Cystatin C may be better than creatinine for digoxin dosing in older adults with atrial fibrillation

Tomáš Šálek1,2 | Martin Vodička3 | Martin Gřiva4,5

1Department of Clinical Biochemistry and Pharmacology, The Tomas Bata Hospital in Zlín, Zlín, Czech Republic
2Department of Biomedical sciences, Medical Faculty, University of Ostrava, Ostrava, Czech Republic
3Pharmacy, The Tomas Bata Hospital in Zlín, Zlín, Czech Republic
4Department of Internal Medicine, The Tomas Bata Hospital in Zlín, Zlín, Czech Republic
5Faculty of Medicine, Palacký University Olomouc, Olomouc, Czech Republic

Correspondence
Tomáš Šálek, Department of Clinical Biochemistry and Pharmacology, The Tomas Bata Hospital in Zlín, Havlíčkova nábřeží 600, 76275 Zlín, Czech Republic. Email: tsalek@seznam.cz

Abstract

Background: Patients taking digoxin are older with high probability of having low muscle mass, and current clinical practice in digoxin dosing relies only on estimated glomerular filtration rate from serum creatinine (eGFRcrea). The aim of the study is to compare eGFRcrea and estimated glomerular filtration rate from serum cystatin C (eGFRcys) in older adult patients with atrial fibrillation (AF) overdosed with digoxin.

Methods: A total of 80 consecutive patients overdosed with digoxin and 33 controls with AF from Department of Internal Medicine were included in the prospective observational study. The median of age of participants was 81 years in both the overdosed and the control group. The eGFRs were calculated using The Chronic Kidney Disease Epidemiology (CKD-EPI) equations using standardized methods for serum creatinine and cystatin C measurement.

Results: The median (IQR) of eGFRcrea was higher than that of eGFRcys (45 mL/min/1.73 m² (35-59) vs 30 (21-38), respectively; P < .0001) in overdosed patients. The median (IQR) of eGFRcrea was higher than that of eGFRcys (61 mL/min/1.73 m² (49-72) vs 40 (30-56), respectively; P < .0001) in control group of patients. Serum predose digoxin concentration in overdosed patients was inversely associated with eGFRcys (ρ = −0.26, P < .05).

Conclusion: Physicians should consider GFR when changing digoxin dosing. eGFRcys would lead to lower digoxin doses and thus prevent overdose.

Keywords
atrial fibrillation, creatinine, cystatin C, digoxin, estimated glomerular filtration rate, glomerular filtration

1 | INTRODUCTION

Digoxin is used in patients with atrial fibrillation and heart failure usually in combination with other drugs such as an angiotensin-converting enzyme inhibitors and beta-blockers. It has positive an inotropic effect on heart muscle. It is eliminated from the body by glomerular filtration rate (GFR). Digoxin has narrow therapeutic reference range. Therapeutic drug monitoring (TDM) is recommended to achieve the targets of 0.5-0.8 µg/L before the dose. Serum digoxin concentrations above 1.2 µg/L are associated with increased mortality.

The typical maintenance dose is 0.125-0.250 mg once daily, but the daily dose can be much lower in patients with decreased GFR and in case of drug interactions.
Knowledge of GFR is very important for digoxin dosing. Serum creatinine is the most common marker of GFR in clinical practice. eGFRcrea is routinely calculated by CKD-EPI equation, but the serum creatinine concentration depends on muscle mass. The majority of patients taking digoxin are elderly patients who lost their muscles with aging and chronic illnesses such as cancer. Patients who lost their muscle mass have falsely lower serum creatinine concentration and falsely higher eGFRcrea. It may lead to overdosing with drugs excreted by kidneys.

Cystatin C is the alternative marker of GFR which is not dependent on muscle mass. It is produced by all nucleated cells at constant rate. Cystatin C is not also ideal marker and can be affected in patients receiving corticosteroids or having thyroid gland dysfunction. eGFR is calculated by CKD-EPI equation for cystatin C. Combined CKD-EPI equation using both creatinine and cystatin C is also available. Both creatinine and cystatin C measurement have been analytically standardized with traceability of measurement to international reference methods and standards. Patients taking digoxin are older with high probability of having low muscle mass, and our hypothesis is that eGFRcys may be more appropriate for digoxin dose adjustment than eGFRcrea. Serum digoxin concentration also reflects GFR because it is eliminated by GFR.

Appropriate drug dosing is very important for patient safety, and it is the reason why we performed the prospective observational study which compare eGFRcys and eGFRcrea in patients overdosed with digoxin.

2 | MATERIALS AND METHODS

2.1 | Patients

A total of 80 consecutive inpatients overdosed with digoxin and 33 patients in control group with serum digoxin concentration within therapeutic reference ranges from Department of Internal Medicine were included to the prospective observational study which lasted from 2016 to April 2020.

The overdosed group study participants were 67 to 103 years old with median of age 81 years. There were 20 males and 60 females in overdosed group.

