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ORIGINAL ARTICLE

Effect of serum creatinine difference between the Jaffe and the enzymatic method on kidney disease detection and staging

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ABSTRACT

Background. Serum creatinine (SCr), mainly determined by the Jaffe or an enzymatic method, is the central marker to assess kidney function. Deviations between these two methods may affect the diagnosis and staging of acute kidney injury (AKI) and chronic kidney disease (CKD).

Methods. The results of the first parallel SCr measurement (Jaffe and enzymatic method) of adult in- and outpatients in the same serum sample at the University Hospital Essen (Essen, Germany) between 2020–2022 were retrospectively evaluated. A Bland–Altman plot with 95% limits of agreement (LoAs) was used to assess the difference between the Jaffe and the enzymatic SCr (eSCr) method. We used the 2009 Chronic Kidney Disease Epidemiology Collaboration equation for determination of estimated glomerular filtration rate (eGFR) according to the Kidney Disease: Improving Global Outcomes guidelines.

Results. A total of 41 144 parallel SCr measurements were evaluated. On average, Jaffe SCr was 0.07 mg/dl higher than eSCr (LoA −0.12; 0.25 mg/dl). In 19% of all cases there was a different CKD stage when comparing eGFR between both SCr methods, of which 98% resulted in a more severe CKD stage determined with Jaffe SCr. In 1.6% of all cases Jaffe SCr was ≥0.3 mg/dl higher than eSCr.

Conclusion. The present study showed that methods of SCr measurement may affect both the diagnosis and staging of AKI and CKD. This must be taken into account when interpreting measurements of renal function in everyday clinical practice, but also when planning and comparing studies on renal diseases. One should therefore stay with one method for SCr measurement, preferably with the enzymatic method.

LAY SUMMARY

Serum creatinine (SCr) is the central marker to assess kidney function, mainly determined by a Jaffe or an enzymatic method. Deviations between these two methods may affect the diagnosis and staging of acute kidney injury (AKI) and chronic kidney disease (CKD). The results of 41 144 parallel SCr measurements (Jaffe and enzymatic method) of

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adult in- and outpatients in the same serum sample at the University Hospital Essen (Essen, Germany) between 2020 and 2022 were retrospectively evaluated. A difference in CKD staging was observed in 19% of all cases, with a more severe grade using the Jaffe method to estimate glomerular filtration rate (GFR). In 1.6% of all cases Jaffe SCr was ≥0.3 mg/dl higher than enzymatic SCr. The present study showed that SCr measurement methods may affect both the diagnosis and staging of AKI and CKD. If data from the two methods are used to generate estimated GFR equations, this could inject additional error into the equation model/algorithm. This must be considered when interpreting measurements of renal function in everyday clinical practice, but also when planning and comparing studies on renal diseases.

Keywords: acute kidney injury, chronic kidney disease, creatinine, enzymatic method, Jaffe method

INTRODUCTION

Kidney diseases have a major effect on global health, as >850 million patients worldwide have kidney diseases, which are a direct cause of global morbidity and mortality and an important risk factor for cardiovascular diseases [1]. Thus, early detection and correct staging of kidney diseases are essential to begin an appropriate therapy in order to reduce patients' morbidity and mortality [2–4].

In current international guidelines by the Kidney Disease: Improving Global Outcomes (KDIGO) group, serum creatinine (SCr) is the central marker to assess kidney function and to grade the severeness of AKI and CKD [5, 6]. SCr can be measured via different methods. Besides the gold standard isotope-dilution mass spectrometry (IDMS), there are alkaline picrate (Jaffe) assays and enzymatic assays that are used in automated platforms in clinical laboratories. A variety of reagents for determining Jaffe SCr and measuring instruments from different suppliers are available. In general, enzymatic assays are known to be less biased compared with Jaffe standardized reference material and less susceptible to interference (e.g. bilirubin, glucose and some drugs like metamizole), but Jaffe assays are still widely used. This could have something to do with decreased reagent costs for the Jaffe method compared with the enzymatic method and that the turnaround time is usually faster for the Jaffe method. In the last 2 decades, Jaffe SCr measuring methods have been gradually standardized [6–8]. But even with the enzymatic method, there can be interference, e.g. from catecholamines like dopamine or dobutamine or in patients with a monoclonal gammopathy [26–28].

