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Estimated glomerular filtration rates are higher when creatinine-based equations are compared with a cystatin C-based equation in coronavirus disease 2019

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Abstract

Objectives: Estimations of glomerular filtration rate (eGFR) are based on analyses of creatinine and cystatin C, respectively. Coronavirus disease 2019 (COVID-19) patients in the intensive care unit (ICU) often have acute kidney injury (AKI) and are at increased risk of drug-induced kidney injury. The aim of this study was to compare creatinine-based eGFR equations to cystatin C-based eGFR in ICU patients with COVID-19.

Methods: After informed consent, we included 370 adult ICU patients with COVID-19. Creatinine and cystatin C were analyzed at admission to the ICU as part of the routine care. Creatinine-based eGFR (ml/min) was calculated using the following equations, developed in chronological order; the Cockcroft–Gault (C-G), Modified Diet in Renal Disease (MDRD)1999, MDRD 2006, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and Lund–Malmö revised (LMR) equations, which were compared with eGFR calculated using the cystatin C-based Caucasian Asian Pediatric Adult (CAPA) equation.

Results: The median eGFR when determined by C-G was 99 ml/min and interquartile range (IQR: 67 ml/min). Corresponding estimations for MDRD1999 were 90 ml/min (IQR: 54); MDRD2006: 85 ml/min (IQR: 51); CKD-EPI: 91 ml/min (IQR: 47); and for LMR 83 ml/min (IQR: 41). eGFR was calculated using cystatin C and the CAPA equation value was 70 ml/min (IQR: 38). All differences between creatinine-based eGFR versus cystatin C-based eGFR were significant ($p < .00001$).

Conclusions: Estimation of GFR based on various analyses of creatinine are higher when compared with a cystatin C-based equation. The C-G equation had the worst performance and should not be used in combination with modern creatinine analysis methods for determination of drug dosage in COVID-19 patients.

KEYWORDS
acute kidney injury, COVID-19, creatinine, critical care, Cystatin C, glomerular filtration rate

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Editorial Comment

The estimation of glomerular infiltration rates (GFR) in COVID-19 patients varies depending on whether a creatinine or cystatinme C equation is used. This study showed higher GFR when using creatinine for the estimation, and that the Cockcroft–Gault equation was least accurate.

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has resulted in high rates of patients admitted to intensive care units (ICUs). Organ dysfunction is common and up to 90% of the patients requiring mechanical ventilation may also develop some degree of acute kidney injury (AKI).[1,2] Patients with kidney injuries are more susceptible for drug side effects from renally excreted or nephrotoxic drugs.[3] When COVID-19 is so severe that treatment in an ICU is necessary, the patients will receive several different drugs. Several various pathomechanisms may be attributable for drug-induced renal failure in the ICU, which may be worsened by numerous concomitant conditions, including application of nephrotoxins.[4] Drugs are often cleared through the kidneys and the kidney function measured as estimated glomerular filtration rate (eGFR) in ml/min is important for correct drug dosage. An overestimation of eGFR will lead to larger drug doses and, ultimately, increased risk of worsened kidney injury and toxicity in other organs.[5] Although clinical variables (reduced effective circulating volume, older age, pre-existent renal impairment) must be taken into account drug-induced organ injury, due to overestimated eGFR, is a threat, the potential risk of undertreatment, for example, insufficient concentrations of beta-actam antibiotics, due to insufficient monitoring of renal function should not be neglected.[6]

Creatinine, a nitrogenous waste product in plasma and urine is frequently used to determine eGFR, as a surrogate variable of renal function. Shortcomings are interferences by gender, age, nutrition, and increases in plasma creatinine concentrations through drug effects, which not only may modify the release of creatinine, but also interfere with analysis.[7,8] Cystatin C, a cysteine protease inhibitor, expressed by nucleated cells, is a sensitive and reliable GFR marker.[9]

