Acute kidney injury defined by cystatin C may be superior for predicting the outcomes of liver cirrhosis with acute gastrointestinal bleeding

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Background & Aims: Acute kidney injury (AKI) is conventionally evaluated by a dynamic change of serum creatinine (Scr). Cystatin C (CysC) seems to be a more accurate biomarker for assessing kidney function. This retrospective multicenter study aims to evaluate whether AKI re-defined by CysC can predict the in-hospital outcomes of patients with liver cirrhosis and acute gastrointestinal bleeding.

Methods: Overall, 677 cirrhotic patients with acute gastrointestinal bleeding, in whom both Scr and CysC levels were detected at admissions, were screened. eGFR_{Scr}, eGFR_{CysC}, and eGFR_{Scr-CysC} were calculated. MELD-Na score and AKI were re-evaluated by CysC instead of Scr. Odds ratios (ORs) were calculated in the logistic regression analyses. The receiver operating characteristic (ROC) curve analyses were performed.

Results: Univariate logistic regression analyses demonstrated that baseline Scr and CysC levels, eGFR_{Scr}, eGFR_{CysC}, and eGFR_{Scr-CysC} were associated with in-hospital death. ROC analyses showed that baseline CysC level, eGFR_{CysC}, eGFR_{Scr-CysC} were significantly associated with in-hospital death.

Conclusions: AKI re-defined by CysC may be superior for predicting the in-hospital mortality of cirrhotic patients with acute gastrointestinal bleeding.

1. Introduction

Acute gastrointestinal bleeding is a common complication of liver cirrhosis [1]. Massive blood loss leads to renal hyoperfusion, secondary to intravascular volume depletion [2,3], and then acute kidney injury (AKI) [4,5], if ineffectively or timely treated. Notably, renal hypofunction.
dysfunction is closely associated with worse outcomes [6] and a higher risk of death [7,8].

Currently, the diagnostic criteria of AKI are mainly based on an increase in serum creatinine (Scr) level and/or a decrease in urine output, suggesting an abrupt reduction in glomerular filtration rate (GFR) [9]. However, Scr is readily affected by protein intake and total muscle mass [10]. Additionally, the diagnostic specificity of Scr is poor in the settings of hyperbilirubinemia, prerenal azotemia, dietary intake changes, and drug-induced changes in tubular secretion of Scr, all of which may influence the Scr level in the absence of renal parenchymal injury [11]. Therefore, novel biomarkers may be critical for the assessment of AKI.

Cystatin C (CysC), a low molecular weight non-glycosylated basic protein, can be freely filtered through the glomerulus, and almost completely re-absorbed and catabolized by proximal tubular cells [12,13]. Considering that the kidney is the only scavenging organ of CysC, CysC may reflect kidney function more accurately [14]. More importantly, CysC level is independent of muscle mass, age, or sex, and hardly influenced by inflammatory conditions or malignancy [15]. CysC may outperform Scr and endogenous Scr clearance rate in early detection of renal injury [16].

In spite of the advantage of serum CysC for prognostic assessment in general population and patients with chronic kidney diseases [17], until now, few studies have explored the role of serum CysC and AKI re-defined by serum CysC for evaluating the in-hospital outcomes of patients with liver cirrhosis and acute gastrointestinal bleeding.

2. Methods

2.1. Study design

In an investigator-initiated multicenter study, which is called as TORCH, we had retrospectively enrolled 1,682 patients with cirrhosis without renal parenchymal damage, who were admitted due to acute gastrointestinal bleeding and had Scr level at their admissions from January 2010 to December 2018 across 13 centers from 8 provinces or municipalities in China. Eligibility criteria had been mentioned in our previous studies. The study was approved by the medical ethical committee of the General of Northern Theater Command [No: Y (2020) 053]. If CysC level was measured at admission, patients would be eligible for the present sub-studies [18–22]. Notably, both Scr and CysC levels were measured at the same time. If malignancy was diagnosed, patients would be excluded from the present sub-study. Source of acute gastrointestinal bleeding was not limited. Age, gender, and repeated admissions were not limited. In-hospital death was the primary outcome of the present sub-study.