Even small deviations between Jaffe and enzymatic SCr (eSCr) may affect the resulting estimated glomerular filtration rate (eGFR) and thus the diagnosis and staging of CKD. A precise description of the laboratory methods used in a study is often lacking, and the reporting of CKD prevalence is heterogeneous among current studies [7]. Whether the difference between standardized Jaffe and eSCr is of clinical relevance is controversially discussed in the literature: several studies concluded that any of the above-mentioned interferences are clinically not relevant [9–11]. On the other hand, some studies have reported serious differences between Jaffe and eSCr measurement resulting in clinically meaningful differences in the eGFR and also CKD staging and the authors demanded that Jaffe SCr should no longer be used to generate more reliable GFR estimates [12–16]. Since the difference between Jaffe and eSCr measurement results is probably small, a large study population is necessary to investigate a possible difference and determinants of the differences. This has not been sufficiently done previously. Furthermore, there is growing knowledge that differences between these two SCr measurement methods might impact the diagnosis of AKI [17–19].

The aim of this study was to investigate the difference between Jaffe SCr and eSCr in a comprehensive cohort of outpatients and inpatients in several medical specialties and to investigate to what extent a possible difference between the results of the measurement methods affects the diagnosis and the staging of AKI and CKD.

MATERIALS AND METHODS

Study design

The results of the first measurement with the Jaffe and eSCr method in the respective same serum sample of adult patients at the University Hospital Essen, Essen, Germany between 2020 and 2022 were retrospectively evaluated. Both SCr measurements were performed at the same time point. All SCr measurements were analysed in the Department of Clinical Chemistry of the University Hospital Essen. Jaffe SCr was determined with the same IDMS traceable method via correlation of patient samples and reference material SRM967 from the National Institute of Standards and Technology (NIST) using Atellica measurement systems (Atellica 930 analyser, Atellica CH Crea_2 assay, Siemens Healthcare Diagnostics, Marburg, Germany) throughout the study period. The eSCr was determined by using the same IDMS traceable method and Atellica measurement systems. The assay is also traceable to NIST SRM967.

Analyses of the coefficient of variation have been performed for every month of the study period to handle analytical sensitivity differences using three differently concentrated creatinine control solutions (L1–L3). For confirmation of a linear behaviour, dilution series were established for both enzymatic and Jaffe creatinine. This was done with two patient serum samples (samples 1 and 2). Sample 1 had a creatinine concentration of ≈12 mg/dl and sample 2 had a creatinine concentration of ≈1.5 mg/dl. The concentrations of both samples were within the initial measurement range of the assays of 0.15–30.0 mg/dl (Jaffe creatinine) and 0.10–30 mg/dl (enzymatic creatinine), respectively. The Atellica CH system diluent was used for the dilution series. Three replicates were created for each dilution. The mean values were then calculated from the measured values of the replicates. The expected values were obtained by calculation starting from the measured value of the undiluted sample with the respective dilution factor. For the Jaffe method, the compensation of −0.3 mg/dl was additionally taken into account here. To assess the linearity, the recovery (%) was calculated. Then the linearity was checked by means of the Calibration Verification/Linearity (CVL) program as recommended by the College

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of American Pathologists. Recoveries should be in the range of 80–100%. The maximum deviation for the evaluation of linearity was set at 15%. Cut-offs for haemolysis, icterus and lipemia (HIL) were set as described in the manufacturer's manual for the two assays.

All patients were—for the purpose of this study—assumed to actually have CKD, so only one eGFR value per patient was used for diagnosis and staging of CKD, without using data on albuminuria for complete CKD staging, as these data or further clinical data were not available. The eGFR was used as a marker of renal function and was determined using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for SCr and the 2012 CKD-EPI equation for SCr and cystatin C, respectively, without adjusting for race, since in our hospital >99% of patients are Caucasians and, in addition to this, the ethnic correction factor proposed for African Americans should not be used for individuals of African origin living in Europe [6, 20, 21, 23, 29, 30]. Cystatin C was measured via immunoturbidimetry (Atellica measurement systems, Siemens Healthcare Diagnostics). In addition, for adults >70 years of age, the BIS1 equation was applied, and for all patients, the European Kidney Function Consortium (EKFC) eGFR equation was applied [22, 31, 32].

