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Assessment of renal function in recently admitted critically ill patients with normal serum creatinine

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Abstract

Background. Detection of renal dysfunction is important in critically ill patients, and in daily practice, serum creatinine is used most often. Other tools allowing the evaluation of renal function are the Cockcroft–Gault and MDRD (Modification of Diet in Renal Disease) equations. These parameters may, however, not be optimal for critically ill patients. The present study evaluated the value of a single serum creatinine measurement, within normal limits, and three commonly used prediction equations for assessment of glomerular function (Cockcroft–Gault, MDRD and the simplified MDRD formula), compared with creatinine clearance (Ccr) measured on a 1 h urine collection in an intensive care unit (ICU) population.

Methods. This was a prospective observational study. A total of 28 adult patients with a serum creatinine <1.5 mg/dl, within the first week of ICU admission, were included in the study. Renal function was assessed with serum creatinine, timed 1 h urinary Ccr, and the Cockcroft–Gault, MDRD and simplified MDRD equations.

Results. Serum creatinine was in the normal range in all patients. Despite this, measured urinary Ccr was <80 ml/min/1.73 m^2 in 13 patients (46.4%), and <60 ml/min/1.73 m^2 in seven patients (25%). Urinary creatinine levels were low, especially in patients with low Ccr, suggesting a depressed production of creatinine caused by pronounced muscle loss. Regression analysis and Bland–Altman plots revealed that neither the Cockcroft–Gault formula nor the MDRD equations were specific enough for assessment of renal function.

Conclusions. In recently admitted critically ill patients with normal serum creatinine, serum creatinine had a low sensitivity for detection of renal dysfunction. Furthermore, the Cockcroft–Gault and MDRD equations were not adequate in assessing renal function.

Keywords: creatinine clearance; glomerular filtration rate; kidney failure, acute; kidney function; prediction equations; serum creatinine

Introduction

Early detection of renal dysfunction and subsequent adequate treatment can prevent progression to severe acute renal failure (ARF) with need for renal replacement therapy in a substantial number of intensive care unit (ICU) patients, and can therefore prevent morbidity, mortality and additional cost [1]. In addition, many medications used in the ICU (e.g. most antibiotics and low molecular weight heparins) need dose adjustment for renal function; underdetection of renal insufficiency can therefore lead to incorrect dosing and increased risk for side effects.

Normal values obtained by a method for the assessment of renal function should correspond to a normal glomerular filtration rate (GFR). On the other hand, the method should also be able to detect a diminished GFR.

The most commonly used marker for the evaluation of renal function in ICU patients is serum creatinine, and the diagnosis of ARF is often defined on a single determination of serum creatinine [2,3]. However, serum creatinine may be not very suitable for this purpose. The serum creatinine level depends not only on renal elimination but also on creatinine generation, volume of distribution and renal elimination. Creatinine is metabolized from creatine released by the muscles, so that muscle mass and metabolic transformation of creatine have an impact on creatinine concentration. Many characteristics apart from renal function may influence creatinine concentration, such

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as age, gender and race: younger patients, males and blacks have higher serum creatinine levels for the same given GFR, compared with older patients, females and Caucasians [4,5]. In addition, serum creatinine and GFR are not linearly but hyperbolically related. Although an increase in serum creatinine from 4 to 8 mg/dl produces the same proportional decrease of GFR as an increase from 1 to 2 mg/dl, its clinical implication is completely different. Finally, critically ill patients are often in a non-steady state condition and it has been shown that changes of GFR are poorly reflected by daily changes in serum creatinine concentrations in patients with ARF [6].

Direct measurement of GFR, the golden standard for assessment of renal function, with exogenous substances such as inulin, non-radioactive contrast agents (iothalamate or iohexol) or radiolabelled compounds (e.g. [^{125}I]iothalamate or technetium 99m-diethylenetriaminepenta-acetic acid) is not performed routinely in the ICU setting for practical reasons.

Urinary creatinine clearance (Ccr), however, can be easily measured in an ICU patient, and is the next best method for evaluation of renal function. However, clearance methods require a steady-state situation, a condition seldom fulfilled in critically ill patients. Changes in, for example, haemodynamic status can result in dramatic changes in renal function over a 24 h observation period. In order to circumvent this, we choose a short timed urine collection for calculation of urinary creatinine clearance in patients with stable renal function. According to previous studies, short time urinary creatinine clearances correlate well with longer urinary collection methods when patients are in a steady state [7,8].