There are a number of problems associated with creatinine-based eGFR equations, in COVID-19 ICU patients. Creatinine-based eGFR equations are mainly based on relatively healthy individuals that are physically active, and have a diet with stable protein content, normal liver function, and normally distributed fluid volumes.[10]

Patients suffering from COVID-19 may have reduced plasma creatinine values due to reduced nutritional intake and reduced muscle mass, but are also at risk of increased creatinine values due to reduced kidney function.[11] Another problem is that the creatinine calibration has changed over the last 25 years. Before the year 2000, the most widely used creatinine methods were Jaffe based. The Jaffe methodology is not fully creatinine specific but also reacts with other substances, for example, glucose and antibiotics, leading to falsely elevated creatinine values.[12] In the beginning of the 21st century there was therefore a shift to isotope dilution mass spectrometry (IDMS) calibration of creatinine methods. This shift in calibration occurred approximately between 2002 and 2008 depending on the manufacturer. There were also additional changes downward during a period after 2008 according to external quality assurance (EQA) programs. It is estimated that the shift in calibration reduced the creatinine values by ~25% with wide variations. Despite the shift in creatinine calibrations the Cockcroft–Gault (C-G) equation is still widely used for drug dosage in combination with current creatinine results leading to an overestimation of absolute eGFR.[13] For example, it is recommended for drug dosage by pharma companies, the U.S. Food and Drug Administration, the European Medicines Agency, and National Medical Product Agencies.[14–16]

The aim of this study was to evaluate the performance of the Cockcroft and Gault,[17] the Modified Diet in Renal Disease (MDRD) from 1999,[18] the IDMS-traceable MDRD from 2006,[19,20] the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI),[21] and the Lund–Malmö revised (LMR)[22] equations with modern creatinine calibrated methods in COVID-19 patients. Cystatin C-based Caucasian Asian Pediatric Adult (CAPA) equation[23] was used as an independent reference method for comparison purposes having predictive value for COVID-19 severity[24] and also predicts mortality in ICU patients.[25] These equations are presented in chronological order. We also decided to note whether diabetes had any impact on $eGFR_{LMR}$ or $eGFR_{CAPA}$ at admission to our ICU.

2 | PATIENTS AND METHODS

2.1 | Setting

This prospective observational study was conducted at the ICU, a mixed surgical/medical ICU, at Uppsala University Hospital, a tertiary care hospital in Uppsala, Sweden.

2.2 | Ethics statement

This study was performed in accordance with the Declaration of Helsinki and its subsequent revisions. The study was approved by the National Ethical Review Agency Dnr 2017-043 (with amendments 2019-00169, 2020-01623, 2020-02719, 2020-05730, AND 2021-01469) and 2022-00526-01. Informed consent was obtained from the patients or from next of kin if the patient was unable to give consent. The protocol of this post hoc analysis of a prospective, observational, noninterventional study that was registered a priori at (Clinical Trials ID: NCT04316884). The study was performed according to relevant directives. The STROBE guidelines were followed in reporting.[26]

2.3 | Study population

Adult patients with severe COVID-19 infections admitted to the ICU in Uppsala University Hospital between March 2020 and March 2021 due to COVID-19 were considered for inclusion in this study. COVID-19 infections were verified with a positive polymerase chain reaction test of a nasopharyngeal sample. A total of 370 patients were included in this study, which is a part of the Uppsala PRONMED-study cohort. Patients that were younger than 18 years of age or pregnant were not considered eligible. Analysis of plasma creatinine and cystatin C were part of routine care of the patients.[27] After weighing and measuring the length of each patient, body mass index (BMI) was calculated as weight (kg) × height $(m)^{-2}$. Patient characteristics in this cohort have previously been described.[28–30] AKI-stage was calculated based on increase in plasma (P-)Creatinine during hospitalization for COVID-19 compared with baseline. Baseline P-Creatinine was determined from the laboratory database in the year before hospitalization if available. CKD was defined as eGFR-creatinine <60 ml/min 1 year or less prior to hospitalization for COVID-19. Diabetes mellitus type 1 and type 2 were noted on ICU admission.

