

StatSensor-i point-of-care creatinine analyzer may identify patients at high-risk of contrast-induced nephropathy

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Abstract. The current study assessed the accuracy of the StatSensor-i (STA) point-of-care creatinine analyzer prior to and following adjustment (offset correction) by linear regression scatter plots produced by the reference samples from patients and volunteers for detecting high risk of contrast-induced nephropathy in patients with an estimated glomerular filtration rate <45 ml/min/1.73 m². Blood samples were obtained from 233 consecutive outpatients scheduled for contrast-enhanced CT studies. Of the 233 patients, 123 patient samples were evaluated prior to adjustment and the other 110 following adjustment. Serum creatinine levels and estimated glomerular filtration rate were measured using the analyzer and compared with the values returned by laboratory tests. Analysis was with the paired t-test, the Pearson correlation coefficient and Bland-Altman plotting. The sensitivity, specificity, positive and negative predictive values (PPV, NPV), and accuracy for detecting patients with an estimated glomerular filtration rate <45 ml/min/1.73 m² were subsequently calculated. Mean serum creatinine levels measured with the analyzer were significantly higher than those returned by laboratory tests before ($P<0.0001$) and after adjustment ($P<0.01$). Following adjustment, the difference in serum creatinine values obtained with the STA analyzer and by laboratory methods did not exceed 0.3 mg/dl. Prior to adjustment, 9.7% of the samples were overdiagnosed as having an estimated glomerular filtration rate of <45 ml/min/1.73 m²; following adjustment, the overdiagnosis rate was 2.7%. The sensitivity, specificity, PPV, NPV and accuracy were 100, 89, 50, 100 and 90.2% before and 100, 96.3, 33.3, 100 and 96.4%

after adjustment, respectively. With the adjusted point-of-care creatinine analyzer, estimated glomerular filtration rate may be reliably evaluated in the radiology suite.

Introduction

Iodine contrast media (ICM) and gadolinium-based contrast agents (GBCA) are essential for diagnostic imaging studies performed to depict the vascular anatomy or to evaluate the blood flow following computed tomography (CT) and magnetic resonance imaging (MRI) studies, respectively. Contrast-induced nephropathy (CIN) is a major and common side effect of ICM use and nephrogenic systemic fibrosis (NSF) is a severe side effect of using GBCA (1,2).

CIN is defined as an absolute increase in serum creatinine (sCr) level of ≥ 0.3 mg/dl, a percentage increase in sCr of $\geq 50\%$, or a reduction in urine output (oliguria of <0.5 ml/kg/h for >6 h) within 48 h (1). The incidence of CIN following contrast-enhanced (CE)-CT has been reported as 2-12% (3). For some patients, CIN may result in the onset of severe renal failure, the need for dialysis, and increased length of hospitalization (3). In patients with severe renal failure, early renal replacement therapy may decrease mortality and the incidence of complications (4).

The symptoms of NSF include skin discoloration, swelling and pain (2). Some patients suffering from reduced joint movement due to skin thickening are forced to use a wheelchair (2). Determining the true incidence of NSF is difficult; however, ~1,600 cases were reported to the US Food and Drug Administration in 2012 (5). Symptomatic treatment with intensive physiotherapy and painkillers is important, however there is currently no specific treatment for NSF (6).

One proposed mechanism of CIN is that interactions of iodine and amino acids damage cell membranes, causing a direct toxic effect on renal tubular and vascular cells (7). Pre-existing chronic kidney disease is considered an independent risk of CIN (8). The pathogenesis of NSF is the slow excretion of GBCA in patients with severe renal impairment (2). Therefore, patients with a glomerular filtration rate (GFR) <45 ml/min/1.73 m² have a high risk of developing CIN and a GFR <30 ml/min/1.73 m² also puts patients at high risk for NSF (1,2). The estimated glomerular filtration rate (eGFR),

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calculated based on patient sex and age and the (sCr) level, is used in place of the GFR by the majority of institutions and used prior to CE-CT and MRI studies to identify patients at high risk of developing CIN and NSF. Outpatients with no recent eGFR data must wait for the sCr value to be returned by laboratory tests prior to undergoing CE-CT or CE-MRI, although in urgent situations, such as patients with suspected strangulated small bowel obstruction which requires the assessment of blood flow by CE-CT, renal function must be determined immediately (1-3).