Renal function can also be estimated by several equations based on serum creatinine and patient characteristics [4,5]. These equations can be easily calculated at the bedside with use of handheld computers. They are, however, not validated in critically ill patients.

Given these considerations, the objective of the study was the assessment of a single serum creatinine value for determination of renal function in a population of recently admitted (<1 week) critically ill patients with serum creatinine levels within the normal range, by comparing this with the measured urinary Ccr. In order to circumvent the impact of fluctuations in physiological conditions, Ccr was determined from a 1 h urine collection at the moment of creatinine determination. Additionaly, we evaluated three equations for determination of renal function.

Patients and methods

The study was conducted in the 20 bed surgical ICU for adult patients in the Ghent University Hospital, a tertiary referral centre. Patients older than 18 years, with an indwelling arterial catheter, a urinary bladder catheter, a diuresis >400 ml/day, a serum creatinine <1.5 mg/dl, not treated by diuretics, and with an ICU stay of <1 week were included in the study. Patients were excluded when there was no information regarding body weight before admission, when they were haemodynamically unstable, when they were recovering from ARF or developing ARF, or when they were transferred from another ICU. In order to ensure that we evaluated patients in a steady-state condition, we also excluded patients in whom the difference between serum creatinine on the day of the experiment and 24 h later was ≥15%. Inclusion and exclusion criteria were defined by our concern to obtain reliable estimates of renal function in a population which, according to current standards, could be considered in steady state, and as having no renal failure.

An exactly timed 1 h urine collection was obtained for measuring the urinary creatinine concentration, and serum creatinine was measured at the end of the 1 h urine collection period. These data allowed us to calculate the timed, 1 h urinary Ccr (Table 1). Additionally, renal function was assessed by application of three well known, and widely used, equations that estimate renal function on the basis of demographic characteristics and biochemical values: the Cockcroft–Gault formula [4], the original MDRD (Modification of Diet in Renal Disease) formula [5] and the simplified MDRD formula [9] (Table 1). Because body weight in most ICU patients is increased due to fluid accumulation, this may falsify the calculations based on equations developed for the general population. Therefore, the predicted body weight, based on gender and height, was calculated for each patient. The predicted body weight for male patients was calculated as $50 + 0.91$ (cm of height $- 152.4$), and for female patients as $45.5 + 0.91$ (cm of height $- 152.4$) [10]. The Cockcroft–Gault equation was calculated once with the predicted body weight, and once with the actual body weight before ICU admission. The MDRD equations calculate the GFR corrected for body surface area (ml/min per 1.73 m^2). To allow comparison, the Cockcroft–Gault equation and measured Ccr were also normalized to 1.73 m^2. The body surface area (m^2) of the patients was calculated as: weight (kg)$^{0.425}$ × height (cm)$^{0.725}$ × 71.84/10 000. The urinary creatinine loss per day was calculated as urinary creatinine concentration (mg/dl) × urinary

Table 1. Formulae for calculation of renal function

Method	Formula
Measured 1 h urinary creatinine clearance	Urinary volume × urinary creatinine concentration × 1.73/ plasma creatinine × 60 min × BSA[a]
Cockcroft–Gault	(140 − age) × body weight × 1.73 (×0.85 if female)/serum creatinine × 72×BSA[a]
MDRD	170 × creatinine$^{-0.999}$ + age$^{-0.176}$ × (0.762 if female) × (1.180 if black) × serum urea$^{-0.170}$ × albumin$^{0.318}$
Simplified MDRD	186 × creatinine$^{-1.154}$ × age$^{-0.203}$ × (1.212 if black) × (0.742 if female)

[a]BSA = body surface area.

volume (ml) $\times$24 h $\times$ 1.73/100/body surface area (m^2), expressed as (mg/24 h/1.73 m^2), and as urinary creatinine concentration (mg/dl) $\times$ urinary volume (ml) $\times$ 24 h/100/ actual body weight (kg) (mg/kg/24 h), expressed as (mg/kg/24 h).