2.2. Data collection

The following data were collected: demographic data (i.e. age and gender), laboratory tests at admission (i.e. red blood cell, hemoglobin, hematocrit, white blood cell, platelet count, total bilirubin, albumin, alanine aminotransferase, blood urea nitrogen, Scr, CysC, and prothrombin time), ascites, mean arterial pressure, and Scr and CysC levels during hospitalizations. Endoscopic findings (i.e. peptic ulcer, esophageal or gastric varices, and portal hypertensive gastropathy) were collected. Endoscopic treatment (i.e. endoscopic variceal ligation, endoscopic variceal sclerotherapy, and endoscopic glue injection), vasoactive drugs during hospitalization (i.e. terlipressin, somatostatin, and octreotide), and blood transfusion were recorded.

2.3. Definition of AKI

According to the International Ascites Club (ICA) consensus in 2015 [23,24], AKI was defined as an increase in Scr level ≥0.3 mg/dL (26.5 μmol/L) within 48 h or ≥50% over baseline within the first 7 days. In the present work, we re-defined AKI by using CysC, as follows: an increase in CysC level of ≥0.3 mg/L within 48 h or an increase in CysC level ≥50% over baseline within the prior 7 days.

2.4. Prognostic scores

Original model for model for end-stage liver disease with serum sodium concentration (MELD-Na) score defined by Scr level, and MELD-Na score re-defined by CysC level were calculated. eGFR was evaluated by CKD-EPI Scr equation (eGFR_{Scr}), CKD-EPI CysC equation (eGFR_{CysC}), and CKD-EPI Scr-CysC equation (eGFR_{Scr-CysC}) in the Appendix.

2.5. Statistical analyses

Continuous variables were expressed as mean ± standard deviation and median (range). Categorical variables were expressed as frequency (percentage) and compared by the Chi-square test. Logistic regression analyses were performed to identify the risk factors significantly associated with in-hospital death. ORs with 95% confidence intervals (CIs) were calculated. A two-tailed p < 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curve analysis
was performed to calculate the area under curve (AUC) and the best cutoff value with its sensitivity and specificity. A comparison of AUCs was conducted by the Delong test. Scattered plots were drawn to demonstrate the correlation between baseline Scr and CysC levels, and Pearson correlation analyses were used to calculate the correlation coefficients. All statistical analyses were performed using SPSS software version 20.0 (IBM Corp, Armonk, NY, USA) and MedCalc software version 11.4.2.0 (MedCalc software, Mariakerke, Belgium).

3. Results

3.1. Patients

A total of 1682 patients were initially assessed for the study inclusion. Among them, 1005 patients were excluded, because 870 patients did not measure CysC level at admission; 313 patients had malignancy; and 178 patients with malignancy did not measure CysC level at admission. Finally, 677 cirrhotic patients with acute gastrointestinal bleeding, who had both Scr and CysC levels detected at the time of admission, were included in the present sub-study.

Baseline characteristics of patients are summarized in Table 1. Median age was 56 years (range: 18–88 years); 454 (67.10%) patients were male. Median Scr level at admission was 64 μmol/L (range: 23–305 μmol/L). Median CysC level at admission was 0.99 mg/L (range: 0.00–3.19 mg/L). Baseline CysC level significantly correlated with Scr level ($p < 0.001$) (Supplementary Figure 1).

Five hundred patients underwent endoscopic examinations, and 430 underwent endoscopic therapy (Supplementary Table 1). Median duration of hospitalization was 13 days (range: 3–46 days). Twenty-two (3.20%) patients died of multiple organ failure ($n = 10$, 45.50%), hemorrhagic shock ($n = 9$, 41.00%), cardiac arrest ($n = 1$, 4.50%), sudden death ($n = 1$, 4.50%), and respiratory failure ($n = 1$, 4.50%).