The StatSensor-i (STA; Nova Biomedical, Waltham, MA, USA), a rapid, hand-held, commercially available point-of-care creatinine analyzer (Fig. 1), measures the sCr levels in blood samples in 30 sec. It is used to screen for chronic kidney disease (CKD) (9), adjusting doses of potentially toxic renal drugs whose administration requires renal function monitoring (10) and to monitor kidney transplant recipients (11). The instrument is also used for evaluating renal function in radiology suites (12-14). To manage the risk of CIN, the accuracy of eGFR values between 30 and 45 ml/min/1.73 m² is particularly important. The correlation of sCr and eGFR determined by laboratory tests and STA is currently unclear, although previous studies have reported an underestimation in sCr without offset collection (14).

The present study assessed the accuracy of the STA analyzer in the detection of patients with a high risk for CIN (eGFR <45 ml/min/1.73 m²) by comparing the values obtained prior to and following adjustment (offset correction) by linear regression scatter plots produced by the reference samples from patients and volunteers.

Patients and methods

Patients. The present retrospective study was approved by the institutional review board of Kohka Public Hospital Review Board (#334; Shiga, Japan). The requirement for informed consent was waived and the patient records and information were anonymized prior to analysis. The pre-adjustment study included 123 consecutive outpatients (74 males, 49 females, mean age 66.7±12.5 years) who underwent CE-CT at Kohka Public Hospital (Koka, Japan) between September 2011 and February 2012. The sCr level of the patients had not been assessed in the month preceding hospital admittance. In the post-adjustment study, 110 consecutive outpatients (62 males, 48 females, mean age 70.1±12.7 years) who underwent CE-CT at Kohka Public Hospital between June and November 2012, were enrolled. There were no exclusion criteria in this study.

Samples. All blood samples were taken in the radiology suite. Prior to CT, peripheral blood samples were obtained by fingertip puncture with a 28-gauge needle (LS Lancet; Nipro Corporation, Osaka, Japan) and assessed with the point-of-care STA analyzer. Cubital vein blood samples obtained with a 20- or a 22-gauge needle (Supercath; Medikit Co., Ltd., Tokyo, Japan) were collected into a blood-collecting vessel containing a blood coagulation accelerant, thrombin (Neotube; Nipro Corporation, Osaka, Japan). The venous samples were analyzed in the laboratory with a creatinine kit (L-type Wako CRE EM; Wako Pure Chemical Industries, Ltd., Osaka, Japan) that applies the enzymatic method in an automatic analyzer

(BioMajesty™ JCA-BM2250; JEOL Ltd., Tokyo, Japan). The eGFR was calculated using a converting equation, as follows: $eGFR = 194 \times (sCr)^{-1.094} \times (age)^{-0.287} \times (-0.739 \text{ for females})$ published by the Japanese Society of Nephrology-Chronic Kidney Disease Initiatives (15). It is necessary to multiply the coefficient (0.739) for females because muscle mass and creatinine values are lower in females than in males.

Adjustment of the STA analyzer. A total of 3 healthy male volunteers (mean age: 41.1±9.0 years) were recruited at Kohka Public Hospital to serve as a control group. All volunteers gave prior informed consent and venous blood samples were collected into the blood-collecting vessel containing thrombin. In the volunteer samples, sCr was measured with the STA and the BM2250 analyzer, which adds 1.0 mg/dl of a creatinine spiking solution (Sigma-Aldrich; Merck KGaA, Darmstadt, Germany) to obtain samples with a creatinine concentration of 2.0-3.0 mg/dl. The volunteer data are presented in Fig. 2 (Fig 2B). For adjustment, linear regression scatter plots were produced for the other 69 samples from patients (40 males, 29 females, mean age 67.2±12.9 years) who underwent CE-CT in the department of radiology in Kohka Public Hospital admitted between March and May 2012, and for samples from the three volunteers that were assayed with the STA and the BM2500 analyzer. Samples that returned sCr values between 0 and 2.0 (n=68), and 0 and 3.0 mg/dl (n=102) were used to adjust the values obtained with the STA analyzer.

On scatter plots with linear regression from sCr <2.0 the values measured with the STA and the BM2250 analyzer exhibited a significant correlation ($r=0.830$, $y=1.105x+0.080$; $P<0.0001$; Fig. 1A). The correlation for samples with sCr <3.0 mg/dl was also significant ($r=0.933$, $y=1.112x+0.095$; $P<0.0001$; Fig. 1B). Therefore, in accordance with a previous study (14), the results obtained with the STA analyzer were adjusted by applying an offset correction on the basis of the slope ($1/1.112=0.899$) and the intercept ($-0.095/1.112=-0.086$) obtained from samples with an sCr value of <3.0 mg/dl was selected, as the correlation was stronger compared with the samples from sCr <2.0 mg/dl.