Statistics. Univariate analysis was performed with the Mann–Whitney U-test and Wilcoxon signed ranks test for continuous variables, and the Fisher exact test for categorical variables. Precision of the equations, compared with Ccr, was evaluated with use of the Spearman correlation coefficient. Furthermore, equations were compared with Ccr with the use of Passing–Bablock regression analysis, and Bland and Altman plots. Bland and Altman plots allow evaluation of the mean difference $\pm$ 2 SDs between two methods of measurement over the average of the measurements by the two methods [11]. Data are presented as median (interquartile range); a double-sided *P*-value of <0.05 was considered significant. Statistics were performed with the help of the statistical software packages MedCalc® (version 5.500.019, MedCalc®, Mariakerke, Belgium) and SPSS 11.0.1 (SPSS Inc. Chicago, IL).

Results

Basis characterisitics

A convenience sample of 28 Caucasian patients (10 female and 18 male) with a median age of 58 years (48–69) and APACHE II score of 21 (12–28) was included in the study. The distribution of the patients according to major admission categories is illustrated in Table 2. The study was performed on day 1 (1–2) of ICU admission. Body weight before admission to the ICU was 70 kg (66–81), predicted body weight was calculated as 68 kg (58–73) and body surface area calculated on the basis of body weight before admission was 1.83 m^2 (1.76–1.92). Serum creatinine was low [0.79 mg/dl (0.67–0.88)]; none of the patients had a serum creatinine value exceeding the upper normal reference value. Also, serum urea was within normal limits [0.24 g/dl (0.17–0.39)]. The difference between serum creatinine values on the day of the study and 24 h later was 3% (−3.4 to 7.2). The 24 h urine volume during the day of the study was comparable with the urine volume obtained after extrapolation of the 1 h urine volume of the study to a 24 h urine volume [1873 ml/24 h (1461–3113) *vs* 1560 (1164–3330); $P = 0.767$]. The measured Ccr was 86 (62.6–121.6) ml/min/1.73 m^2. Urinary creatinine excretion for women was 778 (665–1336) mg/24 h/1.73 m^2, and for men was 1056 (714–1445) mg/24 h/1.73 m^2. As the urinary creatinine excretion in normal subjects has been established at 1230 mg/24 h/1.73 m^2 for females, and 1600 mg/24 h per 1.73 m^2 for males [12], there was a reduction of urinary creatinine excretion of one-third for the whole group of patients.

Table 2. Distribution of patients according to admission category

Admission category	No. of patients
Neurosurgery	9
Abdominal surgery	7
Sepsis	2
Trauma	4
Liver insufficiency	2
Miscellaneous	4
Total	28

Assesment of serum creatinine as a marker for GFR

An unexpected finding was that a significant number of patients had a decreased GFR, despite having a normal serum creatinine. In 13 patients (46.4%), the GFR was $<$80 ml/min/1.73 m^2 and in seven patients (25%), the Ccr was $<$60 ml/min/1.73 m^2.

Patients with a Ccr lower than 80 ml/min/1.73 m^2 had a lower 24 h creatinine excretion (Table 3). A higher proportion of patients with low Ccr were treated with vasoactive therapy or mechanical ventilation. There were no differences in age, gender, APACHE II score or length of preceding ICU stay.

Assessment of three equations for determination of renal function

Renal function, assessed with both Cockcroft–Gault equations and the simplified MDRD equation, was not different from the measured Ccr (Table 4). The correlation coefficient and the regression equation revealed only a moderate, although statistically significant, correlation for the MDRD equation compared with the measured Ccr. All other equations were not correlated with measured Ccr (Table 4). This is also illustrated by the scatter plot with a regression line for each equation *vs* Ccr (Figure 1a–d). There were also no significant correlations between Ccr and the different equations in subgroups of patients with Ccr above and below 80 ml/min/1.73 m^2.