| Variables | No. Pts | Results |
|-----------|---------|---------|
| Age (years) | 677 | 56.00 (18.00–88.00); 56.56 ± 12.02 |
| Male (%) | 677 | 454 (67.10%) |
| Ascents (%) | 677 | 392 (57.90%) |
| MAP (mmHg) | 674 | 83.15 (43.33–153.33); 83.00 ± 13.00 |
| MAP >105 (%) | 674 | 31 (46.00%) |
| MAP <70 (%) | 674 | 94 (13.90%) |
| Laboratory tests | | |
| Red blood cell (10¹²/L) | 676 | 2.68 (0.99–5.09); 2.71 ± 0.74 |
| Hemoglobin (g/L) | 676 | 73.00 (19.00–170.00); 76.70 ± 24.95 |
| Hematocrit (%) | 675 | 22.60 (6.30–47.00); 23.49 ± 6.96 |
| White blood cell (10⁹/L) | 675 | 5.33 (0.74–51.00); 6.54 ± 4.84 |
| Platelet count (10¹²/L) | 675 | 76.00 (4.00–846.00); 96.02 ± 91.20 |
| Total bilirubin (μmol/L) | 676 | 21.80 (4.70–320.20); 31.87 ± 37.33 |
| Albumin (g/L) | 676 | 29.10 (4.00–76.70); 23.49 ± 6.96 |
| Alanine aminotransferase (U/L) | 676 | 24.28 (3.00–730.00); 36.73 ± 54.97 |
| Blood urea nitrogen (mmol/L) | 677 | 8.53 (0.11–38.80); 9.46 ± 4.92 |
| Scr (μmol/L) | 677 | 64.00 (23.00–305.00); 70.01 ± 29.00 |
| CysC (mg/L) | 677 | 0.99 (0.00–3.19); 1.09 ± 0.46 |
| Prothrombin time (seconds) | 667 | 16.50 (10.60–62.80); 17.34 ± 4.35 |
| Original MELD-Na score | 666 | 11.85 (6.43–39.31); 13.26 ± 5.24 |
| MELD-Na score re-defined by CysC | 664 | 12.74 (6.43–42.86); 14.32 ± 5.72 |
| eGFRScr (ml/min/1.73 m²) | 677 | 101.15 (11.52–169.98); 96.75 ± 22.97 |
| eGFRCys (ml/min/1.73 m²) | 676 | 79.20 (15.88–190.72); 81.29 ± 31.36 |
| eGFRCys-Cys (ml/min/1.73 m²) | 676 | 89.79 (13.74–182.79); 87.97 ± 27.09 |

Pts: Patients; MAP: Mean arterial pressure; Scr: Serum creatinine; CysC: Cystatin C; MELD: Model for end-stage liver disease; Na: Sodium; eGFR: Estimated glomerular filtration rate. The results part are expressed as the median (range) and mean ± standard deviation.
The best cutoff value was 1.61 mg/L with a sensitivity of 45.50% and a specificity of 90.70% (Figure 1).

### 3.3. Association of eGFR_{Scr}, eGFRCysC, and eGFR_{Scr-CysC} with in-hospital death

Univariate logistic regression analyses demonstrated that eGFR_{Scr} (OR = 0.970, 95%CI: 0.955–0.986, \( p < 0.001 \)), eGFRCysC (OR = 0.978, 95%CI: 0.963–0.993, \( p = 0.005 \)), and eGFR_{Scr-CysC} (OR = 0.973, 95%CI: 0.957–0.988, \( p = 0.001 \)) were significantly associated with in-hospital death (Table 2). After the adjustment of Child-Pugh score, eGFR_{Scr} (OR = 0.976, 95%CI: 0.960–0.992, \( p = 0.004 \)), eGFRCysC (OR = 0.985, 95%CI: 0.969–1.000, \( p = 0.049 \)) and eGFR_{Scr-CysC} (OR = 0.979, 95%CI: 0.963–0.986, \( p = 0.014 \)) remained significantly associated with in-hospital death.

The AUC of eGFR_{Scr} for predicting the in-hospital death was 0.658 (95%CI: 0.621–0.693, \( p = 0.030 \)), and the best cutoff value was \( \leq 68.95 \, \text{mL/min/1.73 m}^2 \) with a sensitivity of 45.50% and a specificity of 88.50% (Figure 2). The AUC of eGFRCysC for predicting the in-hospital death was 0.674 (95%CI: 0.637–0.709, \( p = 0.012 \)), and the best cutoff value was \( \leq 42.31 \, \text{mL/min/1.73 m}^2 \) with a sensitivity of 45.50% and a specificity of 90.70% (Figure 2). The AUC of eGFR_{Scr-CysC} for predicting the in-hospital death was 0.677 (95%CI: 0.641–0.713, \( p = 0.014 \)), and the best cutoff value was \( \leq 70.17 \, \text{mL/min/1.73 m}^2 \) with a sensitivity of 63.60% and a specificity of 76.80% (Figure 2).