One criterion to define AKI according to the current KDIGO guideline is an increase in SCr of ≥0.3 mg/dl within 48 hours [5]. To imitate a possible effect of a switch of SCr methods on the detection of AKI, we evaluated all SCr results with a difference between Jaffe SCr and eSCr ≥0.3 mg/dl within the same serum sample, as these two values could also be generated in two different measurements within 48 hours; e.g. first, an outpatient SCr measurement with the Jaffe method and an SCr measurement with an enzymatic method after hospital admission or, as a second example, two measurements in two different hospitals when transferring a patient.

Statistical analysis

Frequency distributions and measurements of central tendency and variability were analysed to describe the study population. A Bland–Altman plot was used to determine the SCr difference between the measurement methods (Jaffe versus enzymatic method). Kappa values were used to evaluate the agreement between the classification of CKD stages [33]. All statistical analyses and graphical evaluations were performed with GraphPad Prism version 9.4 (GraphPad Software, San Diego, CA, USA) and SAS version 9.4 (SAS Institute, Cary, NC, USA).

Ethics approval

The study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The study was approved by the local ethics committee of the University of Duisburg-Essen (20-9501-BO).

RESULTS

Study population characteristics

Samples from all departments of the University Hospital Essen were evaluated (Supplementary Table 1). A total of 41 144 parallel SCr measurements were evaluated. This included 62% outpatients, 33% inpatients and 5% patients receiving intensive care. A total of 52% of the patients were male and the mean age was 69 years (range 18–107, median 74). The majority of the samples came from internal medicine (42%), followed by the emergency department (25%) and surgery department (13%).

Impact of the measurement method on SCr

The overall mean SCr was 1.26 mg/dl with the Jaffe method (median 0.97 mg/dl) and 1.20 mg/dl with the enzymatic method (median 0.90 mg/dl) (Supplementary Table 2). On average, SCr determined with the Jaffe method was 0.07 mg/dl higher than SCr determined with the enzymatic method. Ninety-five percent of the differences in SCr between the two measurement methods fell in the range of −0.12 mg/dl and 0.25 mg/dl (Table 1). The difference between the two SCr measurement methods for all measurements is visualized in a Bland–Altman plot (Fig. 1) and separately for all CKD stages (Supplementary Figs. 9–20). The largest average difference between the two SCr measurement methods was in patients ≥70 years of age and outpatients, both 0.07 mg/dl (Table 1).

Impact of the measurement method on eGFR

The overall mean eGFR was 67.2 ml/min/1.73 m^2 with the Jaffe method (median 68.1 ml/min/1.73 m^2) and 71.8 ml/min/1.73 m^2 with enzymatic method (median 75.3 ml/min/1.73 m^2) (Supplementary Table 3). On average, the eGFR difference is −4.6 ml/min/1.73 m^2. Ninety-five percent of the differences in eGFR between the two SCr measurement methods fell in the range of −14.6 ml/min/1.73 m^2 and 5.3 ml/min/1.73 m^2 (Table 2).

Our stratified analyses showed that the largest average difference was detected in females and the lowest average difference was in patients receiving intensive care. The average eGFR difference was slightly higher in outpatients than in inpatients (Table 2). The eGFR difference between the two SCr measurement methods for all measurements is visualized in a Bland–Altman plot (Fig. 2) and separately for all CKD stages (Supplementary Figs. 21–32).

Impact of the measurement method on diagnosis and staging of CKD

The study population included patients in all CKD stages (Supplementary Table 4a, b). The SCr difference, and thus the difference in eGFR, due to the two different measurement methods had an impact on the diagnosis and staging of CKD. There were upgrading (less severe CKD stage) and downgrading (more severe CKD stage) effects with a switch of CKD stage when using the Jaffe or eSCr method for determining eGFR with the CKD-EPI equation in 19% ($n = 7751$) of cases. Among these 7751 disagreements of CKD stage, 99.7% were disagreements between adjacent CKD stages. The largest number of different CKD classifications was between G1/G2 (28%) and G3a/G3b (24%) (Tables 3–5, Supplementary Table 4). We found a kappa value of 0.74 [95% confidence interval (CI) 0.737–0.747]. The presence or absence of kidney disease depended on the SCr method used in 7% of all cases (Table 6). Of all patients with CKD stage G3a according to eSCr, 22.2% had CKD stage G3b or higher according to the corresponding Jaffe SCr.