Bias, as illustrated by the mean difference in the Bland and Altman analysis, was clinically negligible for the Cockcroft–Gault and MDRD equations [Cockcroft–Gault (actual body weight) = −6.2 ml/min/1.73 m^2, Cockcroft–Gault (predicted body weight) = 5.7 ml/min/1.73 m^2, MDRD = 11.2 ml/min/1.73 m^2 and simplified MDRD equation = −9.4 ml/min/1.73 m^2]. The differences between the respective equations and the Ccr, as illustrated by the $\pm$95% confidence interval in the Bland–Altman graphs, were substantial and clinically highly significant [Cockcroft–Gault (actual body weight) = −76.8 to 64.3 ml/min/1.73 m^2, Cockcroft–Gault (predicted body weight) = −67.8 to 79.1 ml/min/1.73 m^2, MDRD = −49.7 to 72.1 ml/min/1.73 m^2 and the simplified MDRD equation = −77.4 to 58.6 ml/min/1.73 m^2] (Figure 2a–d).

Table 3. Comparison of patients with a measured creatinine clearance (Ccr) of greater or lower than 80 ml/min/1.73 m^2

	Ccr >80 ml/min/1.73 m^2	Ccr <80 ml/min/1.73 m^2	*P*
Demographic data			
n	15 (53.6%)	13 (46.2%)	
Age	58 (46–66)	66 (49.5–71.5)	0.299
Gender (male)	10 (66.7%)	8 (61.5%)	0.778
Actual body weight (kg)	72 (65–82)	68 (66–87)	0.982
Predicted body weight (kg)	66 (58–73)	68 (55–72)	0.890
APACHE II score	17 (11–29)	22 (16–28)	0.263
Hospital admission preceding ICU stay	1 (6.7%)	3 (23.1%)	0.216
LOS[a] in ICU preceding study (days)	1 (1–2)	1 (1–2)	0.644
Renal data			
Serum creatinine (mg/dl)	0.73 (0.67–0.84)	0.84 (0.66–0.94)	0.433
1 h urine volume (ml)	80 (50–150)	60 (36–130)	0.127
Measured Ccr (ml/min/1.73 m^2)	120 (100–137)	60 (49–74)	<0.001
Urinary creatinine excretion (mg/24 h/1.73 m^2)	1317 (1143–1486)	680 (634–836)	<0.001
Urinary creatinine excretion (mg/kg/24 h)	20.4 (17.0–21.4)	10.6 (9.2–11.8)	<0.001
Associated organ dysfunction			
Vasoactive therapy	1 (6.7%)	6 (46.2%)	0.016
Mechanical ventilation	4 (26.7%)	9 (69.2%)	0.024

[a]LOS = length of stay.

Table 4. Comparison between measured creatinine clearance and equations for assessment of renal function

	Median (interquartile range)	*R* (*vs* urinary creatinine clearance)[a]	*P*	Regression analysis
Urinary creatinine clearance (ml/min/1.73 m^2)	86 (62.6–121.6)			
Cockcroft–Gault (abw[b]) (ml/min/1.73 m^2)	94 (75.3–116.2)	0.313	0.105	Y = 43.36 + 0.56 X
Cockcroft–Gault (pbw[c]) (ml/min/1.73 m^2)	80.9 (64.3–106.2)	0.312	0.106	Y = 14.84 + 0.70 X
MDRD (ml/min/1.73 m^2)	80 (62.3–94.3)	0.466	0.012	Y = 26.47 + 0.56 X
Simplified MDRD (ml/min/1.73 m^2)	100 (79.3–119.9)	0.366	0.055	Y = 39.45 + 0.73 X

Regression analysis according to Passing–Bablock: Y = equation for assessment of renal function, X = urinary creatinine clearance.
[a]*R* = Pearson correlation coefficient.
[b]abw = actual body weight before admission to the ICU.
[c]pbw = predicted body weight.

Discussion

In this group of recently admitted ICU patients with normal serum creatinine, the Ccr measured on a timed 1 h urine collection varied over a wide range and revealed unexpectedly low values (<80 ml/min/1.73 m^2) in 46.2% of the patients. These data therefore suggest that in recently admitted critically ill patients, serum creatinine is a less reliable tool to detect moderate renal dysfunction than currently accepted.

The most plausible explanation for the low sensitivity of serum creatinine for detection of renal insufficiency in critically ill patients is the depressed production of creatinine, as was suggested by the approximately one-third decrease in 24 h urinary creatinine excretion. Patients with a measured Ccr <80 ml/min/1.73 m^2 had an even more pronounced muscle loss, as evidenced by the low urinary creatinine excretion. This muscle loss was probably caused by protracted illness preceding ICU admission, as there was a trend that more patients in the low GFR group were hospitalized prior to ICU admission.

