Evaluation of cystatin C in malignancy and comparability of estimates of GFR in oncology patients

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\textbf{A B S T R A C T}

\textbf{Objectives:} Cystatin C is the biomarker of choice for use in estimates of kidney function in oncology patients. However as non-renal factors such as muscle mass can influence creatinine concentrations, we evaluated cystatin C as an alternative biomarker and its incorporation in GFR estimating formulae in an oncology setting. Measured GFR is infrequently undertaken in adult clinical practice with the consequent reliance on calculated GFR for patient assessment.

\textbf{Design and methods:} Cystatin C and creatinine concentrations were evaluated from 134 oncology patients prior to commencing chemotherapeutic cycles. Estimates of creatinine clearance (Cockroft-Gault) and GFR (using Hoek, Jonsson, MDRD and CKD-EPI) were evaluated. Cystatin C-based GFR estimates (using CKD-EPI CysC and CKD-EPI SCr/CysC) were compared with the creatinine-based GFR estimates (CG, MDRD and CKD-EPI SCr) within the GFR ranges of 60–89, 45–59 and ≤44 mL/min/1.73 m\textsuperscript{2}.

\textbf{Results:} Cystatin C concentrations were significantly higher in oncology patients both prior to commencing chemotherapy (F: P < 0.01 and M: P < 0.0001) and during cycles of treatment (F: P < 0.0001 and M: P < 0.01) when compared with a reference population. Cystatin C concentrations also increased significantly during chemotherapy (P < 0.0001) in a subset of female patients evaluated. Poor agreement (average 42\%) was demonstrated between CKD-EPI CysC and creatinine-based GFR estimates within the investigated GFR ranges, with improved agreement (average 55\%) when using the combined CKD-EPI SCr/CysC formula.

\textbf{Conclusions:} This study demonstrated a malignancy and treatment-mediated effect on cystatin C measures, which may confound its clinical utility in estimating GFR in oncology patients.

1. Introduction

Kidney injury is a potential complication in patients receiving chemotherapy treatment which requires timely detection and close monitoring. In oncology, calculated estimations of glomerular filtration rate (GFR) are an established means of assessing kidney function in practice. While some oncology centres measure the clearance of an exogenously administered infused substance such as iohexol or inulin, these methods can be challenging, invasive and time-consuming and are infrequently performed in adults commencing chemotherapy regimens [1,2]. While measured GFR (mGFR) is considered the gold standard, it should be noted that error can also be encountered in its measurement and it is susceptible to physiological variability in kidney function [3]. Obtaining the best
estimate of GFR is critically important in oncology as optimisation of drug dose is based on this.

Creatinine is the biomarker of choice for use in GFR-estimating formulae, which include Cockcroft-Gault (CG; estimate of creatinine clearance, CrCl), the Modified Diet and Renal Disease (MDRD) and Chronic Kidney Disease-Epidemiology collaboration (CKD-EPI) formulae. However, despite its universal application, creatinine is influenced by many factors which can affect its utility in practice. Analytical issues and biological factors independent of kidney function such as muscle mass [4] and dietary protein intake [5], which can vary substantially in oncology patients [6], have the potential to significantly affect circulating measures of creatinine and in turn, estimates of GFR. Recent improvements in the adoption of enzymatic creatinine assays have generally overcome the analytical issues previously encountered with non-creatinine chromogens. A deterioration of kidney function by 50% is potentially required before any appreciable increase in serum creatinine concentration is observed [7,8], precluding early detection of impairment. In terms of the utility of creatinine in estimating formulae, it is important to recognize the limitations of its use in CG and MDRD. CG was derived in a male cohort using an unstandardized creatinine method [9], while MDRD is acknowledged to underestimate GFR above 60 mL/min/1.73 m² [10]. This further potentiates the errors encountered using creatinine assessment, prompting the investigation of alternative biomarkers including cystatin C to evaluate kidney function in a cohort of oncology patients.

