0.05 were regarded as statistically significant throughout the study.

Results

Most frequently ordered tests

The most frequently ordered test was arterial blood gas analysis. Creatinine was the second most frequently ordered test on the list (Table I). Aminoglycosides, vancomycin, and digoxin were the most frequently ordered drug tests.

Cystatin C and creatinine plasma levels

During the studied time period there were 1,838 cystatin C test results. Of these requests 1,151 (63%) were for male patients and 687 (37%) were for female patients. The mean age of the patients was 62 years (62 for both males and females).

Median cystatin C concentration in the cohort was 1.96 mg/L (interquartile range 1.38–2.81 mg/L), and mean value was 2.23 mg/L. For males the median cystatin C concentration was 1.99 mg/L (interquartile range 1.39–2.81 mg/L), and for females the median cystatin C concentration was 1.90 mg/L (interquartile range 1.36–2.83 mg/L).

During the time period there were 7,566 requests for creatinine. Of these requests 4,573 (60%) were for male patients, and 2,993 (40%) were for female patients.

Median creatinine concentration in the cohort was 91 $\mu\text{mol/L}$ (interquartile range 67–153 $\mu\text{mol/L}$), and mean value was 131 $\mu\text{mol/L}$. For males the median creatinine concentration was 99 $\mu\text{mol/L}$ (interquartile range 73–166 $\mu\text{mol/L}$), and for females the median creatinine concentration was 80 $\mu\text{mol/L}$ (interquartile range 60–132 $\mu\text{mol/L}$). A total of 2,247 out of 4,573 test results for males were above the reference interval (49%); 1,234 out of 2,993 test results for females were above the reference interval (41%).

In 88% of the patients, plasma cystatin C values indicated reduced kidney function, whereas only 46% of the patients had reduced kidney function as evaluated by their plasma creatinine levels.

eGFR calculated from cystatin C values

Median eGFR_{cystatinC} in the study group was 30.3 mL/min/1.73 m² (interquartile range 17.9–50.1 mL/min/1.73 m²), and mean value was 37.6 mL/min/1.73 m². For males the median eGFR was 29.7 mL/min/1.73 m² (interquartile range 18.1–49.7 mL/min/1.73 m²), and for females the median eGFR_{cystatinC} was 31.7 mL/min/1.73 m² (interquartile range 17.9–51.4 mL/min/1.73 m²).

Out of the 1,838 eGFR_{cystatinC} results, only 146 results (7.9%) were within the reference range, while 92.1% of the results were below the reference interval. Out of the 1,838 eGFR results, 454 results (25%) were higher than 50 mL/min/1.73 m², and 1,279 (70%) were higher than 20 mL/min/1.73 m².

There was a strong negative correlation between age and eGFR ($R = -0.316$, $P < 0.0001$).

Both males ($R = -0.302$; $P < 0.0001$) and females ($R = -0.344$; $P < 0.0001$) showed similar negative correlations (Figures 1 and 2).

