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Estimated glomerular filtration rate using a point of care measure of creatinine in patients with iohexol determinate GFR

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ABSTRACT

Introduction: Determination of creatinine and estimation of Glomerular Filtration Rate (GFR) rapidly before injection of contrast media provides early detection of high-risk patients for acute kidney failure. Hence, a rapid point-of-care (POC) device (result in 30 s) allowing creatinine measurement and eGFR could be of interest. To validate this method, we considered a population referred for measuring GFR.

Methods: Iohexol plasma clearance was used to measure GFR. For each subject, enzymatic creatinine was quantified with two different devices: in plasma with the Roche Cobas analyzer and in capillary blood with the Nova Biomedical POC device. Both values of creatinine were used in the CKD-EPI equation for estimated glomerular filtration rate (eGFR). eGFR using POC was compared to eGFR using Cobas and to mGFR by Passing Bablok regression, calculation of bias, precision and accuracy (or concordance) within 30%. Also, we calculated the rate of discrepant staging (eGFR > 60 or ≤ 60 when mGFR is actually ≤60 and > 60) with both creatinine methods.

Results: 120 subjects (52 ± 13 years, 49% of women) were included. Mean mGFR was 77 ± 27 mL/min/1.73m^2 with 29 patients presenting mGFR < 60 mL/min/1.73m^2. Passing- Bablok regression comparing eGFR obtained with the POC and the Cobas was: $eGFR_{POC} = -0.1$ (95% CI: −7.4; 3.0) + 1.06 (95% CI: 1.00; 1.15) x $eGFR_{COBAS}$. Mean bias was 3.7 ± 14.1 mL/min/1.73m^2. Concordance within 30% was 82%. Compared to mGFR, Passing-Bablok with POC was: $eGFR_{POC} = -11.5$ (95% CI: −22.9; −0.7) + 1.15 (95% CI: 1.02; 1.29) x mGFR. Mean bias was 0.1 ± 17.6 mL/min/1.73m^2. Accuracy within 30% was 81%. Between $eGFR_{COBAS}$ and mGFR, mean bias was −3.7 ± 12.5 mL/min/1.73m^2. Accuracy within 30% was 95%. With POC (and Cobas), 3.3% (0.8%) of patients would have been considered with GFR > 60 mL/min/1.73m^2 whereas mGFR it was ≤60 and 10% (9.2%) of them would have been considered with GFR ≤60 mL/min/1.73m^2 when mGFR was > 60.

Conclusion: Creatinine measured with the POC has an acceptable performance when used with the CKD-EPI equation to estimate GFR. Its ability to detect GFR < 60 mL/min/1.73m^2 is not significantly different from the classical Roche assay. StatSensor Creatinine (Nova Biomedical) can be used for GFR screening before contrast media injection.

1. Introduction

The administration of iodinated contrast media is of great value to the practice of medical imaging, but it is not without risks. One major risk is contrast induced acute kidney injury (CI-AKI). CI-AKI is defined as an increase of serum creatinine concentration of > 0.3 mg/dL (26.5 μmol/L) or a 50% rise from baseline within 48–72 h after receiving intravascular contrast agents [1], and has been associated with increased morbidity and mortality [2].

There are well-known risk factors associated with CI-AKI such as diabetes, advanced age or cardiovascular disease [2]. Among these risk factors, the presence of pre-existing chronic kidney disease (CKD) is one

Abbreviations: GFR, glomerular filtration rate; eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; POC, point of care; CI-AKI, contrast induced acute kidney injury

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of the most important [3]. Guidelines are available for the management of such patients with pre-existing CKD [4]. Because of the risk and available preventive strategies, the European Society of Urogenital Radiology and other guidelines recommend to measure serum creatinine and calculate the evaluation of the Glomerular Filtration Rate (eGFR) before injection of contrast agent in all patients [5].

However, knowing the renal status of patient might be challenging. Many patients do not have a recent kidney function test in their medical records or this result is not always easily and/or quickly available. The turnaround time for serum creatinine testing performed in a central laboratory can sometimes be lengthy and up to several hours [6]. Because of these practical difficulties and potential delay in processing patients through the radiology pathway, determination of eGFR could be omitted.