Cystatin C is a 13 kDa cysteine proteinase inhibitor with a shorter plasma half-life than creatinine, which is thought to facilitate a more rapid detection of alterations in kidney function [11,12]. It has also been postulated to confer improved sensitivity in detecting small changes in eGFR [11]. When compared with creatinine, cystatin C has demonstrated better ability to evaluate kidney function in oncology patients [13]. In addition, cystatin C measurements are less affected by factors known to confound creatinine concentrations, such as muscle mass [14] and protein intake [15], although thyroid function [16] and corticosteroids [17] may influence cystatin C concentration. Its use in cystatin C-based CKD-EPI eGFR formulae further underlines its potential, with evidence suggesting that using CKD-EPI CysC may improve the detection of impaired kidney function in malignancy [18]. When combined with serum cystatin C in the CKD-EPI Scr/CysC formula, the additive value of cystatin C has previously translated to greater detection of GFR values below 90 mL/min/1.73 m² in oncology patients as measured by mGFR [19]. Standardisation of cystatin C assays to a European reference material (ERM DA-471/IFCC) has improved the analytical comparability of cystatin C determination.

Notwithstanding the reported advantages, some studies have demonstrated higher concentrations of cystatin C in patients diagnosed with malignancy without evidence of impaired kidney function [20–22]. Such findings could impair the utility of cystatin C in the estimation of kidney function in oncology patients. The aims of this study were to assess the relationship of cystatin C with creatinine concentration in a cohort of cancer patients receiving chemotherapy treatment and secondly to compare cystatin C-based GFR estimations with currently utilised serum creatinine-based eGFR (and CrCl) formulae.

2. Materials and methods

Ethical approval was received prior to commencement of this study from the Mater University Hospital ethics committee (Ref: 1/378/1387) in accordance with the Declaration of Helsinki. Serum samples were collected in gel separator tubes from 134 oncology patients who provided informed consent to participate in the study (Table 1), 86 of whom were naïve to prior chemotherapeutic treatment. Samples were obtained before commencement of chemotherapy and prior to each cycle in their regimen (number of samples, n = 640), centrifuged at 3500g for 10 min and stored at −70 °C until analysis. Serum samples were also collected from a group of subjects with no defined acute kidney injury (AKI), acute kidney disease (AKD) or chronic kidney disease (CKD) for creatinine (women, n = 113; men, n = 128) and cystatin C (women, n = 120; men, n = 120) assessment as a reference population. Demographic information for all patients and reference populations included in the study is shown in Table 1.

One hundred and twenty-two patients were diagnosed with solid organ tumors of which the most common diagnoses were those of breast, lung, colorectal and ovarian cancer. Breast cancer was the most frequently observed malignancy (n = 63; all women); 20 patients presented with lung cancer (men n = 9; women n = 11); 10 patients with colorectal cancer (men n = 5; women n = 5). Nine patients presented with lymphoma; 1 patient with leukemia. Others included one male patient presenting with angiosarcoma and a female patient with leiomyosarcoma.

For analysis, samples were thawed, mixed and centrifuged at 3500g for 10 min before being analysed using a particle-enhanced turbidimetric immunoassay (PETIA) for cystatin C (Abbott Diagnostics, Abbott Park, IL, USA) and using an enzymatic assay for creatinine (Abbott Diagnostics, Abbott Park, IL, USA). The cystatin C assay was standardized to the European reference material ERM DA-471/IFCC. The enzymatic assay for creatinine was traceable to the isotope dilution mass spectrometry (IDMS-NIST) standard reference material (SRM) 967.

Each patient’s age and actual body weight were used to calculate estimates of CrCl (CG [9]) and estimates of GFR (using Hoek [23], Jonsson [24], MDRD 175 [25], CKD-EPI Scr [26], CKD-EPI CysC [27] and CKD-EPI Scr/CysC [27]). Estimates of GFR (and CrCl, using actual body weight) were censored at 200 mL/min/1.73 m² (200 mL/min for CrCl, w with values exceeding this limit excluded from analysis.

All study data was evaluated for normality using D’Agostino-Pearson omnibus normality test. As results were not normally distributed, non-parametric statistical tests were utilised including the Mann-Whitney U test, Kruskal-Wallis H test and Friedman test with post-hoc analysis using Dunn’s multiple comparisons test. The level of agreement between cystatin C-based and creatinine-based eGFR formulae was performed by assessment of their ability to concordantly calculate eGFR measures within the designated eGFR ranges ( < 44 mL/min/1.73 m², 45–59 mL/min/1.73 m² and 60–89 mL/min/1.73 m²). The < 60 mL/min/1.73 m² range was examined specifically within the ranges of < 44 mL/min/1.73 m² and between 45–59 mL/min/1.73 m² because a cystatin C-based eGFR may be recommended to confirm a diagnosis of CKD in accordance with the National Institute for Health and Clinical
Excellence guidelines.