Following the KDIGO guideline, we further evaluated all patients with an eGFR of 45–59 ml/min/1.73 m^2. We identified 2759 patients who had CKD stage G2 according to eSCr but G3a according to Jaffe SCr. In only 14 of the 2759 patients was cystatin C additionally determined. So no conclusions could be drawn from this.

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Table 1: Average difference of SCr stratified by sex, age and hospital treatment mode of adults at the University Hospital Essen.

Characteristics	Patients, *n*	Average SCr difference	SCr upper limit	SCr lower limit
All patients	41 144	0.07	0.25	−0.12
Male	21 224	0.06	0.26	−0.14
Female	19 920	0.07	0.24	−0.10
Age (years)				
18–29	1718	0.04	0.24	−0.16
30–39	1863	0.04	0.28	−0.20
40–49	2053	0.05	0.30	−0.20
50–59	3728	0.05	0.27	−0.17
60–69	3824	0.05	0.27	−0.17
70–79	15 968	0.07	0.23	−0.08
≥80	11 990	0.07	0.24	−0.09
Outpatient				
All	25 803	0.07	0.25	−0.11
Internal medicine	11 123	0.06	0.26	−0.13
Surgery	1353	0.08	0.21	−0.05
Inpatient				
All	15 341	0.06	0.25	−0.13
Internal medicine	4987	0.05	0.27	−0.18
Surgery	3609	0.07	0.21	−0.08
ICU	1841	0.04	0.30	−0.21

ICU: intensive care unit.
Average difference (Jaffe − eSCr) and upper and lower LoAs are presented in mg/dl.

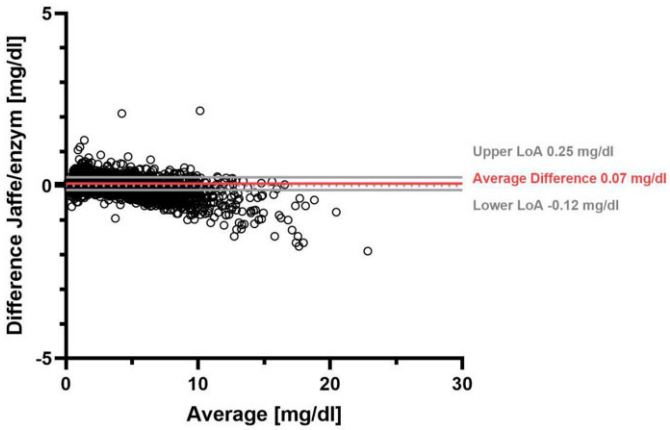

Figure 1: Difference between Jaffe and eSCr. Graph shows a Bland–Altman plot of the difference between serum creatinine determined by the Jaffe and enzymatic methods. Solid grey lines represent upper and lower LoAs, solid red line represents the average difference and the dotted grey line marks the zero line.

Impact of the measurement method on the diagnosis of AKI

The average difference between Jaffe and eSCr in the 668 patients with an SCr difference ≥0.3 mg/dl between the two methods was 0.33 mg/dl and −13.1 ml/min/1.73 m^2 eGFR, respectively (Table 7, Supplementary Tables 5 and 6). Jaffe SCr measurements ≥0.3 mg/dl than eSCr were rare: 1.6% of cases in the total cohort, slightly more often in patients >60 years of age (1.6–2.0%), outpatients (1.7%) and more often in patients receiving intensive care (4.2%).

Impact of the measurement method on adults ≥70 years of age

For all patients ≥70 years of age, the CKD-EPI and BIS1 eGFR equations were applied with Jaffe SCr and eSCr. When applying the CKD-EPI eGFR equation using the Jaffe and eSCr methods, 20.5% of the measurements resulted in a deviating CKD classification. When the BIS1 equation was applied, there were approximately the same proportions of deviations with regard to the resulting CKD stages (19.8%). However, we found that there were more deviations in CKD stage G2/G3a, and thus in the particularly sensitive range regarding a CKD diagnosis. The kappa value here was 0.70 (95% CI 0.689–0.703) and 0.72 (95% CI 0.710–0.724), respectively (Supplementary Table 7). The number of cases with a switch of CKD grade between G3a/G3b was substantially lower when applying the BIS1 eGFR equation (Supplementary Table 8).