2.4 | Laboratory analyses and AKI calculations

Blood samples for analyses were obtained at admission to the ICU as part of our routine procedure. Test tubes were centrifuged at room temperature at 1500 × g for 10 min. The plasma samples were frozen at −70°C until analyzed. Creatinine and cystatin C were analyzed on an Architect ci16200 (Abbot Laboratories, Abbott Park, Illinois) with IDMS-calibrated enzymatic creatinine reagents from the same manufacturer and cystatin C reagents from Gentian AS (Moss, Norway). Cystatin C-based eGFR was calculated from plasma cystatin C by means of the International Federation of Clinical Chemistry equation CAPA (Cystatin C-based $eGFR_{CAPA}$).[23] When developing the CAPA equation all cystatin C analyses were performed at the same laboratory as the present analyses.[23] The laboratory has been participating in the Swedish EQA program organized by Equalis (Uppsala, Sweden) and has maintained a good calibration over time according to the EQA samples. Plasma creatinine (μmol/L) was analyzed using an IDMS calibrated enzymatic method on Roche Cobas Pro (Roche Diagnostics, Rotkreuz, Switzerland) at the department of clinical chemistry and pharmacology, Uppsala University Hospital, Uppsala. The laboratory is accredited by Swedac (Borås, Sweden) according to SS-EN ISO 15189 and is participating in Equalis (Uppsala, Sweden) EQA programs for creatinine.

Absolute GFR in ml/min was estimated using the 1976 C-G, the 1999 MDRD, the 2006 IDMS-traceable MDRD, the 2009 CKD-EPI, the 2011 LMR, and the 2014 CAPA equation. All equations used have previously been described in detail.[22,31] All equations except C-G primarily estimate relative GFR in ml/min/1.73/m^2. Because of this, their results were deindexed for body surface area using the DuBois equation.[32,33] Notably, the CAPA equation had a median bias of −5.7 ml/min (recalculated from a median relative bias of −5.2 ml/min/1.73/m^2)in the validation set of Swedish adults (median mGFR 56 ml/min, recalculated from relative mGFR) when the equation was developed.[23] In the combined Swedish CAPA development and validation cohort ($n = 3495$, median mGFR 56 ml/min) the overall median bias for CG, IDMS-traceable MDRD, CKD-EPI, and LMR were 8.3, 3.6, 5.2, and 0.7 ml/min, respectively.[34]

2.5 | Statistical analyses

Data are presented as median and IQR. Chi-Square, 5 × 5 calculation was used to evaluate creatinine-based equations on different eGFR intervals. The two-tailed Wilcoxon Signed-Rank test was used to calculate differences between absolute creatinine-based eGFR equations versus the absolute cystatin C-based $eGFR_{CAPA}$ equation. The two-tailed Mann–Whitney *U* test was used to compare continuous data in independent samples. Bias plots (Bland-Altman[35]) were created using MedCalc Statistical Software 14.8.1, MedCalc Software, Ostend, Belgium. Statistics were calculated using R (https://www.r-project.org, version 4.0.2). A $p < .05$ was considered significant.