3. Results

3.1. Evaluation of cystatin C and creatinine in an oncology population

Creatinine and cystatin C concentrations were significantly higher ($P < 0.0001$; Mann-Whitney test; Fig. 1A and D) in men within the reference subject cohort. Based on this observation, subsequent analyses of biomarker measures in the oncology cohort were stratified by gender.

Creatinine concentrations were marginally lower in female oncology patients during the chemotherapeutic regimen when compared with the female reference population ($61 \mu\text{mol/L vs } 66 \mu\text{mol/L}, P = 0.01$; Kruskal-Wallis; Fig. 1B). Similar findings were observed in the assessment of creatinine concentrations between the male reference population and that of male oncology patients both prior to commencing the chemotherapeutic regimen and during cycles of treatment ($81 \mu\text{mol/L and } 79 \mu\text{mol/L},$ respectively vs $86 \mu\text{mol/L}, P < 0.04$; Kruskal-Wallis; Fig. 1C). This contrasted with higher cystatin C concentrations demonstrated prior to commencing chemotherapeutic regimen (Women: $0.83 \text{mg/L vs } 0.72 \text{mg/L},$ Men: $1.03 \text{mg/L vs } 0.79 \text{mg/L}, P < 0.01, P < 0.0001$; Kruskal-Wallis) and also during chemotherapy in both female and male oncology patients (Women: $0.81 \text{mg/L},$ Men: $0.86 \text{mg/L}, P < 0.0001, P < 0.01;$ Kruskal-Wallis) when compared with female and male reference populations, respectively (Fig. 1E and F). While cystatin C measures were significantly lower during chemotherapy treatment in male patients when compared with measures prior to commencing chemotherapeutic regimen, these measures were still higher than that of the male reference population ($P < 0.01$; Kruskal-Wallis).

### Table 1
Demographics of patient cohort at enrolment.

| General characteristic                        | Overall cohort [Men, Women] |
|-----------------------------------------------|----------------------------|
| Number of patients                            | 134 [26,108]               |
| Mean age at enrolment (SD) (years)            | 57 (12)                    |
| Age range at enrolment (years)                | [63 (12), 55 (12)]         |
| Mean weight at enrolment (SD) (Kg)            | 71 (15)                    |
| Weight range at enrolment (Kg)                | [84 (12), 68 (14)]         |
| Mean BSA at enrolment $n = 84$ (SD) (m$^2$)   | 1.76 (0.20)                |
| Mean BMI at enrolment $n = 84$ (SD)           | 27 (6)                     |
| BMI range at enrolment $n = 84$               | [28 (4), 27 (7)]           |
| Cancer assessment                             |                            |
| Solid organ tumor                             | 122 [21,101]               |
| Hematological Malignancy                      | 10 [4,6]                   |
| Other                                         | 2 [1,1]                    |
| Reference population (Creatinine)             |                            |
| Number of subjects                            | 241 [128,113]              |
| Age range at enrolment (years)                | 19–81                      |
| Median creatinine concentration (IQR) (µmol/L)| 75 (66–87)                 |
| Reference population (Cystatin C)             |                            |
| Number of subjects                            | 240 [120,120]              |
| Age range at enrolment (years)                | 23–81                      |
| Median cystatin C concentration (IQR) (mg/L)  | 0.77 (0.70–0.85)           |

IQR, inter-quartile range; SD, standard deviation; BSA, body surface area; BMI, body mass index.
3.2. Effect of malignancy on cystatin C concentration

There was a significant difference in creatinine concentration in female oncology patients when examined by malignancy (numbers of female patients: breast, n=63; lung, n=12; ovarian cancer, n=18 and lymphoma, n=5; number of samples, n=591) and compared with the female reference population (P < 0.01; Kruskal-Wallis; Fig. 2A). When examined more closely, this difference was attributed to significantly lower creatinine concentrations in breast cancer patients (P < 0.01). This contrasted with higher cystatin C concentrations in female breast and lung cancer patients when compared with the female reference population (number of samples, n=580; P < 0.0001; Kruskal-Wallis; Fig. 2B). In addition, cystatin C concentrations in lung cancer patients were significantly higher compared with breast, ovarian cancer and lymphoma patients (P < 0.05, P < 0.05 and P < 0.01, respectively; Kruskal-Wallis).