Impact of the measurement method on CKD stages applying the EKFC equation

When applying the EKFC eGFR equation using the Jaffe and eSCr methods, 21.1% of the measurements resulted in a deviating CKD classification, so approximately the same proportion of deviations compared with applying the CKD-EPI eGFR equation. The kappa value here was 0.71 (95% CI 0.707–0.718). The number of cases with a switch of CKD grade between G3a/G3b was higher when applying the EKFC eGFR equation (Tables 8 and 9) compared with the CKD-EPI eGFR equation (Tables 4 and 5).

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Table 2: Average difference of eGFR stratified by sex, age and hospital treatment mode of adults at the University Hospital Essen

Characteristics	Patients, *n*	eGFR average difference	eGFR upper limit	eGFR lower limit
All patients	41 144	−4.6	5.3	−14.6
Male	21 224	−4.1	5.2	−13.3
Female	19 920	−5.2	5.3	−15.7
Age (years)				
18–29	1718	−5.0	9.0	−19.1
30–39	1863	−4.6	7.5	−16.6
40–49	2053	−5.0	6.7	−16.6
50–59	3728	−4.4	6.2	−15.1
60–69	3824	−4.1	6.4	−14.7
70–79	15 968	−5.0	4.4	−14.4
≥80	11 990	−4.2	4.5	−12.9
Outpatient				
All	25 803	−5.0	4.8	−14.8
Internal medicine	11 123	−5.1	4.8	−15.0
Surgery	1353	−4.8	4.5	−14.1
Inpatient				
All	15 341	−4.0	6.1	−14.1
Internal medicine	4987	−3.6	6.0	−13.1
Surgery	3609	−4.6	5.2	−14.3
ICU	1841	−2.5	10.5	−15.5

ICU: intensive care unit.
Average difference and upper and lower LoAs are presented in ml/min/1.73 m^2. eGFR was determined according to the 2009 CKD-EPI equation [20].

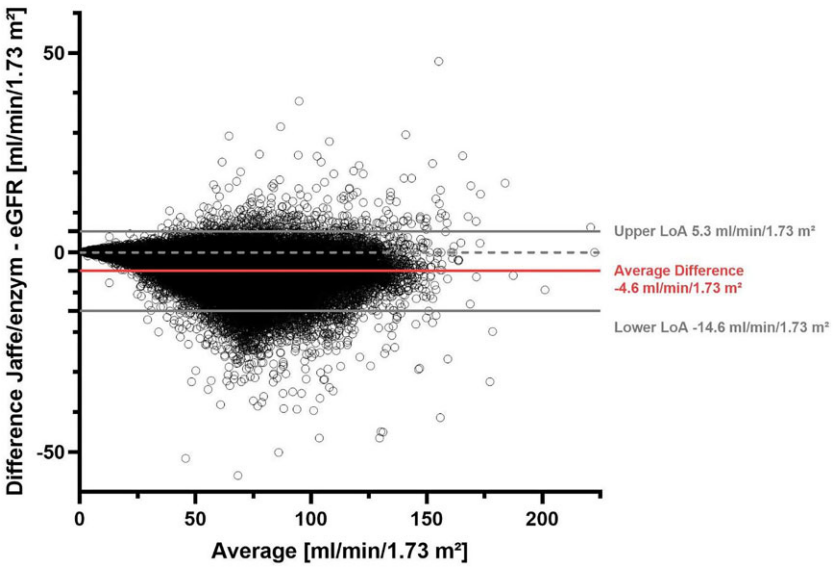

Figure 2: Difference between Jaffe eGFR and enzymatic eGFR. Graph shows a Bland–Altman plot of the difference between eGFR determined with Jaffe SCr and eSCr. Solid grey lines represent upper and lower LoAs, solid red line represents the average difference and the dotted grey line marks the zero line.

Results on analytical sensitivity differences, linearity and HIL indices

The mean coefficient of variation for the enzymatic creatinine for the whole study period for the three differently concentrated creatinine control solutions (L1–L3) were L1 2.07% (minimum 0.93%, maximum. 6.24%), L2 1.69% (minimum 0.66%, maximum 5.37%) and L3 1.12% (minimum 0.34%, maximum 5.32%). The mean coefficient of variation for the Jaffe creatinine for the whole study period for L1 was 2.65% (minimum 1.26%, maximum 6.31%), for L2 2.13% (minimum 0.73%, maximum 5.78%) and for L3 1.58% (minimum 0.63%, maximum 5.15%).