3 | RESULTS

3.1 | Patient characteristics

Patients were aged 19–86 years ([median: 64 years]; IQR [Q3–Q1] = 18), 266 out of the 370 patients were males. BMI was between 18 and 67 kg/m^2 ([median: 29]; IQR [Q3–Q1] = 8) and Simplified Physiology Score[36,37] was between 24 and 88 ([median: 53]; IQR [Q3–Q1] = 12). A total of 34 patients needed renal replacement therapy between 2 and 43 days ([median: 9.5 days]; IQR [Q3–Q1] = 12.5). On Day 1, median plasma creatinine was 80 μmol/L (IQR: 34 μmol/L). Corresponding values for cystatin C were 1.2 mg/L (IQR: 0.6 mg/L). eGFR (creatinine) median was 75 ml/min (IQR: 30). EGFR (cystatin C) median was 59 ml/min (IQR: 36). Thirty-eight percent had CKD at inclusion. Eleven percent of the patients needed renal replacement therapy during ICU stay. Number of days with COVID-19 before admission to ICU was (median 10 days [IQR: 4]). Mortality rates during ICU stay and after 90 days were 18% and 29%, respectively. In total, 31% of the patients had diabetes mellitus on admission to ICU. In diabetics, $eGFR_{LMR}$ was 62 (31), whereas $eGFR_{CAPA}$ was 49 (33; $p = .001$).

3.2 | Determinations of eGFR

The Bland Altman plots (Figures 1A–E) show differences between each creatinine-based equation minus the cystatin C CAPA equation. Previous reports have shown that a significant proportion of intensive care patients had eGFR values below 50 ml/min/1.73 m^2.[38]