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**Table 2.** Univariate analysis of predictors for in-hospital death.

| Variables                  | No. Pts | Odds Ratio | 95% Confidence Interval | \( p \) Value |
|----------------------------|---------|------------|-------------------------|--------------|
| Age (years)                | 677     | 1.020      | 0.984–1.058              | 0.274        |
| Sex (female/male)          | 677     | 0.855      | 0.353–2.070              | 0.729        |
| Red blood cell (10^{13}/L) | 676     | 0.467      | 0.246–0.888              | 0.020        |
| Hemoglobin (g/L)           | 676     | 0.996      | 0.979–1.014              | 0.693        |
| Hematocrit (%)             | 675     | 0.967      | 0.906–1.032              | 0.311        |
| White blood cell (10^{9}/L)| 675     | 1.056      | 0.998–1.118              | 0.061        |
| Platelet count (10^{12}/L) | 675     | 1.000      | 0.994–1.005              | 0.863        |
| Total bilirubin (\mumol/L)| 676     | 1.012      | 1.006–1.017              | <0.001       |
| Albumin (g/L)              | 676     | 0.875      | 0.819–0.936              | <0.001       |
| Alanine aminotransferase (U/L) | 676     | 1.008      | 1.004–1.012              | <0.001       |
| Blood urea nitrogen (mmol/L)| 676     | 1.097      | 1.027–1.171              | 0.006        |
| Scr (\mumol/L)             | 677     | 1.015      | 1.007–1.024              | <0.001       |
| CysC (mg/L)                | 677     | 3.366      | 1.788–6.334              | <0.001       |
| Prothrombin time (seconds) | 667     | 1.084      | 1.023–1.148              | 0.006        |
| Original MELD-Na score     | 666     | 1.156      | 1.088–1.228              | <0.001       |
| MELD-Na score re-defined by CysC | 664     | 1.153      | 1.086–1.224              | <0.001       |
| eGFR_{Scr} (ml/min/1.73m^2) | 677    | 0.970      | 0.955–0.986              | <0.001       |
| eGFRCysC (ml/min/1.73m^2)   | 676    | 0.978      | 0.963–0.993              | 0.005        |
| eGFR_{Scr-CysC} (ml/min/1.73m^2) | 676 | 0.973 | 0.957–0.988 | 0.001 |

Pts: Patients; Scr: Serum creatinine; CysC: Cystatin C; MELD: Model for end-stage liver disease; eGFR: Estimated glomerular filtration rate.

Bold and italic indicate \( p < 0.05 \).
3.4. Association of MELD-Na score defined by Scr and CysC with in-hospital death

Univariate logistic regression analyses demonstrated that original MELD-Na score defined by Scr (OR = 1.156, 95%CI: 1.088–1.228, p < 0.001) and MELD-Na score re-defined by CysC (OR = 1.153, 95%CI: 1.086–224, p < 0.001) were significantly associated with in-hospital death (Table 2).

The AUC of original MELD-Na score defined by Scr for predicting the in-hospital death was 0.767 (95%CI: 0.733–0.799, p < 0.001), and the best cutoff value was >13.65 with a sensitivity of 81.80% and a specificity of 65.00% (Figure 3). The AUC of MELD-Na score re-defined by CysC for predicting the in-hospital death was 0.751 (95%CI: 0.716–0.783, p < 0.001), and the best cutoff value was >13.65 with a sensitivity of 86.40% and a specificity of 56.90% (Figure 3).

3.5. Association of AKI defined by Scr and CysC with in-hospital death

Among the 677 patients included, 531 patients had both Scr and CysC levels re-tested during their hospitalizations. Scr level was re-tested in 310 patients within 48 h, of whom 30 could be diagnosed with AKI due to an absolute increase in Scr level ≥0.3 mg/L from baseline; Scr level was re-tested in 503 patients within the first 7 days, of whom 33 could be diagnosed with AKI due to a percentage of increase in Scr level ≥50% from baseline; and 16 patients met both of the two criteria. Thus, 47 (9.70%) patients were diagnosed with AKI by Scr (Figure 4).

CysC level was re-tested in 310 patients within 48 h, of whom 24 could be diagnosed with AKI due to an absolute increase in CysC level ≥0.3 mg/L from baseline; CysC level was re-tested in 503...
patients within the first 7 days, of whom 35 could be diagnosed with AKI due to a percentage of increase in CysC level $\geq 50\%$ from baseline; 9 patients met both of the two criteria. Thus, 50 (9.90%) patients were diagnosed with AKI re-defined by CysC (Figure 4).

The in-hospital mortality was not statistically significantly different between patients with and without conventional AKI defined by Scr (8.50% [4/47] versus 3.30% [15/456], $p = 0.074$). The in-hospital mortality was significantly higher in patients with AKI re-defined by CysC than those without (10.00% [5/50] versus 3.10% [14/453], $p = 0.015$).