A quick determination of creatinine using a Point of Care (POC) device would facilitate the assessment of kidney function and potentially reduce the risk of CI-AKI. One such point of care device is StatSensor Creatinine (Nova Biomedical, Waltham, MA) which is a low maintenance handheld POC device that can be used for monitoring creatinine/eGFR directly in capillary and venous whole blood (1.2 μL) providing a result within 30 s.

Previous analytical and comparison studies have shown that this device could be comparable to classical laboratory methods [7,8]. The use of POC devices as a tool for monitoring renal function in different patient settings has been previously reported [9,10]. However, all studies until now have compared creatinine and eGFR results to creatinine measured in the laboratory. The plasma clearance of iohexol (a non-ionic contrast medium) is considered as a reference method for measured GFR (mGFR) [11]. We compared eGFR obtained with the POC creatinine method with results of mGFR in addition to our routine method for eGFR.

2. Materials and methods

2.1. Patient enrolment and specimen collection

This prospective observational study included adult patients undergoing renal function assessment at the CHU Liege Hospital between 2014 and 2018. Whole blood specimens were obtained by venipuncture and collected into tubes containing lithium heparin anti-coagulant. Capillary blood was collected in order to perform POC testing, which is designed for hospital use as it allows traceability of strips lot number, patients and healthcare providers. All measurements were obtained on the same day.

2.2. Creatinine measurement methods and calculation of eGFR

Capillary blood specimens were tested directly using StatSensor Creatinine (Nova Biomedical Waltham, MA) before iohexol injection. The POC device is based on an enzymatic amperometric method employing an enzyme cascade reaction (CV = 4.9–11.2%). Lithium heparin whole blood venous specimens were centrifuged to obtain plasma for testing on the Cobas 8000 (Roche Diagnostics). The laboratory analyzer is using an enzymatic determination of creatinine (creatininase/sarcosine oxidase based method, CV = 1.2–1.8%). From the laboratory and POC creatinine values, eGFR was calculated using the Chronic Kidney Disease and Epidemiology equation (CKD-EPI) [12].

2.3. Measurement of GFR

Iohexol was administered as Omnipaque® 240 mg I/mL (Amersham Health (South Plainfield, NJ, USA). Venous blood samples were drawn at five time points (120, 180, 240, 300 and 360 min) after the injection of 5 mL of iohexol. The blood was allowed to stand for 30–60 min before being centrifuged at 1000–1300 *g* for 10 min. Plasma concentrations of iohexol were determined by high performance liquid chromatography with a diode array detector (HPLC-DAD) as previously described [13]. A curve was obtained expressing iohexol elimination, and GFR was then calculated according to the Brochner-Mortensen method. All mGFR results were indexed for body surface area.

2.4. Statistical methods

Data were analyzed using MedCalc software (version 17.5.5, Belgium). Bland-Altman plots were used to show the agreement between mGFR and eGFR. Passing-Bablok regression was used for method comparison. Then, bias (the difference between eGFR- mGFR, systematic error) were calculated. Precision was evaluated by the standard deviation of the bias (random error). We calculated the accuracy within 30%, i.e. the percentage of eGFR results being within +/− 30% of mGFR. When eGFR results were compared between themselves, we used the term concordance within 30%. Difference in accuracy/concordance between eGFRs was tested with the exact McNemar test. The threshold of statistical significance was set at $p = .05$. Finally, we also tested the ability of eGFR to classify subjects/patients in the same CKD stage as mGFR, using the usual threshold of 60 mL/min/1.73m^2.

3. Results

3.1. Patient demographics

One hundred and twenty patients were enrolled in the study including 61 men and 59 women (Table 1). The mean age was 52.5 ± 13.1 years. The mean mGFR was 77 ± 27 mL/min/1.73m^2, ranging from 15 to 131 mL/min/1.73m^2. The average eGFR was 73 ± 28 mL/min/1.73m^2, ranging from 15 to 157 mL/min/1.73m^2 using Roche Cobas and 77 ± 30 mL/min/1.73m^2, ranging from 15 to 165 mL/min/1.73m^2 using the POC. Twenty-nine subjects (24.2%) had a measured GFR lower than 60 mL/min/1.73m^2.

3.2. Correlation between StatSensor and Cobas creatinine measurements

There was a good correlation between creatinine results obtained with POC and the laboratory method ($r = 0.93$; $P < .0001$). Passing-Bablok regression analysis did not show significant difference between the methods: Creatinine (POC) = 1.02 x Creatinine (Cobas) – 0.07 (95% CI of 0.93 to 1.15 and − 0.20 to 0.020, for slope and intercept, respectively) (Fig. 1).