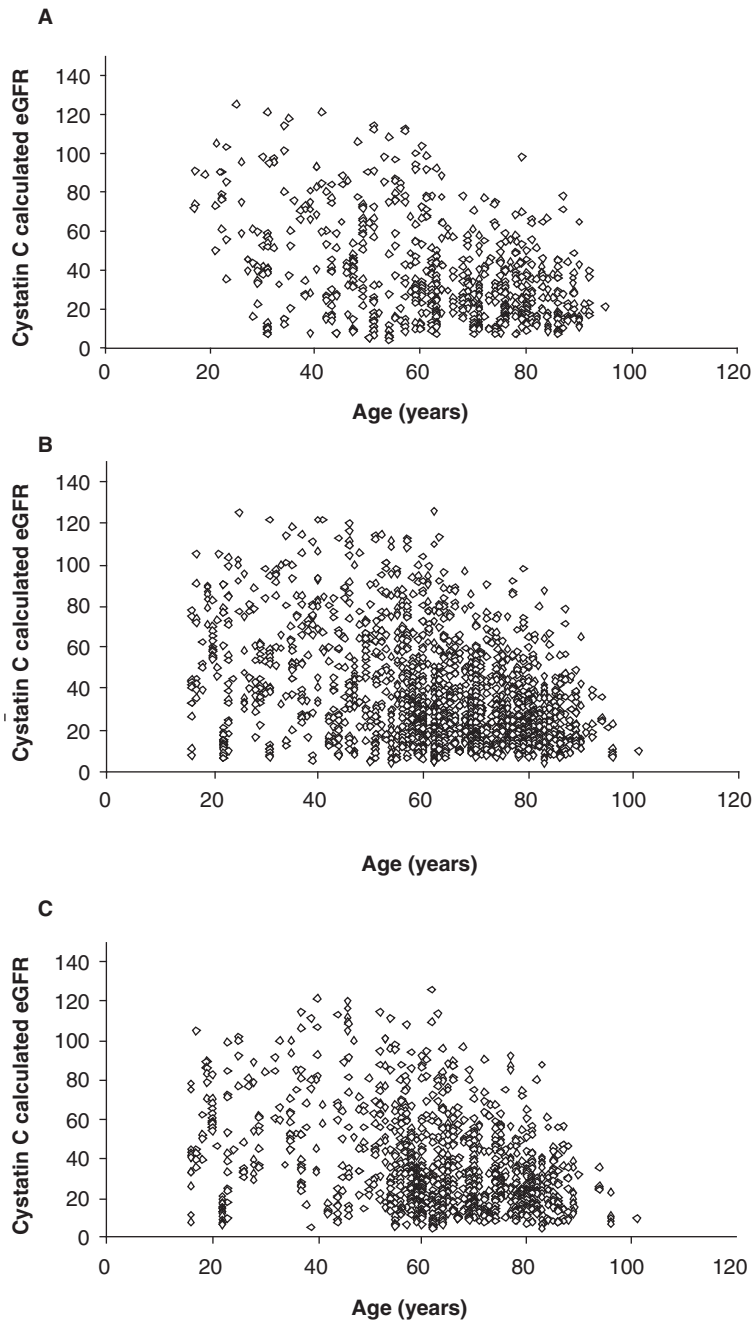


Figure 1. A: Age versus cystatin C-estimated glomerular filtration rate (eGFR) for all patients ($n = 1,838$). B: Age versus cystatin C-estimated glomerular filtration rate (eGFR) for males ($n = 1,151$). C: Age versus cystatin C-estimated glomerular filtration rate (eGFR) for females ($n = 687$).

Paired plasma cystatin C and creatinine analyses

There were 1,777 test requests that contained both cystatin C and creatinine results performed on the same test tube. Of these requests 1,110 were for males and 667 for females. These samples were from 734 different patients (median 2.42 samples per patient).

Median creatinine concentration in this subgroup was 127 $\mu\text{mol/L}$ (interquartile range 87–207 $\mu\text{mol/L}$), and mean value was 167 $\mu\text{mol/L}$.

For males the median creatinine concentration was 134 $\mu\text{mol/L}$ (interquartile range 95–212 $\mu\text{mol/L}$), and for females the median creatinine concentration was 111 $\mu\text{mol/L}$ (interquartile range 76–199 $\mu\text{mol/L}$). A total of 789 out of 1,110 test results for males

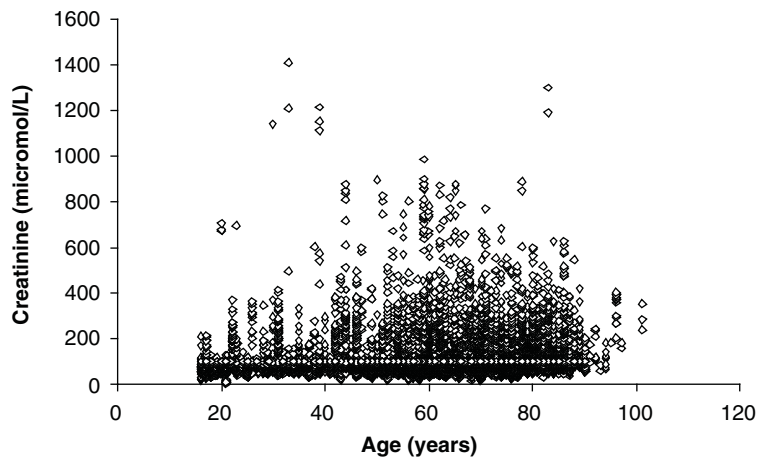


Figure 2. Age versus plasma creatinine for all patients ($n = 7,566$).

were in the reference interval (71%); 418 out of 667 test results for females were in the reference interval (63%). In total 1,207 out of 1,777 plasma creatinine results were pathological (68%).

Out of the MDRD-estimated GFR results 47% were ≤ 80 mL/min/1.73 m², 30% were ≤ 50 mL/min/1.73 m², and 7% ≤ 20 mL/min/1.73 m². Median MDRD eGFR was 48 mL/min/1.73 m² (Table II). Out of the 1,777 cystatin C-estimated GFR results 93% were ≤ 80 mL/min/1.73 m², 74% were ≤ 50 mL/min/1.73 m², and 23% were ≤ 20 mL/min/1.73 m². Median MDRD eGFR was 39 mL/min/1.73 m². The Spearman rank correlation between the two methods was $R = 0.753$ (Figure 3). MDRD-estimated GFR yielded higher values than cystatin C-estimated GFR (Figure 4). The mean difference between eGFR_{MDRD} and eGFR_{cystatinC} was 39 mL/min/1.73 m² for eGFR_{cystatinC} values ≤ 60 mL/min/1.73 m².