Both the results of sample 1 and sample 2 showed good recovery down to the lower limit of the measurement range (Supplementary Tables 9 and 10). The linearity of the method for both samples could also be confirmed in the dilution series (Supplementary Figs. 1–4). The recoveries in the dilution series with the Jaffe method showed good results (Supplementary Tables 11 and 12). In the range near the lower limit of the measurement range, the recoveries for both samples were ≈120%. However, since in this range even small changes in absolute values have a strong effect on the recoveries, the recoveries here are considered acceptable. As with the enzymatic method, the linearity of the creatinine according to Jaffe could be confirmed in the measurement range checked (Supplementary Figs. 5–8).

The analysis of the HIL indices yielded the following results: 121 samples (0.3%) contained a conjugated bilirubin >20 mg/dl,

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Table 3: Average difference of SCr and eGFR stratified by CKD stages of adults at the University Hospital Essen.

CKD stage	Patients, *n*	eGFR average difference	eGFR upper limit	eGFR lower limit	SCr average difference	SCr upper limit	SCr lower limit
G1	10 343	−5.3	6.2	−16.9	0.07	0.19	−0.06
G2	17 648	−6.0	4.1	−16.0	0.07	0.20	−0.05
G3a	5693	−3.6	3.6	−10.8	0.07	0.22	−0.07
G3b	3829	−2.1	2.8	−6.9	0.07	0.25	−0.10
G4	2163	−0.8	1.9	−3.4	0.06	0.30	−0.18
G5	1468	0.1	1.0	−0.9	−0.09	0.49	−0.66

Average difference and upper and lower LoAs are presented in mg/dl and eGFR as ml/min/1.73 m^2. eGFR was determined according to the 2009 CKD-EPI equation [20] using eSCr.

Table 4: CKD stages depending on SCr measurement method (CKD-EPI eGFR equation).

	eSCr, *n*						
Jaffe, *n*	G1	G2	G3A	G3B	G4	G5	Total
G1	7424	112	0	0	0	0	7536
G2	2915	14 760	128	0	0	0	17 803
G3A	1	2759	4300	59	0	0	7119
G3B	3	16	1264	3400	49	0	4732
G4	0	1	1	370	2061	20	2453
G5	0	0	0	0	53	1448	1501
Total	10 343	17 648	5693	3829	2163	1468	41 144

eGFR was determined according to the 2009 CKD-EPI equation [20].

Table 5: Proportion of patients with higher CKD stage due to the use of Jaffe SCr (CKD-EPI eGFR equation).

G1 / G2+	28.2 %
G2 / G3a+	15.7 %
G3a / G3b+	22.2 %
G3b / G4+	9.7 %
G4 / G5	2.5 %

Underlying eGFR according to the 2009 CKD-EPI equation [19]. Orange background: CKD stage with eSCr; grey background: switched CKD stages with Jaffe SCr. Percentages show the proportion of deviated CKD classification (e.g. 28.2% of all patients with CKD stage G1 according to eSCr had CKD stage G2 or even higher CKD stages according to the corresponding Jaffe SCr). Percentages of upgrading effects are not shown.

46 samples (0.1%) contained haemoglobin ≥500 mg/dl and 11 samples (0.03%) contained lipemia ≥500 mg/dl.

DISCUSSION

Key findings

This study evaluated the size and effects of differences between Jaffe and eSCr measurement results on the diagnosis and staging of AKI and CKD in a comprehensive cohort of outpatients and inpatients in several medical specialties, which has—to our knowledge—not yet been done on this scale and detail. Although the absolute average SCr difference was small, there were clinically relevant effects regarding CKD classification with up- and downgrading in approximately one-fifth of the cases when using the current Jaffe SCr measurement method. The largest proportion of different CKD classifications was between G1/G2 and G3a/G3b. Deviating eGFR results corresponding to CKD stage 3a or higher have the greatest clinical impact: 22.2% of all patients with CKD stage G3a according to eSCr had CKD stage G3b or higher according to the corresponding Jaffe SCr. The number of cases with a CKD switch in the stages G3a/G3b in patients >70 years of age was substantially lower when applying the BIS1 eGFR equation. The number of cases with a switch of CKD grade between G3a/G3b was higher when applying the EKFC eGFR equation compared with applying the CKD-EPI equation. A difference between Jaffe and eSCr ≥0.3 mg/dl is rare (1–2% of the cases) but may occur, leading to a misdiagnosis of AKI. It is noteworthy that most cases with such a substantial SCr difference have been detected in patients treated in intensive care, and thus in a group that is particularly vulnerable to AKI.