3.3. Comparison of eGFR with POC and Cobas

Passing-Bablok regression was as followed: eGFR (POC) = 1.06 x eGFR (Cobas) -0.13 (95% CI of 1.00 to 1.15 and − 7.38 to 3.00, for slope and intercept, respectively). The mean absolute bias for POC eGFR compared to laboratory eGFR results was 3.7 ± 14.1 mL/min/1.73m^2 (Fig. 1) with a mean percent bias of 6.5 ± 21.2%. Concordance within 30% was calculated at 82%.

Table 1
Demographics of 120 adult patients undergoing GFR measurement included in the study.

Parameter	Male	Female	Total
Distribution	61	59	120
Age range years (MEAN ± SD)	48.0 ± 12.9	57.0 ± 11.8	52.5 ± 13.0
Weight kg (MEAN ± SD)	86.1 ± 20.4	68.1 ± 16.5	77.2 ± 20.6
Height cm (MEAN ± SD)	176.7 ± 8.3	162.5 ± 6.8	169.7 ± 10.4
Creatinine mg/dL (COBAS)	1.38 ± 0.7	0.98 ± 0.4	1.18 ± 0.6
(Mean ± SD AND Range)	0.42–4.17	0.58–2.83	0.42–4.17
MGFR mL/min/1.73M^2	77.6 ± 28.9	75.3 ± 24.0	76.5 ± 26.5
(Mean ± SD AND range)	15.0–129.0	21.0–131.0	15.0–131.0

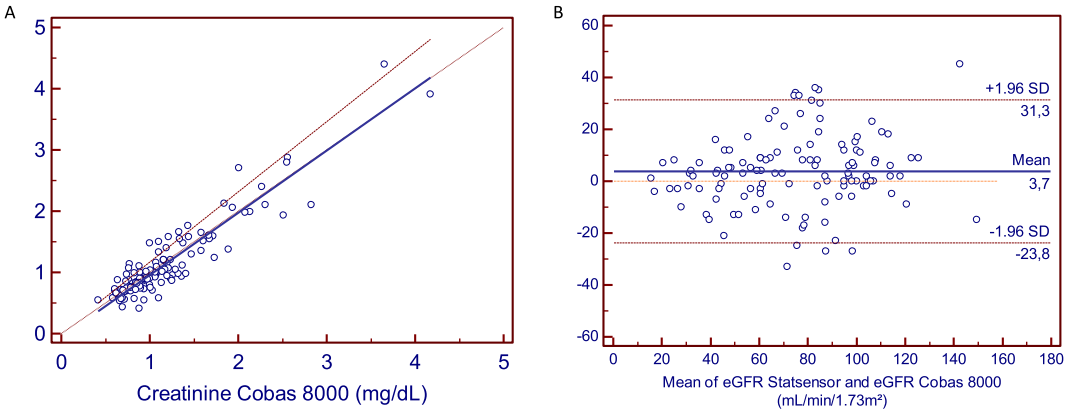

Fig. 1. (A) Passing-Bablok regression analysis of the comparison of creatinine determination using the POC (Statsensor) and the Cobas 8000 analyzer. Creatinine (Statsensor) = 1.02 x Creatinine (Cobas) - 0,07. (B) Bland-Altman chart of the eGFR (mL/min/1.73m^2) obtained with the POC (Statsensor) in comparison to the Cobas 8000.

3.4. Comparison of eGFR with mGFR

Compared to mGFR, Passing-Bablok regression obtained with POC was as followed: eGFR (POC) = 1.15 x mGFR -11.5 (95% CI: 1.02 to 1.29 and − 22.9 to −0.7 for slope and intercept, respectively). Mean bias was 0.1 ± 17.6 mL/min/1.73m^2 (Fig. 2). Accuracy within 30% was calculated at 81%. Between eGFR (Cobas) and mGFR, Passing-Bablok regression was: eGFR (Cobas) = 1.05 x mGFR - 6.22 (95% CI: 0.97 to 1.14 and − 13.14 to −0.32 for slope and intercept, respectively). Mean bias was −3.7 ± 12.5 mL/min/1.73m^2 (Fig. 2). Accuracy within 30% was calculated at 95%, which is statistically different and better than results with the POC (P = .0017).