Discussion

Plasma creatinine’s role as GFR marker assumes a steady state condition of creatinine distribution. However creatinine levels in plasma and urine are subject to variations during critical illness for several reasons.

Critically ill patients often have increased body water volume and decreased muscle mass and may have impaired liver function. Other factors that may influence creatinine production are trauma, fever, and immobilization. There is also the problem of tubular secretion of creatinine to some extent while low urine production may cause tubular reabsorption. Thus, creatinine is not an optimal marker for detection of acute renal failure in intensive care patients; there is on-going search for better GFR markers, and cystatin C and proANP (Atrial natriuretic peptide) have been suggested as alternatives (19). One study that compared cystatin C and creatinine reported that cystatin C and creatinine performed equally well in intensive care patients (20). Two other studies showed cystatin C to be superior to creatinine. One of the studies reported that serum cystatin C detected acute renal failure 1 to 2 days earlier than creatinine (21). The other study compared cystatin C and creatinine with 24-h urine collection and creatinine clearance. Cystatin C was significantly better than creatinine to detect reduced GFR (22). Neither of these studies compared GFR estimated from cystatin C and creatinine with GFR measurement using an exogenous marker such as iohexol, iothalamate, or chromium-51-EDTA.

In this study we show that, apart from arterial blood gas analysis, GFR markers are the most frequently requested tests in the ICU. Furthermore we show that there are considerable differences between the studied markers creatinine, eGFR_{MDRD}, and eGFR_{cystatinC} for estimating GFR in ICU patients. Reduced GFR is very common in this ICU population, especially when using cystatin C for estimating GFR. There was a strong negative correlation between age and eGFR_{cystatinC}, while the correlation between age and creatinine was less pronounced. This could be expected as both GFR and muscle mass decrease

Table II. Percentage of patients with GFR below 20, 50, and 80 mL/min/1.73 m², respectively, based on eGFR_{MDRD} and eGFR_{cystatinC} calculations.

	≤ 20 mL/min/1.73m ²	≤ 50 mL/min/1.73 m ²	≤ 80 mL/min/1.73 m ²
eGFR _{cystatinC}	30%	75%	92%
eGFR _{MDRD}	7%	30%	47%

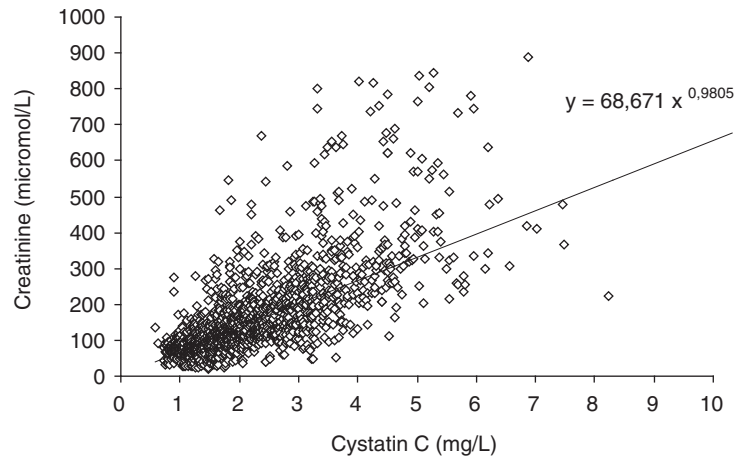


Figure 3. Correlation between cystatin C and creatinine in individual patients ($n = 1,668$).

with age. An increased plasma creatinine due to reduced GFR is thus partly disguised by the reduced muscle mass. Cystatin C detected twice as high a frequency of reduced GFR in spite of a high degree of correlation between these two methods.

Plasma creatinine, $eGFR_{MDRD}$, and cystatin C assays can all provide rapid test results. Creatinine often over-estimates GFR in patients with slight reductions of GFR (11). It is also difficult to evaluate creatinine in elderly patients with low muscle mass. These patients may have creatinine values in the normal range due to the combination of low muscle mass and reduced GFR. This is in agreement with the present results with 92% of the cystatin C values indicating reduced kidney function, while only 46%

of the creatinine test results indicated a reduced kidney function. A considerable gap between the results, 93% versus 47% for $eGFR$ with cystatin C and $eGFR$ with MDRD, respectively, persisted even when the two methods were performed on the same plasma sample. In this study we used the reference value ≥ 80 mL/min/1.73 m² regardless of patient age as a decreased $eGFR$ in the range of 50–80 mL/min/1.73 m² was associated with increased mortality in elderly individuals (23–26).