The control group participants were 67-103 years old with median of age 81 years. The control group consisted of 19 females and 14 males. All patients in both groups had atrial fibrillation.

All patients had the same dose of 0.125 mg once daily and were taking digoxin longer than 1 month. The reference ranges for serum digoxin concentrations were 0.5-1.2 µg/L. The overdosing was defined as serum digoxin concentration above 1.2 µg/L before next planned dose administration.

2.2 | Laboratory tests

Serum digoxin, creatinine, and cystatin C were measured from the same blood sample before next planned dose on Abbott Architect analyser.

Digoxin measurement was performed by immunoturbidimetric assay. Creatinine was determined by enzymatic spectrophotometric test traceable to international standard reference material NIST SRM 967.

Cystatin C was measured by particle enhanced immunoturbidimetric method. Method is standardized to international standard DA ERM 471. eGFRcrea and eGFRcys were calculated according to CKD-EPI equations.

2.3 | Statistical methods

All calculations were performed by MedCalc software version 17.4 (MedCalc Software bvba).

The D’Agostino-Pearson test was performed to assess the normal distribution. The normal distribution was rejected. Data were expressed as median and interquartile range. We used Spearman’s rank correlation coefficient for association analysis between eGFR methods and serum digoxin concentration. Differences of eGFRsin overdosed patients were tested by the Wilcoxon test for paired samples.

Mann-Whitney test for independent samples was used for comparison of eGFRs between overdosed patients and patients in control group.

The Bland-Altman plot was used for visualization of differences between eGFRcrea and eGFRcys results in overdosed patients, which cannot be visualized by correlation analysis. The values of P < .05 were considered statistically significant.

The study was approved by The Ethics committee of Tomas Bata Hospital in Zlín, Czech Republic and performed according to the Declaration of Helsinki. The informed consent was obtained from all patients.

3 | RESULTS

The median (range) of age in control group was no higher than age in overdosed patients (81 years (59-92) vs 81 (67-103), respectively; P = .50).

Clinical characteristics of overdosed patients are shown in Table 1.

The median (IQR) of predose digoxin concentration in overdosed patients was 1.67 µg/L (1.40-2.04). The lowest value was 1.23 µg/L, and the highest value was 3.01 µg/L.

The median (IQR) of predose digoxin concentration in control group was 0.77 µg/L (0.70 - 0.97). The lowest value was 0.57 µg/L, and the highest value was 1.14 µg/L.

The median (IQR) of eGFRcrea was higher than that of eGFRcys in overdosed patients (45 mL/min/1.73 m² (35-59) vs 30 (21-38), respectively; P < .0001). The median (IQR) of eGFRcrea was higher than that of eGFRcys in control group of patients (61 mL/min/1.73 m² (49-72) vs 40 (30-56), respectively; P < .0001).

\[ eGFR_{crea} > eGFR_{cys} \text{ in overdosed patients} \]

\[ eGFR_{cys} < eGFR_{crea} \text{ in control group} \]

\[ P < .0001 \]
The median (IQR) of eGFRcrea in control group was higher than eGFRcrea in overdosed patients (61 mL/min/1.73 m² (49-72) vs 45 (35-59), respectively; \(P = .0009\)).

The median (IQR) of eGFRcys in control group was higher than eGFRcys in overdosed patients (40 mL/min/1.73 m² (30-56) vs 30 (21-38), respectively; \(P = .0006\)).

The Spearman rank correlation coefficients between eGFRcrea, eGFRcys, and serum digoxin concentration in overdosed patients are shown in Table 2.

The differences between eGFRcrea and eGFRcys in overdosed patients are shown in Figure 1.

### TABLE 1  Clinical characteristics of overdosed patients

| Variable                                      | Number of patients |
|----------------------------------------------|--------------------|
| Atrial fibrillation                          | 80                 |
| Hypertension                                 | 69                 |
| Diabetes mellitus                            | 43                 |
| Coronary artery disease                      | 55                 |
| Heart failure                                | 68                 |
| Treatment with digoxin                       | 80                 |
| Treatment with agents blocking the renin-angiotensin-aldosterone system | 60 |
| Treatment with beta-blockers                 | 57                 |
| Treatment with calcium channel blockers      | 17                 |
| Treatment with furosemide                    | 63                 |
| Treatment with statins                       | 18                 |
| Anticoagulation treatment                    | 63                 |
| Antiplatelet treatment                       | 7                  |

### TABLE 2  Correlation table

| Digoxin | eGFRcrea \(^{a}\) | eGFRcys \(^{b}\) |
|---------|-------------------|-----------------|
| Correlation coefficient \(^{c}\) | -0.20 | -0.26 |
| \(P^{**}\) | .08 | .02 |
| \(n^{d}\) | 80 | 80 |

| eGFRcrea | Correlation coefficient | 0.76 |
|---------|-------------------------|------|
| \(P^{*}\) | P < .0001 |
| \(n\) | 80 | 80 |

| eGFRcys | Correlation coefficient | 0.76 |
|---------|-------------------------|------|
| \(P^{*}\) | P < .0001 |
| \(n\) | 80 | 80 |

\(^{a}\) Estimated glomerular filtration rate from serum creatinine.