Fig. 1. Gender-specific evaluation of creatinine in a normal population (A) and in female (B) and male (C) oncology patients with cystatin C evaluation in a normal population (D) and in female (E) and male (F) oncology patients. n = Number of normal subjects +/- oncology patients. *P < 0.05, **P < 0.01, ****P < 0.0001; Kruskal-Wallis. Results are presented as median with the inter-quantile range.
3.3. Investigation of cystatin C concentration during chemotherapy treatment

In a subset of female breast cancer patients (n=45) who were assessed in each of the first 5 cycles of their chemotherapy, cystatin C concentration increased significantly ($P < 0.0001$; Friedman; Fig. 3), with significantly higher values at the 5th cycle of chemotherapy when compared with baseline naïve to treatment (NTT) measures ($P < 0.0001$; Dunn's multiple comparison test). Creatinine concentrations and eGFR measures taken during this assessment period did not change significantly.

Fig. 2. Comparison of creatinine and cystatin C in females by malignancy. Number of subjects: normal population, n=120; n=breast, n=63; lung, n=12; ovarian cancer, n=18 and lymphoma, n=5). *$P < 0.05$, **$P < 0.01$, ****$P < 0.0001$; Kruskal-Wallis. Results are presented as median with the inter-quantile range.

Fig. 3. Changes in cystatin C levels in a subset of breast cancer patients during the first 5 cycles of chemotherapy as compared with creatinine and eGFR measures. Number of patients, n=45. *$P < 0.05$, **$P < 0.001$, ****$P < 0.0001$; Friedman test. NTT, Naïve to treatment. Results are presented as median with the inter-quantile range.
3.4. Evaluation of cystatin C in GFR estimating formulae

In a comparison of eGFR formulae using creatinine (CG, MDRD 175, CKD-EPI Scr), cystatin C (Hoek, Jonsson, CKD-EPI CysC) and a combination of both biomarkers (CKD-EPI Scr/CysC) significant differences between formulae were observed ($P < 0.0001$, Kruskal-Wallis; Fig. 4). The characteristics of each formula and the significant differences between formulae are presented in Table 2. Of note, the CKD-EPI formulae generated narrower eGFR ranges when compared with CG, MDRD 175, Hoek and Jonsson. There was considerable discordance between cystatin C-based CKD-EPI formulae when compared with serum creatinine-based GFR estimating formulae, with an average of 42% concordance within the investigated GFR ranges of 60–89 mL/min/1.73 m² (CKD Stage 2), 45–59 mL/min/1.73 m² (CKD Stage 3 A) and ≤ 44 mL/min/1.73 m² (Stages 3B, 4 and 5) (Table 3). This finding was particularly evident at serum creatinine-determined eGFR levels of between 45–59 mL/min/1.73 m². While the combined CKD-EPI formulae was found to improve the levels of concordance (average 55% values in agreement) particularly when compared with MDRD and CKD-EPI Scr, the least concordance was observed between 45–59 mL/min/1.73 m².

4. Discussion

Cystatin C has gained considerable recognition for the assessment of kidney function in recent years, following promotion in the