We included plasma creatinine in this comparison as many GFR evaluations in Sweden are based on the creatinine concentration. The GFR estimations from plasma creatinine values are performed in the wards either by a rough estimate based on the creatinine

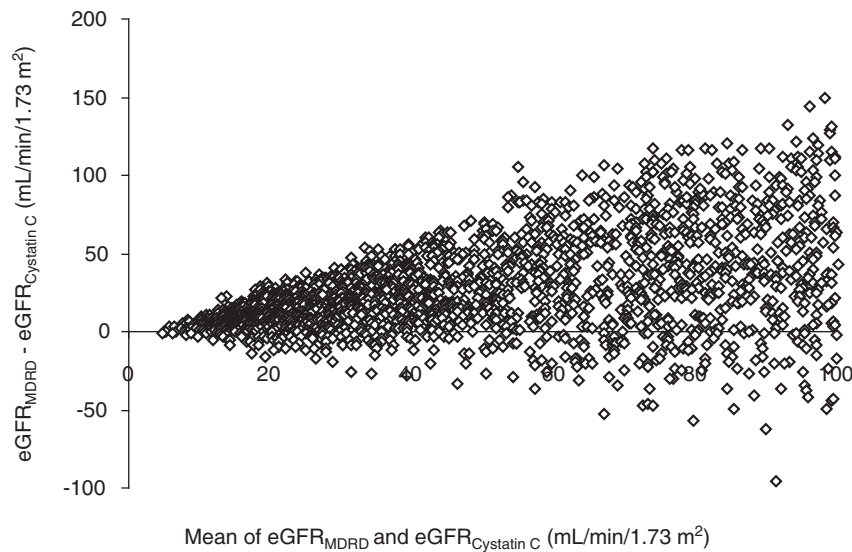


Figure 4. Bland–Altman bias plot for $eGFR_{cystatinC}$ and $eGFR_{MDRD}$. The results are presented as the mean of the two methods (x -axis) plotted against the difference between the two methods (y -axis) ($n = 1,777$).

value or by using nomogram for the Cockcroft-Gault equation (8). The equations are very rarely performed utilizing computers.

The problems associated with calculating GFR in the wards have led to the development of formulas to automatically convert cystatin C in mg/L to a calculated GFR in mL/min/1.73 m² (17,27). This is in agreement with guidelines that laboratories should calculate and report an estimated glomerular filtration rate (eGFR) using the MDRD formula with every request for plasma creatinine concentration (28). In the ICU, MDRD and plasma creatinine concentration detected similar numbers of patients with reduced GFR, and both methods detected a lower number of patients with reduced GFR in comparison with cystatin C-estimated GFR.

Cystatin C has also been suggested to be superior to creatinine measurements for intensive care use although this has also been questioned (16,29).

In this study we compared cystatin C as GFR marker with creatinine concentration and eGFR_{MDRD}. The study shows that a higher proportion of the intensive care patients had impaired kidney function when using eGFR_{cystatinC}. Several of the drugs used in the intensive care unit are eliminated by the kidneys, and their turn-over is thus influenced by the GFR. Determination of plasma concentrations of digoxin, gentamycin, tobramycin, and vancomycin are all among the top 40 test requests in the intensive care unit, and they are all influenced by the GFR. Even though concentration of these drugs can be measured, initial therapy is started based on GFR estimates. Furthermore, levels of several widely used pharmaceuticals with renal elimination are not routinely assessed. Examples of such drugs used in critical care are H₂-antagonists, beta-blockers, and antibiotics such as penicillins and cephalosporins. Inadequate dosage of these pharmaceuticals may lead to insufficient therapy or adverse effects, which highlight the need for optimal GFR markers or the advantage of pharmaceuticals without renal elimination.

Conclusions

The present study shows that GFR is frequently assessed in the ICU, and many intensive care patients have reduced GFR, and the study emphasizes the need to monitor GFR in this patient group. The use of cystatin C instead of creatinine will increase the number of patients identified with decreased GFR. Since most ICUs use plasma or serum creatinine for GFR monitoring, they may miss several patients with reduced eGFR_{cystatinC}. The discrepancy

between the two methods may influence the pharmaceutical treatment of the patients and shows that there is a need to improve GFR measurements in intensive care. Without an optimal GFR marker, using drugs that are less GFR-dependent should be considered. With the existing methodological differences in mind, there is a need for further studies that compare GFR estimated from cystatin C and creatinine with GFR measurement with an exogenous marker such as iothexol, iothalamate, or chromium-51-EDTA in intensive care patients.

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