Serum creatinine is the result of generation, distribution and excretion of creatinine; a lower generation will therefore result in a lower serum concentration for the same GFR, if distribution and excretion remain the same. Serum creatinine is produced by non-enzymatic hydrolysis of creatine, the major sources of this creatine being the release from endogenous muscles and exogenous nutritional intake of meat. Muscle wasting will initially result in an increase in the serum creatinine level but, once the reduction in decreased muscle mass becomes more pronounced, there will be a decreased release of creatine from the muscles, and subsequently a decreased serum creatinine. The low levels of urinary creatinine excretion in our patients suggest that an important degree of muscle loss had occurred already, possibly even caused by catabolism preceding their

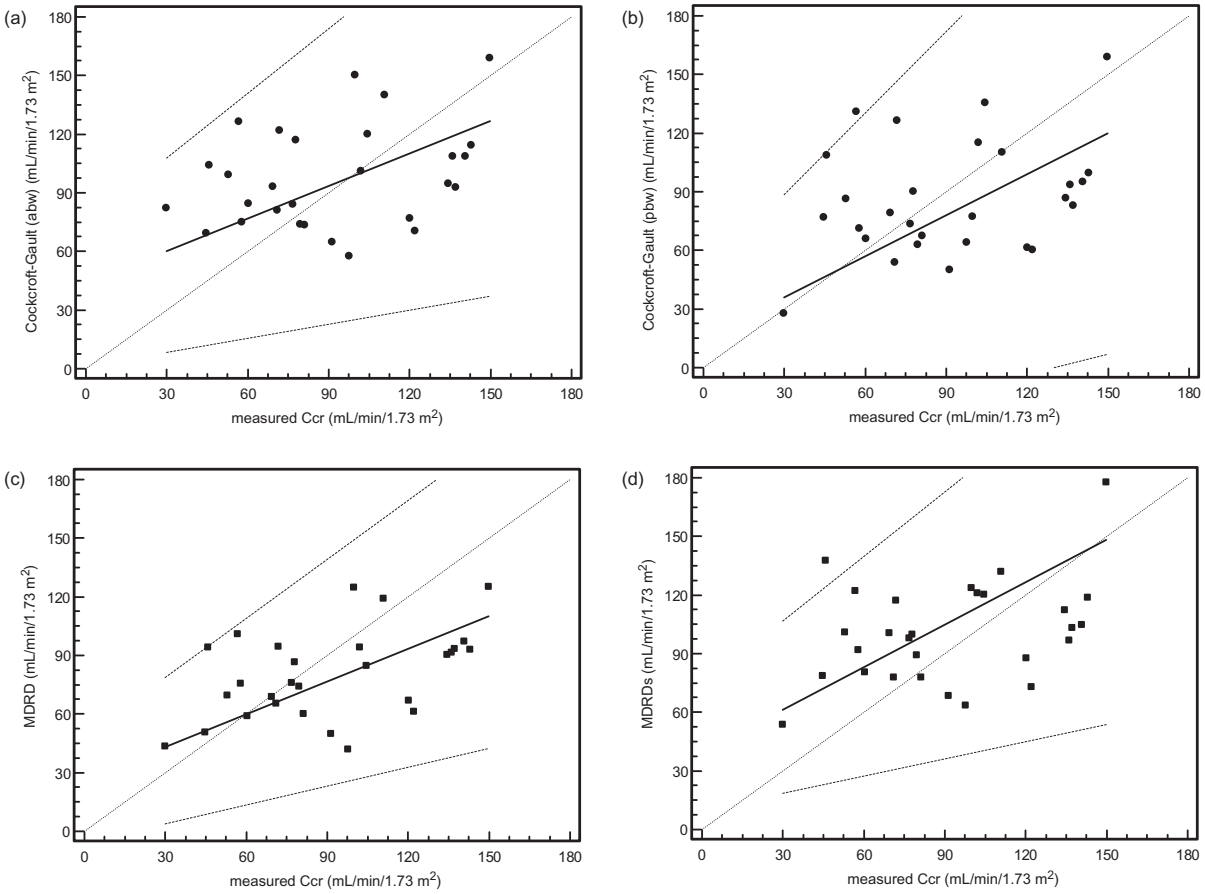

Fig. 1. Scatter plot with a linear regression line: various equations compared with measured creatinine clearance (Ccr): (**a**) Cockcroft–Gault calculated on actual body weight (abw) before ICU admission; (**b**) Cockcroft–Gault calculated on predicted body weight (pbw); (**c**) MDRD; and (**d**) simplified MDRD. The 95% confidence interval is indicated by the dashed lines.