Statistical analysis. The two sets of sCr and eGFR values obtained with the BM2250 and the STA analyzer were compared using the paired t-test. Linear regression scatter plots of sCr and eGFR values returned by STA and by BM2250 were constructed and assessed by Pearson's correlation coefficient. The association between the two datasets was evaluated by Bland-Altman plot analysis. The results of statistical analysis performed on samples assessed prior to and following STA adjustment were compared. The sensitivity, specificity, positive and negative predict value (PPV, NPV) and the accuracy for detecting patients at high-risk for CIN (eGFR <45 ml/min/1.73 m²) were calculated. For the statistical tests, Microsoft Office Excel 2010 for Windows was used (Microsoft Corporation, Redmond, WA, USA). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Prior to adjustment, the mean sCr level was significantly lower when measured with the BM2250 compared with the STA

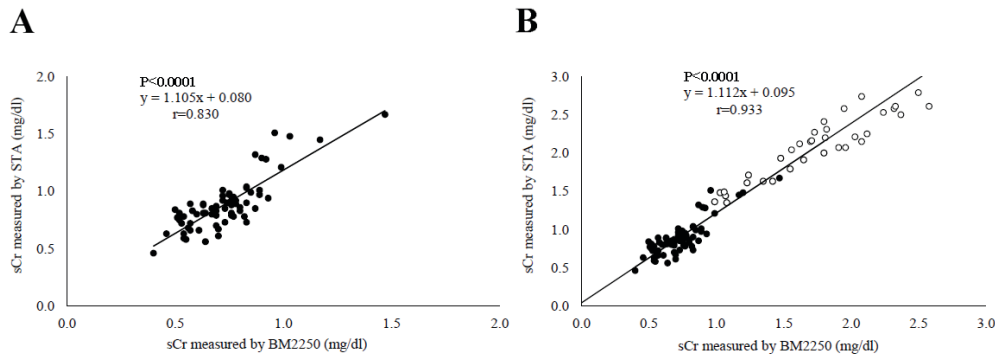


Figure 1. Scatter plots with linear regression in ranges of sCr (A) <2.0 and (B) <3.0 mg/dl. Black dots, data from patient samples; white dots, data from volunteers; sCr, serum creatinine; STA, StatSensor-i; BM2250, BioMajesty™ automatic analyzer.

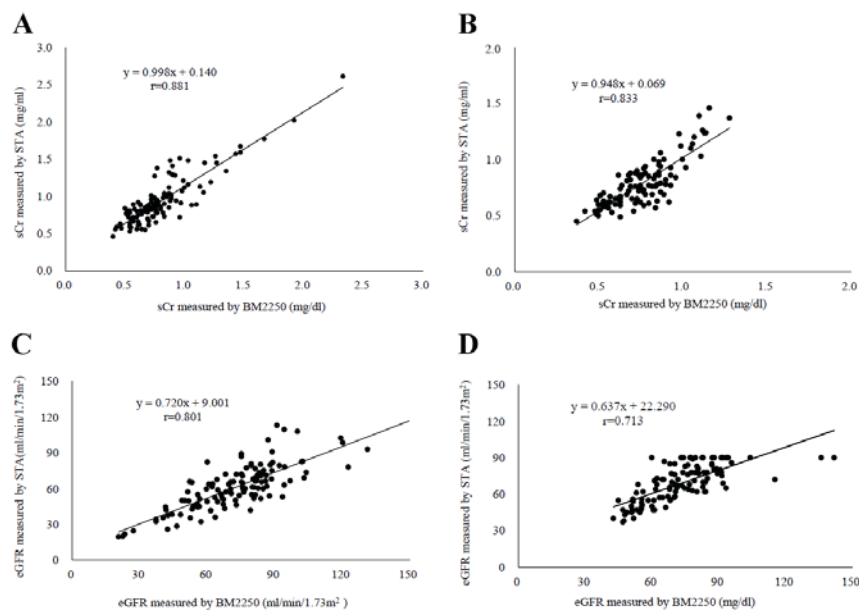


Figure 2. Linear regression scatter plots of sCr and eGFR measured with the STA and the BM2250 analyzer prior to and following adjustment. The sCr value (A) prior to ($r=0.881$, $y=0.998x+0.140$) and (B) following ($r=0.833$, $y=0.948x+0.069$) adjustment. The eGFR value (C) prior to ($r=0.801$, $y=0.720x+9.001$) and (D) following ($r=0.713$, $y=0.637x+22.290$) adjustment. All $P<0.0001$. sCr, serum creatinine; eGFR, estimated glomerular filtration rate; STA, StatSensor-i; BM2250, BioMajesty™ automatic analyzer.