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**Table 2**

|                          | CG ($\text{mL/min}$) | Hoek$^{23}$ | Jonsson$^{24}$ | MDRD 175$^{25}$ | CKD EPI Scr$^{26}$ | CKD EPI CysC$^{27}$ | CKD EPI Scr/CysC$^{27}$ |
|--------------------------|----------------------|-------------|----------------|-----------------|---------------------|----------------------|--------------------------|
| **Number of samples evaluated** | 628                  | 606         | 586            | 634             | 638                 | 612                  | 596                      |
| **eGFR (mL/min/1.73 m²)**  |                      |             |                |                 |                     |                      |                          |
| Minimum                  | 32                   | 39          | 32             | 39              | 38                  | 33                   | 38                       |
| 25% Percentile           | 78                   | 79          | 85             | 75              | 83                  | 78                   | 83                       |
| Median                   | 104                  | 93          | 104            | 90              | 96                  | 97                   | 96                       |
| 75% Percentile           | 128                  | 109         | 128            | 107             | 106                 | 109                  | 108                      |
| Maximum                  | 196                  | 197         | 199            | 194             | 155                 | 172                  | 162                      |
| **Formulae comparison**  |                      |             |                |                 |                     |                      |                          |
| CG                       | –                    | –           | –              | –               | –                   | –                    | –                        |
| Hoek                     | NS                   | NS          | –              | NS              | NS                  | NS                   | NS                       |
| Jonsson                  | NS                   | –           | –              | NS              | NS                  | –                    | –                        |
| MDRD                     | NS                   | NS          | NS             | NS              | –                   | NS                   | NS                       |

GFR (and CrCl) estimates censored at 200 mL/min/1.73 m² (200 mL/min).

* $P < 0.5$.

** $P < 0.05$.

*** $P < 0.001$.

**** $P < 0.0001$. NS, Not significant. Formula comparison inclusive of all significant differences identified between all formulae using Dunn’s multiple comparison test.
Table 3
Comparison of eGFR measure assignment in the assigned ranges of <44 mL/min/1.73 m², 45–59 mL/min/1.73 m² and 60–89 mL/min/1.73 m² between current creatinine-based and cystatin C-based-GFR estimating formulae.

|                | CKD-EPI CysC |             |             | CKD-EPI SCR/CysC |             |             |
|----------------|--------------|-------------|-------------|------------------|-------------|-------------|
| mL/min/1.73m²  | <44          | 45-59       | 60-89       | >90              | <44         | 45-59       | 60-89       | >90              |
| CG estimated GFR |              |             |             | Total n          |             |             |             | Total n          |
| <44 mL/min     | 9 (50)       | 8 (44)      | 1 (6)       | 0 (0)            | 18          | 7 (39)      | 10 (56)     | 1 (5)            | 0 (0)          | 18          |
| 45-59 mL/min/1.73 m² | 0 (0)       | 9 (28)      | 23 (72)     | 0 (0)            | 32          | 0 (0)       | 9 (29)      | 23 (71)          | 0 (0)          | 32          |
| 60-89 mL/min/1.73 m² | 3 (2)       | 16 (11)     | 64 (42)     | 69 (45)          | 152         | 2 (1)       | 13 (9)      | 81 (53)          | 56 (37)        | 152         |
| MDRD estimated GFR |              |             |             | Total n          |             |             |             | Total n          |
| <44 mL/min.1.73m² | 3 (43)       | 3 (43)      | 0 (0)       | 1 (14)           | 7           | 5 (71)      | 1 (14)      | 1 (14)           | 0 (0)          | 7           |
| 45-59 mL/min.1.73 m² | 8 (19)       | 15 (36)     | 15 (36)     | 4 (10)           | 42          | 4 (10)      | 22 (52)     | 16 (38)          | 0 (0)          | 42          |
| 60-89 mL/min.1.73 m² | 1 (<1)       | 19 (8)      | 103 (43)    | 118 (49)         | 241         | 0 (0)       | 9 (4)       | 132 (55)         | 100 (42)       | 241         |
| CKD-EPI SCR estimated GFR |              |             |             | Total n          |             |             |             | Total n          |
| <44 mL/min.1.73m² | 3 (50)       | 3 (50)      | 0 (0)       | 0 (0)            | 6           | 5 (83)      | 1 (17)      | 0 (0)            | 0 (0)          | 6           |
| 45-59 mL/min.1.73 m² | 6 (18)       | 12 (35)     | 13 (38)     | 3 (9)            | 34          | 4 (12)      | 17 (50)     | 13 (38)          | 0 (0)          | 34          |
| 60-89 mL/min/1.73 m² | 3 (2)        | 19 (11)     | 81 (48)     | 65 (39)          | 168         | 0 (0)       | 14 (8)      | 117 (70)         | 37 (22)        | 168         |