ICU admission. Two other factors may have contributed further to the relatively low serum creatinine levels in proportion to the assessed renal function. The dietary intake of creatine was negligible as all study patients received artificial enteral and/or parenteral nutrition. In addition, creatine is also produced by the liver, and disturbed liver metabolism is often present in critically ill patients.

A higher proportion of patients in the group with Ccr $<80\,ml/min/1.73\,m^2$ were treated with vasoactive therapy and mechanical ventilation. Despite the fact that we selected patients who were haemodynamically stable, we cannot rule out that the low urinary creatinine excretion may also be a reflection of transient reductions in GFR associated with vasoactive therapy, blood pressure fluctuations and changes in rates of fluid administration.

There is a striking analogy of our findings with those obtained in patients with cirrhosis or quadriplegia [13,14]. In both patient groups, serum creatinine levels are lower for the same given GFR compared with a normal population, and reduction in muscle mass plays an important role in both conditions. Equations for assessment of renal function are also not valid for these patients.

It can be argued that we studied a relatively old patient population (median age 58 years), in whom a relatively lower muscle mass could already have been apparent. It is uncertain whether the same conclusions will hold for patients of a younger age. Nevertheless, it should be stressed that the age of the present population reflects the age of patients currently admitted to the ICU ward [15].

In addition, the Cockcroft–Gault equation, calculated either on actual body weight before admission or on predicted body weight, and the MDRD formulae did not correspond very stringently with measured Ccr. The MDRD formulae were derived from patients with elevated serum creatinine; the applicability to patients with normal serum creatinine levels is therefore unclear. In addition to this, all formulae were validated initially on populations of non-ICU patients in whom the specific factors that may influence the serum creatinine values in ICU patients probably did not have the same impact or did not even play a role. The same line of reasoning holds true for serum albumin and serum urea, both used in the MDRD formula, but not in the Cockcroft–Gault equation. Serum albumin levels can often be low in ICU patients, e.g. by dilution by fluid overload, by leakage of albumin into the extravascular