Univariate logistic regression analyses demonstrated that AKI re-defined by CysC (OR = 3.484, 95%CI: 1.200–10.119, $p = 0.022$) was significantly associated with in-hospital death, but not conventional AKI defined by Scr (OR = 2.735, 95%CI: 0.869–8.607, $p = 0.085$).

4. Discussion

Early diagnosis and intervention of acute kidney damage should be warranted. Traditionally, Scr level alone and GFR estimation based on Scr level are main parameters for evaluating kidney function [25]. However, an increase in Scr level may not develop until renal function has been severely impaired [26]. Recently, CysC level has been gradually recognized a more sensitive and valuable marker for renal function [27]. It also yields a higher accuracy for evaluating the mortality in various groups of patients, such as patients with heart failure [28], patients undergoing liver transplantation [29], and patients with ascites and normal Scr level [30]. But diabetes, thyroid disorders, and cardiac dysfunction influence the levels of CysC in human blood [31].

The present study was designed to explore the superiority of CysC level over Scr level for predicting the in-hospital death in patients with liver cirrhosis and acute gastrointestinal bleeding. Several major findings are as follows. First, as for the single kidney function parameter, CysC level at baseline, rather than Scr level at baseline, can significantly predict the risk of in-hospital death. Second, as for the GFR estimation equation, eGFR_{scr}, eGFR_{cysc}, and eGFR_{scr-cysc} have a significant predictive ability. Third, as for the MELD-Na score calculation, both original MELD-Na score defined by Scr and MELD-Na score re-defined by CysC are significantly associated with in-hospital death. Fourth, as for the AKI evaluation, AKI re-defined by CysC may be more valuable than original AKI defined by Scr for the outcome prediction. Notably, the present study re-defined the AKI by CysC in accordance with the cutoff value of Scr from original AKI definition. The predictive validity of the new AKI re-defined by CysC may be further improved by optimizing the cutoff value of CysC.

When our statistical results are deeply analyzed, it can be observed that the AUC of baseline Scr or CysC level alone is not inferior to that of eGFR_{scr} or eGFR_{cysc} for predicting in-hospital death (AUC: 0.637 or 0.673 versus 0.658 or 0.674). On the other hand, it has been shown that a combination of Scr and CysC seems to be more accurate for estimating GFR, particularly in patients with near-normal kidney function. eGFR_{scr-cysc} is also effective for assessing renal function in patients with liver cirrhosis [32]. However, such a combination did not improve the predictive ability of mortality in our patients (AUC = 0.677).
It should be acknowledged that the assessment of renal function by single Scr or CysC level, eGFR_{Scr}, eGFR_{CysC}, or eGFR_{Scr-CysC} has a bit inferior predictive performance than original MELD-Na score defined by Scr or MELD-Na score re-defined by CysC (AUC: 0.767 or 0.751). This phenomenon is readily explained by the components of MELD-Na score, which include liver function parameters except for Scr. As known, the prognostic role of MELD-Na score has been widely recognized in patients’ end-stage liver disease [33], liver transplant candidates [34], and HBV-related acute-on-chronic liver failure (ACLF) patients [35].

Except for kidney biomarkers in blood species, those in urine species are also of clinical significance. Urinary neutrophil gelatinase-associated lipocalin (NGAL), an indicator of renal tubular damage, has been proposed as a biomarker of renal dysfunction [36] and a predictor of ACLF and mortality in liver cirrhosis [37]. However, urine NGAL was unavailable in the present study, and its impact on outcomes of cirrhotic patients with acute gastrointestinal bleeding could not be evaluated.

Except for the retrospective study design as a major limitation, we should also acknowledge that: (1) our study populations are cirrhotic patients with acute gastrointestinal bleeding, but not other complications of liver cirrhosis; (2) our patients have a low incidence of AKI, suggesting less severe diseases; (3) a dynamic change of AKI stage has not been further analyzed; and (4) the data regarding infection had not been collected in the multicenter study.

In summary, CysC level alone or incorporated into the GFR estimation equation, MELD-Na score, and AKI definition can effectively predict the in-hospital death of patients with cirrhosis and acute gastrointestinal bleeding. When the AKI is re-defined by CysC, its predictive validity may be elevated in such patients. Certainly, the usefulness of the CysC-based prediction model needs to be confirmed in prospective large-scale studies.

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Informed consent

Informed consent was exempted in this study.