analyzer (0.80 ± 0.29 , range 0.75-2.33 mg/dl vs. 0.94 ± 0.33 , range 0.46-2.61 mg/dl; $P<0.0001$; Table I). The mean eGFR calculated from the BM2250 data was higher than the mean eGFR obtained from STA data (75.3 ± 21.4 , range 20.7-155.5 ml/min/1.73 m² vs. 61.6 ± 19.2 , range 19.5-113.5 ml/min/1.73 m²; $P<0.0001$; Table II). Following adjustment, the mean sCr measured with the BM2250 analyzer was significantly lower than the sCr obtained with the STA instrument (0.76 ± 0.18 , range 0.37-1.28 mg/dl vs. 0.79 ± 0.21 , range 0.45-1.46 mg/dl; $P<0.01$; Table II) and the mean eGFR was significantly higher when calculated with the BM2250, rather than STA data (72.7 ± 17.2 , range 42.7-142.0 ml/min/1.73 m² vs. 68.6 ± 15.3 , range 37.0-90.0 ml/min/1.73 m²; $P<0.001$; Table II). Consequently, adjustment decreased the measurement error of sCr and eGFR measured with the BM2250 and the STA because the P-value increased following adjustment.

In the assessment of Pearson's correlation coefficient, there was a significant correlation between sCr values obtained

with the STA and the BM2250 analyzer prior to ($r=0.881$, $y=0.998x+0.140$; $P<0.0001$; Fig. 2A) and following adjustment ($r=0.833$, $y=0.948x+0.069$; $P<0.0001$; Fig. 2B). These correlation coefficient revealed the adjustment improved the correlation sCr values obtained with the BM2250 and with the STA. There was a significant correlation between the eGFR measured prior to ($r=0.801$, $y=0.720x+9.001$; $P<0.0001$; Fig. 2C) and following adjustment ($r=0.713$, $y=0.637x+22.290$; $P<0.0001$; Fig. 2D). The correlation coefficient of eGFR decreased in spite of improvements to the correlation sCr value following adjustment, as eGFR is affected by sCr and also sex and age. Based on the above results, the adjustment reduced the measurement error of sCr and eGFR and improved the sCr correlation values obtained with the BM2250 and the STA.

Pre-adjustment Bland-Altman plots revealed a difference in sCr levels of >0.3 mg/dl in 13 of the 123 patient samples (10.6%); the eGFR differed by >15 ml/min/1.73 m² in 50 samples (40.7%; Fig. 3A and B). Following the adjustment, there

Table I. Differences in serum creatinine level between BM2250 and STA prior and following adjustment of STA.

Variables	BM2250	STA	P-value
Prior to adjustment			
Mean \pm SD (mg/dl)	0.80 \pm 0.29	0.94 \pm 0.33	<0.0001
Range (mg/dl)	0.75-2.33	0.87-2.61	
Following adjustment			
Mean \pm SD (mg/dl)	0.76 \pm 0.18	0.79 \pm 0.21	<0.01
Range (mg/dl)	0.37-1.28	0.45-1.46	

STA, StatSensor-i; BM2250, BioMajesty™ automatic analyzer; SD, standard deviation.

Table II. The difference of estimated glomerular filtration rate (ml/min/1.73 m²) between BM2250 and STA prior and following adjustment of STA.

Variables	BM2250	STA	P-value
Prior to adjustment			
Mean \pm SD (ml/min/1.73 m ²)	75.3 \pm 21.4	61.6 \pm 19.2	<0.0001
Range (ml/min/1.73 m ²)	20.7-155.5	19.5-113.5	
Following adjustment			
Mean \pm SD (ml/min/1.73 m ²)	72.7 \pm 17.2	68.6 \pm 15.3	<0.001
Range (ml/min/1.73 m ²)	42.7-142.0	37.0-90.0	

STA, StatSensor-i; BM2250, BioMajesty™ automatic analyzer; SD, standard deviation.