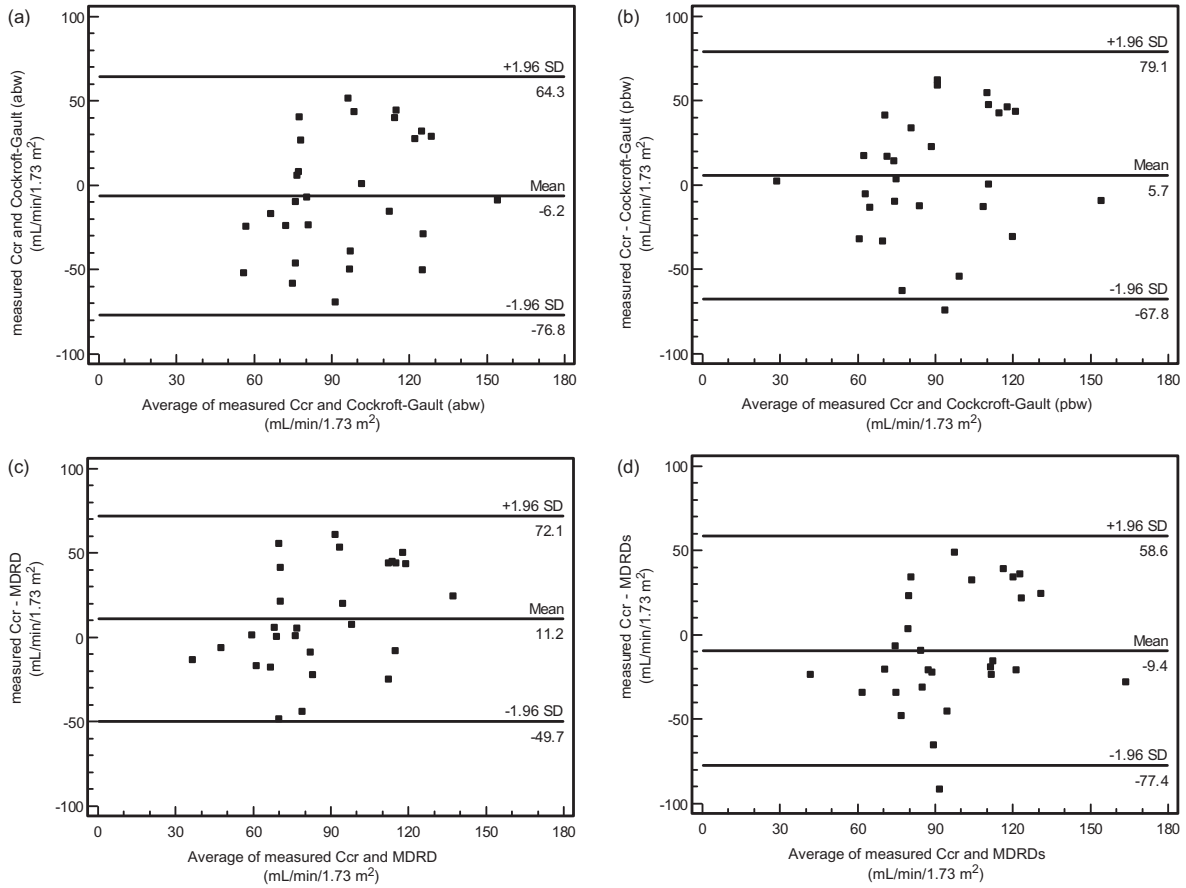

Fig. 2. Bland and Altman analysis of measured creatinine clearance (Ccr) compared with various equations for renal function: (**a**) Cockcroft–Gault calculated on actual body weight (abw) before ICU admission; (**b**) Cockcroft–Gault calculated on predicted body weight (pbw); (**c**) MDRD; and (**d**) simplified MDRD.

compartment as a consequence of a capillary leak syndrome, or by decreased production in the course of an inflammatory response. Serum urea in this population is subject to changes due to intravascular volume status, gastrointestinal haemorrhage and catabolism. Hence, serum creatinine, albumin and urea values could have been influenced by many variables not present in the original reference populations.

It might be a concern that a 1 h urine sample is not representative of the urine production during a 24 h period. However, it needs to be emphasized that the 24 h urine volume was comparable with the urine volume obtained after extrapolation of the 1 h urine volume to a 24 h urine volume.

An important practical implication of our study is that early recognition of ARF in patients with normal creatinine values on the basis of one single creatinine measurement may be suboptimal. Evaluation of renal function on the basis of a timed urinary clearance is the most direct method, if urine collections are obtained in a proper way, based on correct timing, and after emptying of the urine bladder. Assessments of renal function with the Cockcroft–Gault or the MDRD equations in our setting were not valuable alternatives.

Since the discussion for an appropriate definition for ARF is still ongoing [3,16,17], a definition of ARF should not be based only on a specific threshold value of serum creatinine. This is in agreement with the proposed definition of ARF by the Acute Dialysis Quality Initiative (ADQI) Working Group. This group proposes to use the change in serum creatinine and/or diminished urinary output as a threshold for the definition of ARF (http://www.adqi.net) [18]. Alternatively, one could also use other markers of glomerular filtration, e.g. cystatin C, a marker already available for routine use in some hospitals, or the kidney injury molecule-1 (KIM-1), a marker currently under investigation [19]. A meta-analysis has shown that cystatin C is superior to serum creatinine as a marker of renal function; however, information on the validity of cystatin C in critically ill patients is still scarce [20].

In conclusion, we found that in this cohort of critically ill patients studied within the first week of ICU admission, and with normal serum creatinine values, serum creatinine proved a very insensitive screening test for the early detection of renal dysfunction. The most probable explanation is that a decreased creatinine load resulted in a lower serum creatinine for a given GFR. The Cockcroft–Gault and the MDRD equations proved not acceptable as alternatives. Therefore, a timed urinary creatinine clearance

should be used to detect impaired renal function in critically ill patients with normal serum creatinine level.

Conflict of interest statement. None declared.

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