3.5. Ability of eGFR results to correctly classify patients (< or > 60 ml/min/1.73m^2)

The concordance of POC eGFR and Cobas eGFR with mGFR for categorizing CKD stage was 58% (70/120) (Fig. 3) and 63% (76/120), respectively. Those results did not differ statistically (P = .5091). Of the twenty-nine patients with mGFR < 60 mL/min/1.73m^2 twenty seven were identified by POC eGFR (93.1%) and twenty eight (96.6%) by laboratory eGFR. Twelve (13%) of patients using the POC and sixteen (18%) with Cobas would have been considered with GFR ≤60 mL/min/1.73m^2 when it was > 60. Thirteen of the seventeen patients with mGFR < 45 mL/min/1.73m^2 were identified by the POC (76.5%) and twelve by the routine analyzer (70.6%).

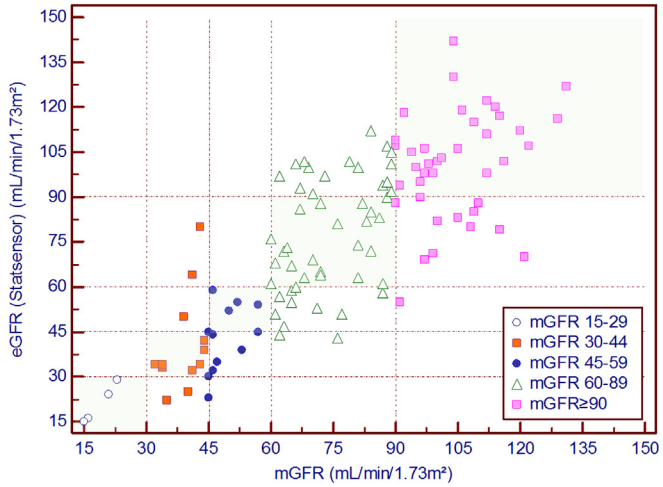

Fig. 3. Concordance of eGFR (mL/min/1.73m^2) obtained with Statsensor with mGFR (mL/min/1.73m^2) for categorizing CKD stages.
Zone of concordance calculated at 58% (70/120).

4. Discussion

Screening of kidney function prior to contrast media injection is recommended in the context of CI-AKI. We evaluated a POC device, the Statsensor Creatinine (Nova Biomedical) which has been evaluated previously [14]. We compared eGFR obtained with the POC to results of

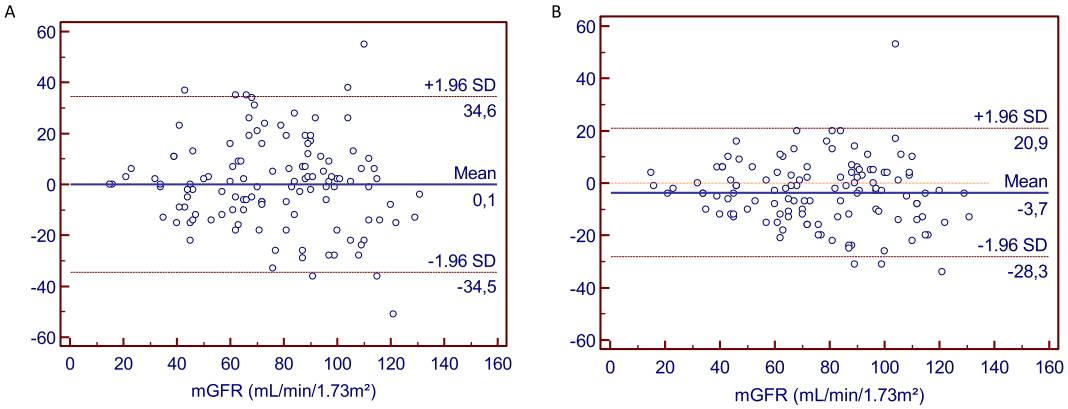

Fig. 2. (A) Bland-Altman chart of the eGFR (mL/min/1.73m^2) obtained with the POC (Statsensor) in comparison to mGFR (mL/min/1.73m^2). (B) Bland-Altman chart of the eGFR (mL/min/1.73m^2) obtained with the Cobas 8000 in comparison to mGFR (mL/min/1.73m^2).

mGFR in addition to our routine method for eGFR. Our data showed that the POC device is suitable for GFR screening and low GFR detection before contrast media injection, even if its global performance to estimate GFR is slightly lower than creatinine measured by the laboratory.