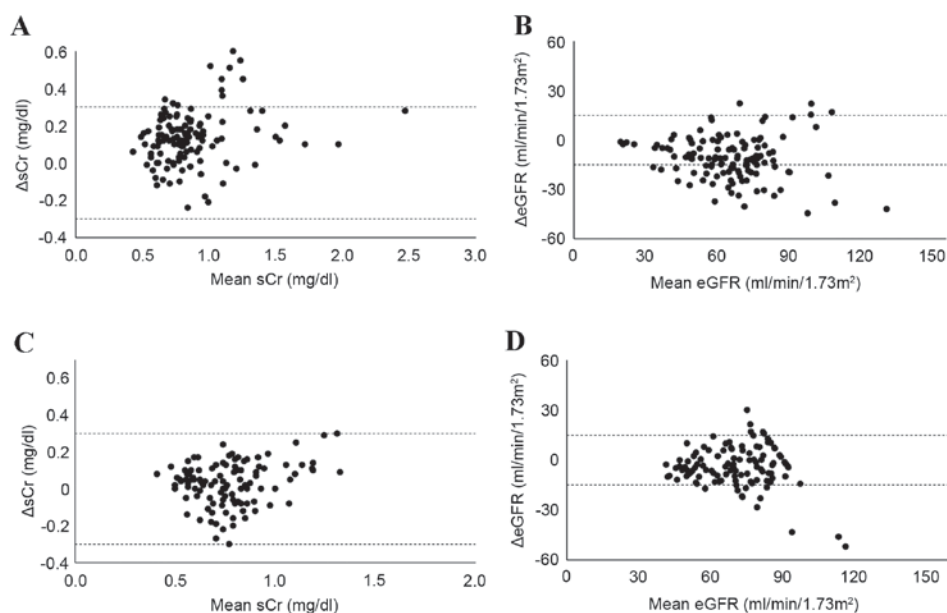


Figure 3. Bland-Altman plots of differences between sCr and eGFR values measured with the STA and the BM2250 analyzer prior to and following adjustment. The value of (A) sCr and (B) eGFR prior to adjustment. The value of (C) sCr and (D) eGFR following adjustment. Δ sCr=(creatinine value measured by STA)-(creatinine value measured by BM2250); Δ eGFR=(eGFR measured by STA)-(eGFR measured by BM2250); sCr; serum creatinine; eGFR, estimated glomerular filtration rate; STA, StatSensor-i; BM2250, BioMajesty™ automatic analyzer.

was no difference >0.3 mg/dl in the sCr values. Differences exceeding 15 ml/min/1.73 m² in the eGFR were only detected among 17 of the 110 patient samples (15.5%; Fig. 3C and D).

Of the 123 pre-adjustment samples, 24 (19.5%) had an eGFR <45 ml/min/1.73 m² according to the STA analyzer; 12 of 24 samples assessed with the BM2250 analyzer exhibited

eGFR values of ≥ 45 ml/min/1.73 m². Therefore, the STA analyzer overdiagnosed 12 of the 123 unadjusted samples (9.8%).

Following adjustment, 5 of 110 samples (4.5%) exhibited eGFR < 45 ml/min/1.73 m²; in 2 of 5 samples eGFR ≥ 45 ml/min/1.73 m². Consequently, 3 out of 110 samples (2.7%) were overdiagnosed by the STA analyzer. The sensitivity, specificity, PPV, NPV and accuracy for the detection of patients at high risk for CIN (eGFR < 45 ml/min/1.73 m²) were 100, 89, 50, 100 and 90.2% prior to and 100, 96.3, 33.3, 100 and 96.4% following adjustment, respectively.

Discussion

According to the National Kidney Foundation, ~13% of adults and 44% of individuals >65 years old have CKD, defined as a GFR < 60 ml/min/1.73 m² (16,17) and its incidence has markedly increased over the past 30 years (18,19). Therefore, to avoid side effects such as CIN or NSF, a renal function test to measure GFR should be performed in patients with CKD, to determine the appropriateness of using contrast agents for imaging studies. The majority of institutions substitute the eGFR, calculated on the basis of the patient gender and age and sCr levels, for the GFR, as GFR is a more complex measurement for which 24 h urine collection is necessary. The European Society of Urogenital Radiology guidelines state that in high-risk patients, a GFR < 45 ml/min/1.73 m² and risk factors for CIN (such as dehydration, diabetic nephropathy, congestive heart failure, recent myocardial infarction, peri-procedural hypotension, low hematocrit level, age over 70, concurrent administration of nephrotoxic drugs, and acute renal failure) justifies the transfusion of 0.9% saline or 1.26% sodium bicarbonate, a reduction in the contrast medium and measurement of the GFR 48-72 h following administration of iodine contrast agents (1). As a general rule, ICM should not be used in patients with a GFR < 30 ml/min/1.73 m² as the incidence of CIN is inversely proportional to the eGFR.