Statement

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Appendix

MELD(i)\(=0.957 \times \ln(\text{Scr})+0.378 \times \ln(\text{bilirubin})+1.120 \times \ln(\text{INR})+0.643\)

Then, round to the tenth decimal place and multiply by 10.

If MELD(i)\(>11\), perform additional MELD calculation, as follows:

\[
\text{MELD(Na)}= \text{MELD(i)}+1.32 \times (137-\text{Na})-0.033 \times \text{MELD(i)} \times (137-\text{Na})
\]

**Additional rules:**

- All values in US units (Scr and bilirubin in mg/dL, Na in mEq/L, and INR unitless).
- If bilirubin, Scr, or INR is \(<1.0\), use \(1.0\).
- If any of the following is true, use Scr \(4.0\).
  - Scr \(>4.0\).
  - \(\geq 2\) dialysis treatments within the prior 7 days.
  - 24 h of continuous veno-venous hemodialysis within the prior 7 days.
- If Na \(<125\) mmol/L, use 125. If Na \(>137\) mmol/L, use 137.
- Maximum MELD score = 40.

In the present study, we re-defined MELD by using CysC, as follows:

\[
\text{MELD(i)}=0.957 \times \ln(\text{CysC})+0.378 \times \ln(\text{bilirubin})+1.120 \times \ln(\text{INR})+0.643
\]

Then, round to the tenth decimal place and multiply by 10.

If MELD(i)\(>11\), perform additional MELD calculation, as follows:

\[
\text{MELD(Na)}-\text{CysC}= \text{MELD(i)}+1.32 \times (137-\text{Na})-0.033 \times \text{MELD(i)} \times (137-\text{Na})
\]

**Additional rules:**

- All values in US units (CysC in mg/L, bilirubin in mg/dL, Na in mEq/L, and INR unitless).
- If bilirubin, CysC, or INR is \(<1.0\), use \(1.0\).
- If any of the following is true, use CysC \(4.0\).
  - CysC \(>4.0\).
  - \(\geq 2\) dialysis treatments within the prior 7 days.
  - 24 h of continuous veno-venous hemodialysis within the prior 7 days.
- If Na \(<125\) mmol/L, use 125. If Na \(>137\) mmol/L, use 137.
- Maximum MELD score = 40 [38].

**ADULT GFR ESTIMATING EQUATIONS** were as follows [39]:

2009 CKD-EPI Scr equation:

\[
141 \times \min(\text{Scr/}k, 1)^a \times \max(\text{Scr/}k, 1)-1.209 \times 0.993\text{Age} \times 1.018 \times 1.159 \times 0.9738\text{Sex} = \text{Scr}\]

where Scr is serum creatinine (in mg/dL), \(k\) is 0.7 for females and 0.9 for males, \(^a\) is \(-0.329\) for females and \(-0.411\) for males, \(\text{min}\) is the minimum of Scr/\(k\) or 1, and max is the maximum of Scr/\(k\) or 1.

2012 CKD-EPI CysC equation:

\[
133 \times \min(\text{CysC/}k, 1)^a \times \max(\text{CysC/}k, 1)-1.328 \times 0.996\text{Age} \times 0.932\text{Sex} = \text{CysC}\]

where CysC is serum cystatin C (in mg/L), \(k\) is the minimum of CysC/\(k\) or 0.8, and \(\text{max}\) is the maximum of CysC/\(k\) or 1.

2012 CKD-EPI Scr\(_{\text{Cyst}}\) CysC equation:

\[
135 \times \min(\text{Scr/}k, 1)^a \times \max(\text{Scr/}k, 1)-0.601 \times \min(\text{CysC/}k, 1)-0.375 \times \max(\text{CysC/}k, 1)-0.711 \times 0.995\text{Age} \times 0.969\text{Sex} = \text{Scr}_{\text{Cyst}}\]

where Scr is serum creatinine (in mg/dL), CysC is serum cystatin C (in mg/L), \(k\) is 0.7 for females and 0.9 for males, \(^a\) is \(-0.248\) for females and \(-0.207\) for males, \(\text{min}(\text{Scr/}k, 1)\) indicates the minimum of Scr/\(k\) or 1, \(\text{max}(\text{Scr/}k, 1)\) indicates the maximum of Scr/\(k\) or 1, \(\text{min}(\text{CysC/}k, 1)\) indicates the minimum of CysC/\(k\) or 1, and \(\text{max}(\text{CysC/}k, 1)\) indicates the maximum of CysC/\(k\) or 1.