Radiology guidelines based on ESUR recommendations advise to delay the imaging procedure, if possible without harm to the patient, until an estimation of the renal function is available. Patients with an eGFR < 45 mL/min/1.73 m^2 are classified as at risk of CI-AKI. Determination of creatinine levels and GFR estimation before contrast media injection allows early detection of at-risk patients for CI-AKI. Identifying those patients can lead to consider alternative imaging method without iodine-based contrast agent or preventive hydration.

In clinical practice, because of organizational issues, GFR screening before contrast agent injection could be bypassed. POC capillary blood creatinine/eGFR testing provides an opportunity for immediate assessment of patient kidney function prior to administration of iodinated contrast medium. Previous studies showed that POC based creatinine determinations may be accurate for clinical use, in diagnosis and monitoring patients with acute kidney injury, especially in intensive care units [15,16]. POC creatinine testing has also shown feasibility in radiology environment [17]. Shorter turnaround time for the test results could reduce waiting time and improve patients management in interventional radiology, cardiology as well as emergency departments [17,18].

It is also described in the literature that the risk of CI-AKI increases with the elevation of the ratio of total contrast volume to eGFR [20], and POC creatinine testing before imaging has been reported to significantly reduce the contrast media volume injected [21].

Capillary samples taken by fingerprick play a role in the analytical error and imprecision in the POC testing. Insufficient analytical validity of the POC compared to standardized methods in the central laboratory has been described before [10]. According to the Ricos Database for quality requirements, desirable specification for inaccuracy of the creatinine was calculated at 3.96% [22]. Compared to our routine method, mean bias was calculated at 3.7% in our study which is in agreement with Ricos requirements. A comparable bias of 3.56 has recently been reported by Snaith and colleagues [23] where a comparison was established between the Statsensor and the same routine method than ours (Roche Cobas 8000). At the opposite, Bogaert and colleagues reported a poorer performance. Just as in our study, the POC was challenged against a Roche analyzer but unlike us, some of their samples were spiked whole blood [24].

When compared to the iohexol determinate GFR, POC performance seems valid for the screening of high-risk patients because its performance for GFR CKD classification is comparable to the routine method. However, POC devices for GFR screening must be integrated into the workflow in the healthcare units they are available, otherwise the clinical utility is limited. Some authors have reported an overestimation of creatinine measured with POC which can overestimate rates of CI-AKI [25] and therefore lead to lengthy delays or even inappropriate medical care. Further studies assessing usefulness and clinical consequences of a GFR estimation using a POC device are needed.

To our knowledge no assessment has been made yet comparing eGFR derived from whole blood capillary and whole blood venous point of care creatinine measurements with the iohexol determinate GFR. This is a strength of the present study since this method is a gold-standard for GFR measurement [26]. Other strengths of the study include prospective design and simultaneous collection of samples.

Our study has several limitations. First of all, it is a single center study involving a relatively small number of patients, especially CKD patients. Second, subjects undergoing iohexol measure of GFR are not random patients. They are usually organ donors, children or patients for whom the clinician had doubtful eGFR using creatinine determination. As a result, a selection bias might exist. However no children were included in our study population. Thus, the effect of extreme hematocrit levels was not tested, which might be considered as another limitation of the study. Nevertheless, in the present study the objective of implementing creatinine POC device was to prevent CI-AKI and target an adult population. In case clinicians are unsure about a result in a patient known for an extreme hematocrit level, a verification by the routine method in plasma or serum which remains available 24 h a day, 7 days a week can be requested.

5. Conclusion

Creatinine measured with the POC has an acceptable performance when used with the CKD-EPI equation to estimate GFR. Its ability to detect GFR < 60 mL/min/1.73m^2 is not significantly different from the classical Roche assay. Using the POC for renal function screening, we have shown that we would miss few patients with a renal function impairment, which is the most important goal in the context of radiology. StatSensor (Nova Biomedical) can be used in the GFR screening before contrast media injection. However, because of higher analytical imprecision compared to the central laboratory method, the POC device seems only suitable specific contexts where creatinine results are urgently needed.

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