In patients scheduled for CT whose eGFR > 45 ml/min/1.73 m², a standard dose of ICM is typically administered. If their eGFR is between 45 and 30 ml/min/1.73 m², a reduced dose (70-80%) of ICM is injected and a drip of 500 ml saline is administered. When the eGFR is < 30 ml/min/1.73 m², an alternative modality is used, such as ultrasound, MRI or unenhanced CT studies. To determine whether it is necessary to reduce the dose of ICM and to stop the administration of ICM for the prevention of CIN, radiologists must ascertain whether the eGFR is > 45, between 45 and 30, or < 30 ml/min/1.73 m². Measurement errors around an eGFR between 30 and 45 ml/min/1.73 m² affect the CT protocol, that is, a reduction of ICM dose or alternative imaging methods are required (3). Therefore, as accuracy in this eGFR range (sCr range 1.0-2.5 mg/dl) is essential, the samples used for adjustment in the present study had to include the sCr (range 1.0-2.5 mg/dl). However, strict accuracy may not be required in patients with sCr > 3.0 mg/dl suggestive of high-grade CKD, as measurement errors in such patients tend not to affect the protocol used for CE-CT studies (3). Therefore, the current study did not use samples with an sCr value > 3.0 mg/dl. As the correlation coefficient was improved in samples with a

sCr of < 3.0 mg/dl, compared with a sCr of < 2.0 mg/dl, the present study performed adjustment in samples with an sCr value < 3.0 mg/dl.

Whereas sCr overestimation may lead to the decision to stop the administration of ICM for CT studies, its underestimation and the decision to administer the usual contrast dose may elicit CIN in patients with CKD. It has previously been reported that the STA analyzer was highly sensitive in determining whether renal function was normal or impaired and that without adjustment, it may underestimate sCr levels (9,14). The present study demonstrates that it overestimates sCr with and without adjustment.

Prior to adjustment, the sCr value was > 0.3 mg/dl in 10.6% of the 123 patient samples; the measurement error for the eGFR exceeded 15 ml/min/1.73 m² in 40.7%. Following adjustment, the error range in sCr measurements remained < 0.3 mg/dl and the measurement error for the eGFR fell from 40.7 to 15.5%. Measurement errors of > 15 ml/min/1.73 m² were observed in patients with an eGFR > 60 ml/min/1.73 m². They did not lead to a change in the protocol for CE-CT in the current study.

Discrepancies between the STA and the BM2250 analyzer with respect to identifying samples with an eGFR < 45 ml/min/1.73 m² also decreased following adjustment. With the STA analyzer, 9.8% of the samples were overdiagnosed prior to adjustment and 2.7% were overdiagnosed following adjustment. As adjustment increased the specificity and accuracy for the detection of patients at high risk of CIN (eGFR < 45 ml/min/1.73 m²), the STA analyzer is useful for the evaluation of renal function in patients scheduled for CE-CT.

The current study had a number of limitations: 33/102 samples used for adjustment were obtained from healthy volunteers, as there were few patients with sCr levels ≥ 2.0 mg/dl. Patient samples were drawn from a fingertip, whereas volunteer samples were collected from a vein for measurement by STA. This may have resulted in an improved correlation coefficient for samples with sCr value < 3.0 mg/dl. The present study did not evaluate other laboratory values, although glucose interference (≥ 200 mg/dl) results in higher sCr levels (20) and red blood cell, plasma water fractions and hematocrit explain 91.8% of differences in sCr values obtained with the STA analyzer (21). Finally, the present study could not ascertain whether the eGFR was < 30 ml/min/1.73 m² both prior to and following adjustment, as few samples were available from patients with an eGFR < 30 ml/min/1.73 m².

In conclusion, appropriate adjustment reduced measurement errors in values obtained with the STA analyzer. Adjustment of the STA instrument is essential for the evaluation of renal function prior to administration of contrast media. The point-of-care creatinine analyzer (STA) may alert individuals to the danger of CIN in high-risk patients.

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