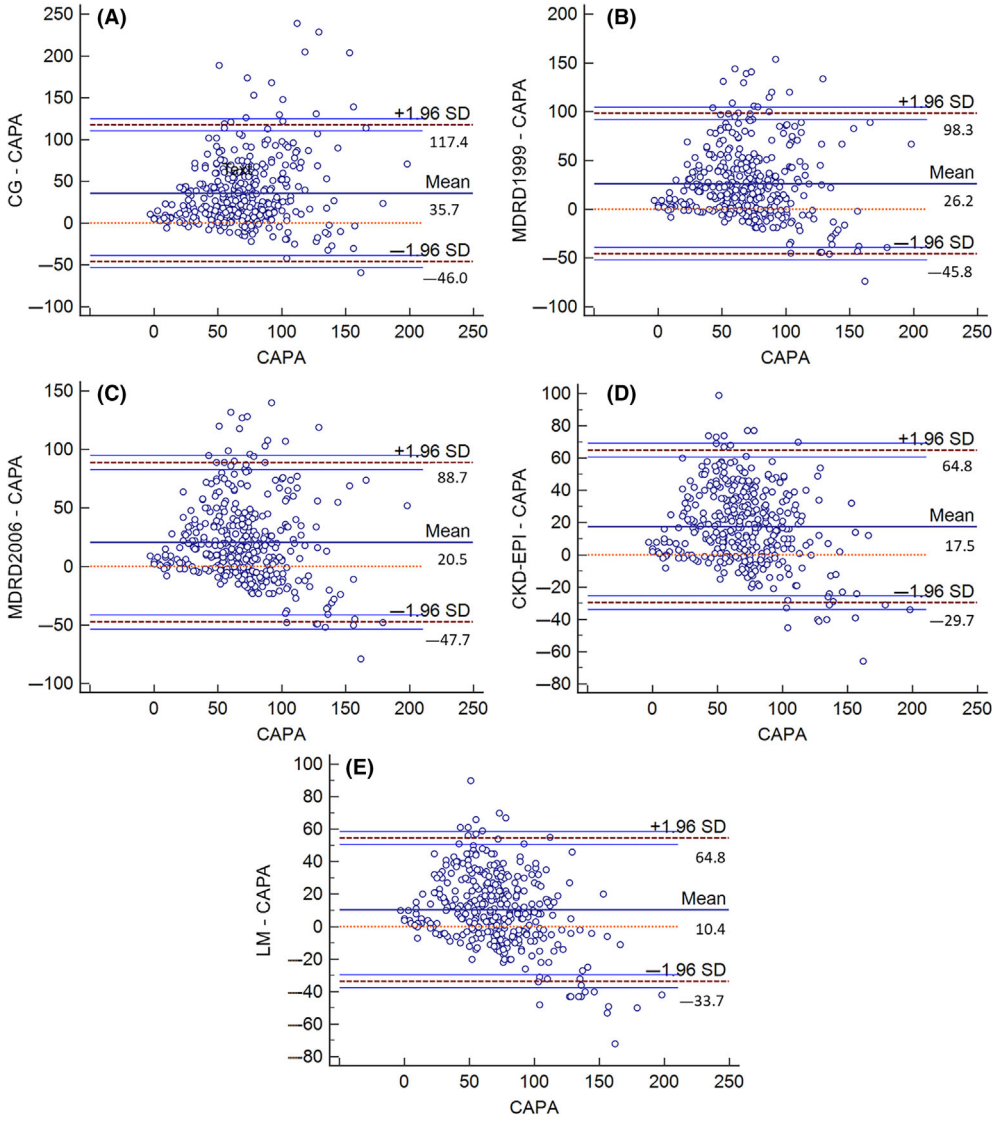

FIGURE 1 Bias plot (Bland Altman) derived from a cohort of intensive care-treated patients with coronavirus disease 2019 (COVID-19)

TABLE 1 Estimated glomerular filtration rate (eGFR; ml/min) using the creatinine-based Cockcroft–Gault (CG), Modified Diet in Renal Disease from 1999 (MDRD1999), IDMS-traceable MDRD from 2006 (MDRD2006), the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), the Lund–Malmö revised (LMR) equations, and the cystatin C-based CAPA equation ($eGFR_{CAPA}$).

Equation to estimate GFR	Median	IQR
CG***	99	67
MDRD1999***	90	54
MDRD2006***	85	51
CKD-EPI***	91	47
LMR***	83	41
CAPA	70	38

Note: IQR is third–first quartile.
Abbreviations: CAPA, IDMS, isotope dilution mass spectrometry; IQR, interquartile range.
***$p < .00001$.

TABLE 2 Median bias differences in absolute eGFR between the creatinine-based equations Cockcroft–Gault (CG), Modified Diet in Renal Disease from 1999 (MDRD1999), IDMS-traceable MDRD from 2006 (MDRD2006), the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and the Lund–Malmö revised (LMR) and the combined Swedish CAPA development and validation cohort.[23,34]

	Bias, median difference (ml/min) relative CAPA equation	
GFR equations	Present cohort	The CAPA development and validation cohort
CG	29	14.0
MDRD1999	20	NR
MDRD2006	15	9.3
CKD-EPI	21	10.9
LMR	13	6.4
CAPA	Reference	Reference

Abbreviations: CAPA, Caucasian Asian Pediatric Adult; eGFR, estimated glomerular filtration rate; IDMS, isotope dilution mass spectrometry; NR, not recorded.

TABLE 3 Cross tabulation showing number of patients in different absolute eGFR intervals (ml/min). Cystatin C-based CAPA equation ($eGFR_{CAPA}$), creatinine-based Cockcroft–Gault (CG), Modified Diet in Renal Disease from 1999 (MDRD1999), IDMS-traceable MDRD from 2006 (MDRD2006), the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and the Lund–Malmö revised (LMR).

	>60 ml/min	45–60 ml/min	30–45 ml/min	15–30 ml/min	<15 ml/min
CG	304	29	18	10	9
MDRD1999	296	41	11	11	11
MDRD2006	288	47	10	14	11
CKD-EPI	293	42	11	12	12
LMR	282	45	16	15	12
Cystatin C_{CAPA}	233	67	32	21	17

Abbreviations: CAPA, Caucasian Asian Pediatric Adult; eGFR, estimated glomerular filtration rate; IDMS, isotope dilution mass spectrometry.

These dispersions are reflected in the increased percentage of eGFR for creatinine-based equations >50 ml/min compared with eGFR determined by the cystatin C-based CAPA equation, which are as follows: C-G +28%, MDRD1999 + 22%, MDRD2006 + 18%, CKD-EPI + 14%, and LMR + 4%, respectively.