Comparison with previous studies and prospects

Several studies have evaluated the effect of the SCr measurement method on the determination of eGFR and the staging of CKD in children and adults [9, 11, 25]. Lovrenčić *et al.* [9] and Cheuiche *et al.* [11] have studied a possible impact in diabetes patients. Lovrenčić *et al.* concluded that the percentage of patients with a switch of CKD stage due to a switch in the SCr measurement method is <10% and therefore not clinically relevant, while Cheuiche *et al.* showed that eGFR determined with eSCr had a slightly better agreement with measured GFR than did eGFR based on Jaffe SCr, but without any substantial effect on the CKD class. Both studies evaluated small cohorts of 648 and 123 patients, respectively. A similar result was also reported by Syme *et al.* [10], who found differing CKD staging in only 4% of 5303 measurements. However, the present study, conducted in a much larger cohort, shows a substantially greater variability of CKD stages, especially in stage G3a. Further, our results can essentially confirm the theoretical approach of Drion *et al.* [13] in a real patient group of comparable size. Drion *et al.* developed regression equations for the analytical variations of SCr measurements. When they applied clinical SCr data to the regression equations, there were downgrading effects in up to 78% in CKD stage G1 when using Modification of Diet in Renal Disease equation for eGFR determination. In the present study we showed similar downgrading effects when applying the CKD-EPI equation. Our results are in line with a recent study by Gottlieb

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Table 6: Presence or absence of kidney disease depending on SCr measurement method.

eGFR >60 ml/min/1.73 m^2 with both Jaffe SCr and eSCr	25 211
eGFR <60 ml/min/1.73 m^2 with both Jaffe SCr and eSCr	13 025
eGFR >60 ml/min/1.73 m^2 with Jaffe SCr and eGFR <60 ml/min/1.73 m^2 with eSCr	128
eGFR <60 ml/min/1.73 m^2 with Jaffe SCr and eGFR >60 ml/min/1.73 m^2 with eSCr	2780

eGFR determined according to the 2009 CKD-EPI equation [20].

Table 7: Proportion of measurements with a SCr difference between the Jaffe and enzymatic method ≥0.3 mg/dl of adults at the University Hospital Essen.

Characteristics	All patients, *n*	Patients with SCr difference ≥0.3 mg/dl *n* (%)
All	41 144	668 (1.6)
Male	21 224	346 (1.6)
Female	19 920	319 (1.6)
Age (years)		
18–29	1718	19 (1.1)
30–39	1863	21 (1.1)
40–49	2053	21 (1.0)
50–59	3728	38 (1.0)
60–69	3824	76 (2.0)
70–79	15 968	260 (1.6)
≥80	11 990	226 (1.9)
Outpatients		
All	25 803	438 (1.7)
Internal medicine	11 123	95 (0.9)
Surgery	1353	16 (1.2)
Inpatients		
All	15 341	230 (1.5)
Internal medicine	4987	73 (1.5)
Surgery	3609	37 (1.0)
ICU	1841	77 (4.2)

ICU: intensive care unit.

Table 8: CKD stages depending on SCr measurement method (EKFC eGFR equation).

	eSCr						
Jaffe	G1	G2	G3A	G3B	G4	G5	Total
G1	7427	31	1	0	0	0	7459
G2	3043	14 501	91	3	0	0	17 638
G3A	12	2489	4139	470	0	0	7109
G3B	2	25	1981	3105	190	0	5303
G4	0	2	1	205	1920	31	2165
G5	0	0	0	0	100	1370	1470
Total	10 483	17 048	6213	3783	2210	1407	41 144

eGFR determined according to the EKFC equation [31, 32].

Table 9: Proportion of patients with higher CKD stage due to the use of Jaffe SCr (EKFC eGFR equation).

G1 / G2+	29.2 %
G2 / G3a+	14.8 %
G3a / G3b+	31,9 %
G3b / G4+	5,4 %
G4 / G5	4,5 %

Underlying eGFR was determined according to the EKFC equation [31, 32]. Orange background: CKD stage with eSCr; grey background: switched CKD stages with Jaffe SCr. Percentages show the proportion of deviated CKD classification (e.g. 29.2% of all patients with CKD stage G1 according to eSCr had CKD stage G2 or even higher CKD stages according to the corresponding Jaffe SCr). Percentages of upgrading effects are not shown.

et al., who evaluated the correlation of SCr- and cystatin C–based eGFR. They pointed out that although the eGFR of the majority of the patients resulted in the same CKD stage, in 34% of the patients the cystatin C–based eGFR resulted in a different CKD stage [24].