\(^{b}\) eGFRcys—estimated glomerular filtration rate from serum cystatin C.

\(^{c}\) Spearman’s rank correlation coefficient.

\(^{d}\) n—number of participants.

\(^{**}\) P the level of significance.

The median (IQR) of eGFRcrea in control group was higher than eGFRcrea in overdosed patients (61 mL/min/1.73 m² (49-72) vs 45 (35-59), respectively; \(P = .0009\)).

The median (IQR) of eGFRcys in control group was higher than eGFRcys in overdosed patients (40 mL/min/1.73 m² (30-56) vs 30 (21-38), respectively; \(P = .0006\)).

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### DISCUSSION

In this study, we compared eGFRcrea and eGFRcys in geriatric patients with AF and increased predose level of digoxin.

We showed that median of eGFRcrea was higher than eGFRcys in both the overdosed and the control group. The Bland-Altman plot visualized this large systematic difference (bias).

The large cross-sectional study by Legrand et al found a trend towards increasing differences between eGFRcrea and eGFRcys estimates with increasing age due to muscle mass loss. The study included 2532 participants from a cohort of community-dwelling older adults aged from 60 to 93 years.\(^{10}\) It is consistent with our main results of lower eGFRcys compared to eGFRcrea in both older people overdosed with digoxin and control group.

Cystatin C does not depend on muscle mass. Discordant results between eGFRcrea and eGFRcys are likely to be frequent in many subgroups of elderly patients. Wang et al also reported lower eGFRcys compared to eGFRcrea in veterans receiving anticoagulant treatment.\(^{11}\) Lower eGFRcys compared to eGFRcrea was found in the cohort of 112 oncology patients before cisplatin therapy by Šálek et al.\(^{12}\) Iversen et al reported significant discrepancies in eGFR and CKD classification when switching between CKD-EPI eGFR equations in acutely hospitalized elderly patients. Switching from a creatinine-based equation to its corresponding cystatin C-based equation resulted in lower GFR estimates, and these differences were larger than in community-dwelling older populations.\(^{13}\) These studies support our results due to muscle wasting in all three situations.

The dose of digoxin should be adjusted according to GFR. We need a reliable method for determining GFR in clinical practice. The recommendations for estimation of GFR have changed substantially over the past years.

Since 1886, creatinine has been available as a marker of kidney function. Creatinine was determined by nonspecific Jaffé reaction but this method measured creatinine with positive bias and is not currently recommended.\(^{14}\)

Since 2005, creatinine measurement has been standardized. Enzymatic determination is recommended for clinical laboratories. But Volpi et al\(^{15}\) discussed that even after standardization, serum creatinine always reflects muscle mass which is reduced in elderly patients due to aging and chronic diseases. These patients have overestimated GFR from serum creatinine, and it may explain our results with higher eGFRcrea. Muscle wasting is also associated with progression of CKD.\(^{16}\)

There are increasing number of reports on advantages of cystatin C for TDM of renally excreted drugs such as amikacin\(^{17}\) and vancomycin.\(^{18}\) Cystatin C may be more reliable marker of GFR than creatinine because it does not depend on muscle mass, body surface area, diet, sex, and age. It is also very important in acute care medicine.\(^{19}\)

Serum digoxin concentration also reflects GFR. Hallberg and colleagues found inverse correlation between serum digoxin concentration and cystatin C.\(^{20}\) We found similar value of inverse correlation between serum digoxin concentration and cystatin C. It also
slightly supports our hypothesis that eGFRcys is superior to eGFRcrea for digoxin dosing. The association between serum digoxin concentration and eGFRcys is relatively low. It may be explained by the fact that a serum digoxin concentration is affected by a volume of distribution.

Šálek et al described that patients overdosed with gentamicin in acute care setting had lower both eGFRcrea and eGFRcys compared to control group of patients with gentamicin within reference ranges. Similar relations of eGFRcrea and eGFRcys were found in patients overdosed with digoxin and in controls in this study.

The limitation of this work is that we did not use inulin clearance as the gold standard of GFR measurement. Another limitation lies in the small number of patients.

We did not perform any assessment of muscle mass. Vinge et al showed that creatinine is a much better marker for muscle mass than for GFR in persons with normal GFR. Nishida et al described that muscle mass might be estimated by using the creatinine/ (cystatin C × body weight) ratio. It means that serum creatinine concentration strongly depends on skeletal muscle mass.

In summary, physicians should consider GFR when changing digoxin dosing. eGFRcys was lower in both the overdosed and the control group. eGFRcys would lead to lower digoxin doses and thus prevent overdose. Cystatin C may be better marker for digoxin dosing than creatinine because patients who take digoxin are usually older adults with high probability of sarcopenia. The discrepancy between eGFRcrea and eGFRcys may indicate that muscles were lost. Combined equation eGFRcrea + cys may be the best solution.

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