The highest GFR values are seen in some estimations where the C-G equation is used (Figure 1A). This equation, which is the oldest one, is associated with the most expressed difference when compared with the cystatin C CAPA equation. Except for CKD-EPI, more recent creatinine-based equations tend to be more densely concentrated around the abscissa. All creatinine-based equations exhibited significantly higher values ($p < .00001$) than the reference method (Table 1).

Table 2 shows how the choice of creatinine-based equation influences absolute eGFR values in our cohort when CAPA was used as reference.

There were considerable variations in the number of patients within each GFR interval, depending on which eGFR equation that was applied. When GFR was estimated by cystatin C-based $eGFR_{CAPA}$, more than one-third of our patients were considered to have eGFR <60 ml/min, which is by far higher than in any of the creatinine-based equations (Table 3). When the five creatinine-based equations were compared towards each other regarding the number of patients in each absolute eGFR interval, the chi-square statistic was 11.45, being nonsignificant ($p = .77$).

4 | DISCUSSION

In this noninterventional, observational study, where sampling was performed for future analyses, in critically ill COVID-19 patients, we found expressed differences in eGFR, depending on which equation that was used. The rationale for evaluating eGFRs determined by various equations in severely ill COVID-19 patients was partly based on the fact that AKI turned out to be a frequent finding in such patients.[1,2,39] Furthermore, our cohort constitutes a fairly homogenous one, facilitating comparisons between various methods. Against this background, we deduce that our results are generalizable, at least, ICU patients in a broader perspective. It should also be taken into account that sampling was initiated during the early phase of the pandemic when nobody knew which consequences this disease would cause on society.

Estimations of GFR by CG, MDRD1999, MDRD2006, CKD-EPI, and LMR were all higher when compared with cystatin C-based $eGFR_{CAPA}$. It cannot be excluded that differences in eGFR, especially $eGFR_{CG}$, between various equations may have some clinical implications, as several drugs, for example, aminoglycosides, used in the ICU have narrow therapeutic windows and toxic potential. AKI is one, out of several, well-known comorbidities that increase the risk for drug-induced ototoxicity[40] and/or nephrotoxicity.[41,42] Although creatinine measurements have several well-known drawbacks, interfering with its measurement, it is frequently used as a determinant of GFR. Glucocorticoid treatment, which has become a hallmark in the treatment of COVID-19 patients in need of respiratory support, may affect both creatinine and cystatin C.[43,44] Steroid effects are most likely dose-dependent and time-dependent which makes it difficult to give an exact number as that implies that a specific dose has been administered. Less than one-third of the patients received dexamethasone during the study period. Although the difference at 50 ml/min in eGFR between creatinine-based and cystatin C CAPA-based equations was set arbitrarily, it reflects a substantial difference in renal performance that may be considered in drug dosage. We used 60 ml/min (or 60 ml/min/1.73 m^2) as cutoff, since this limit is the one most frequently used for adjustment of drugs. If the GFR value is below this point there should be a dose reduction for drugs that are cleared by the kidneys. There are also other lower cutoff limits but 60 ml/min is the most common. In total, 60 ml/min/1.73 m^2 is also the cutoff used for CKD Stage 3.[45]

Differences in GFR between creatinine-based and cystatin C-based equations, respectively, observed in this entire cohort followed the same pattern regardless of whether or not the patients had diabetes mellitus at ICU admission. However, Day 1 was not a true baseline value since the patients had already been sick with COVID-19 before admission to ICU. Whether this period with COVID-19 may be attributable for this observed difference in eGFR cannot be evaluated from present data. In a previous study, the difficulty of estimating GFR in type 2 diabetes mellitus patients was noted.[46]