The influence of the SCr method on the diagnosis of AKI has been the focus of few studies. Some recent case reports showed that differences between the Jaffe and eSCr method can lead to a misdiagnosis of AKI when comparing outpatient and in-patient laboratory results for the same patient or between hospitals when transferring a patient [17–19]. In the present study, this effect was investigated for the first time in a large cohort. We confirmed that in a relevant proportion (i.e. 1.6%) of patients there is such a large difference between the SCr measurement methods that an AKI criterion would be fulfilled. Furthermore, it should be emphasized that limits of agreement of −0.12 and 0.25 mg/dl (Fig. 1) show that even if one takes out the most extreme 5% of differences, one still has differences that are difficult to tolerate. In conclusion, the difference between Jaffe SCr and eSCr in terms of absolute difference is small. However, the use of SCr to determine eGFR may lead to clinically relevant deviations in terms of kidney disease detection and staging.

The results of this study are relevant for future studies and daily clinical work in several ways. First, the diagnosis of CKD is influenced by the SCr measurement method used for determination of eGFR, especially in the range of 45–89 ml/min/1.73 m^2, and should be combined with measurement of cystatin C and the most suitable eGFR equation for a patient. This is also relevant insofar as the eGFR slope will probably also be used as a surrogate endpoint in clinical trials in the future [34]. Further, new eGFR equations, like the EKFC equation, are also sensitive to an SCr difference between the Jaffe and eSCr methods. Therefore, one should stay with one method for SCr measurement; preferably with the enzymatic method. Second, SCr differences between the Jaffe and enzymatic methods can lead to misdiagnosis of AKI. Clinicians should take this into account when interpreting SCr results of a patient from different laboratories with different measurement methods. Third, these differences are relevant when planning a multicentre study or comparing results of different studies dealing with kidney diseases.

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Strengths and limitations

Our study has several strengths. To our knowledge, this is the first study that evaluated the size and effects of differences between Jaffe and eSCr measurements on the diagnosis and staging of AKI and CKD in this scale and detail. It showed a substantial effect on both diagnosis and staging of AKI and CKD. This effect is underlined by low kappa values. Also, the mean coefficient of variation and the proportion of patients with problematic HIL indices were low. Nevertheless, there are some limitations that must be taken into account.

A limitation of the analyses is that only the eGFR could be used to determine the CKD stage. All patients with an eGFR >60 ml/min/1.73 m^2 were therefore classified as having CKD, even if the diagnosis could not be made with certainty in CKD stage G1 and G2. Only the first measurement with both methods of each patient was evaluated. Therefore, it is possible that an elevated SCr is an expression of an AKI or acute kidney disease and not of a pre-existing CKD. Moreover, we also used Jaffe SCr for applying the CKD-EPI, EKFC and BIS eGFR equations. These eGFR equations have been validated only using eSCr, but it is very likely when determining Jaffe SCr in a clinical context that this measurement result is used for estimating GFR. Another limitation is the lack of measured GFR with the gold standard technique.

Furthermore, possible interferences in the Jaffe SCr and eSCr measurements, e.g. by glucose, bilirubin or drugs that could possibly increase the difference between Jaffe and eSCr, were not fully taken into account. Analysis of the HIL indices in this cohort showed that extremely high HIL concentrations are rare, but these should be considered individually.

CONCLUSION

The present study showed that the method of SCr measurement may have a substantial effect on both the diagnosis and staging of AKI and CKD. This must be taken into account when interpreting measurements of renal function in everyday clinical practice, but also when planning and comparing studies on renal diseases. One should therefore stay with one method for SCr measurement; preferably with the enzymatic method.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

K.B., A.K. and B.K. were responsible for conceptualization. K.B., S.S. and A.M. were responsible for data analysis. A.K., A.S. and L.V. were responsible for resources. K.B. was responsible for visualization. K.B. wrote original draft. S.S., B.K. and A.K. were responsible for supervision. All authors reviewed and edited the manuscript and read and approved the final version.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

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