There is no ultimate determinant of glomerular function, although iohexol, a radiographic contrast medium, fulfills several requirements of an ideal GFR marker.[47–49] Inulin or 51Cr-EDTA have limited value in measuring GFR in ICU patients,[44,50,51] whose kinetics of GFR may change rapidly[52,53] and hereby contribute to drug-induced toxicity,

which also may be influenced by pharmacokinetics, compartmental dispersion, metabolism, and elimination. Hypoalbuminemia increases the free fraction of several antibiotics in plasma and hereby its elimination when cleared via the renal route.[54,55] Furthermore, increased distribution volume may similarly be seen in conditions associated with the development of endothelial damage and increased vascular permeability leading to capillary leak syndrome.[56] Augmented renal clearance may also be encountered in increased cardiac output, for example, during the hypermetabolic phase of sepsis.[57] Therapeutic drug monitoring is of uttermost importance, especially in the ICU, where rapid shifts in clinical situations rapidly occur.[58]

Whether accurate determination of GFR in real time, from the point-of-care aspect, is to be a realistic and useful tool in the ICU is yet to be clinically evaluated in large scale, but a tracer agent, MB-102, has fluorescence property, allowing it to be transdermally detected after bolus intravenous administration, may possibly point in that direction.[59] Still, critical evaluation during a prolonged period is necessary if MB-102 determined eGFR is to be used for drug dosing in ICUs.

4.1 | Strengths

As far as we know, we are the first to report, expressed median differences between creatinine-based equations and cystatin C-based eGFR in a COVID-19 cohort. An asset of the study is that samples were collected prospectively in consecutive patients in an essentially homogenous material. Also, when the CAPA equation was developed all cystatin C assays[23] were performed in the same laboratory analyzing the present samples, which contradicts the possibility of any major difference in calibration of analytes.

4.2 | Limitations

The study also has some limitations. The main weakness is that our comparator (cystatin C-based eGFR) does not perfectly mirror actual renal function but is itself based upon an equation, having a median bias of −5.7 ml/min but with less bias differences relative to the creatinine-based equations in the CAPA development and validation cohort[23,34] compared with the present cohort. Another drawback, is the fact that the current cohort consists of patients with severe COVID-19, whereas the equations used were derived from more clinically stable cohorts. Although our results do not suggest such a shortcoming, this possibility cannot a priori be excluded. From a clinical perspective, we consider this comparator to be a relevant standard. Cystatin C seems to be less affected than creatinine by dynamic events of long durations, for example, loss of muscle mass.[11] Such consequences of severe disease are frequently seen in ICU-patients. The use of cystatin C is validated in ICU-patients.[25,60] Furthermore, samples were taken at admission to ICU. It is therefore not possible to determine whether reduced GFR is due to preexisting CKD or to the development of AKI before entry to the ICU. Another weakness is the fact that data were collected from a COVID-19 cohort in a single hospital, which makes extrapolation of our results to other conditions more unreliable.

5 | CONCLUSIONS

In a cohort of critically ill COVID-19 patients, we noted that eGFR determined by creatinine-based equations were higher than when renal performance was evaluated by a cystatin C-based equation. This is most prominent with the C-G equation and this equation should not be used in today's ICUs but replaced with either modern creatinine equations that are adapted to modern creatinine methods or cystatin C-based $eGFR_{CAPA}$. If a creatinine-based equation is to be used for determination of eGFR, we advocate the application of LMR, which essentially is in agreement with cystatin C-based $eGFR_{CAPA}$.

AUTHOR CONTRIBUTIONS

Anders O. Larsson, Mats B. Eriksson, Miklos Lipcsey, Robert Frithiof, Michael Hultström, and Ulf Nyman conceived this study. All authors and the Intensive Care COVID-19 research group collected patient data. Anders O. Larsson analyzed the blood samples. Anders O. Larsson, Mats B. Eriksson, and Miklos Lipcsey performed data analysis. Anders O. Larsson, Mats B. Eriksson, and Miklos Lipcsey drafted the original article. All authors participated in the revisions of the article. All authors read and approved the final article for publication.

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DATA AVAILABILITY STATEMENT

Datasets used and/or analyzed during this study are available from the corresponding author on reasonable request (https://doi.org/10.17044/scilifelab.14229410).

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