Total n refers to the total number of eGFR values within the specified eGFR range of each row (<44 mL/min/1.73 m², 45–59 mL/min/1.73 m² and 60–89 mL/min/1.73 m²), as calculated by either CG, MDRD or CKD-EPI SCR. These values are compared with what would be calculated using the same data in either CKD-EPI CysC or CKD-EPI SCR/CysC in the associated columns.
KDIGO 2012 guidelines [28] and recent NICE guidelines (CKD in adults; CG182 [29]) as an alternative to less accurate creatinine measures. Oncology patients are recognised to be at significant risk of developing kidney insufficiency [30] which warrants close monitoring of kidney function to detect the earliest possible indications of injury. Furthermore, optimal dose of treatments such as carbo- and cisplatin are critically dependent on provision of the most accurate eGFR. Over 50% of cancer patients may develop cachexia and loss of muscle mass while malnutrition is also frequently observed [6], which has the potential to significantly affect the non-renal factors which influence serum creatinine concentrations. Cystatin C offers the potential to overcome the limitations of creatinine in potentially providing a more accurate evaluation of kidney function in oncology patients, including in cases of malnutrition and sarcopenia.

In our study, no patient developed significant kidney impairment during this study (one patient had pre-existing Stage 3 CKD). Creatinine measures were comparable with a reference population except for female oncology patients, where levels were slightly lower when compared with a normal female population. As we have not examined muscle mass or nutritional status in this patient cohort, we cannot exclude the potential influence of either of these factors in mediating the differences in creatinine levels observed.

We observed significantly higher concentrations of cystatin C in our oncology cohort both prior to and during chemotherapy treatment. When examined more specifically according to cancer type in a subset of female patients (n = 98: breast, n = 63; lung, n = 12; lymphoma, n = 5; ovarian, n = 18; Fig. 2), we observed significantly higher concentrations in those diagnosed with breast and lung cancer. Creatinine concentrations were significantly lower in breast cancer patients when compared with a reference female population which indicates that poor levels of kidney function were not likely to be mediating the increased measures of cystatin C observed in breast cancer patients. Taken together, these findings were suggestive of a malignancy-mediated effect on cystatin C and corroborate published findings depicting elevated cystatin C concentrations in various malignancies including breast, prostate [20] and colorectal cancer [31]. As cystatin C concentrations increased significantly during chemotherapy in a subset of 45 breast cancer patients and were not accompanied by a significant increase in creatinine concentration or decrease in eGFR measures, these findings suggest chemotherapy treatment may also influence cystatin C concentrations either as a direct result of the treatment or its effects on malignancy. The potential for malignancy and treatment-mediated effects (in particular, corticosteroid treatment) to influence cystatin C concentrations could additionally confound the clinical utility of cystatin C in assessing kidney function in oncology patients. A recent study [32] in patients with heart failure showed significant increases in cystatin C in patient receiving corticosteroids. As corticosteroids are commonly used in oncology, our findings underline the importance of investigating non-GFR determinants of biomarker measurements in various patient populations in order to ensure their appropriate utilisation, as highlighted previously by Levey and Eckfeldt [33].

This study demonstrated significant differences in cystatin C and creatinine-based estimating formulae (P < 0.0001; Kruskal-Wallis) with the CG, MDRD, Hoek and Jonsson formulae demonstrating greater maxima than the CKD-EPI formulae. This may be explained by the influence of patient weight and failure to accommodate creatinine assay standardisation (CG), the known potential for underestimation of GFR > 60 mL/min/1.73 m² (MDRD) and the derivation of the estimating formulae prior to the standardisation of the cystatin C assay in 2011 (Hoek and Jonsson) are likely to account for the greater variation of these formulae when compared with CKD-EPI. These statistical differences may translate into clinically significant implications for patients. There is no consensus method for estimating renal function with CG used in chemotherapeutic drug dosing, whereas formulae such as MDRD or CKD-EPI are commonly used to evaluate kidney function in diagnostic laboratories. The loyalty to CG is not based on accuracy in determining kidney function, but rather on the vast experience which has been accrued from its many years of utility and on the reliance on such experience which drives its future use. Furthermore, clinical trials for chemotherapeutic drug dosing are commonly based on CG assessment, which suitably complements the accumulated experience. While gold standard practice is to measure GFR [34], this method is not practical for routine assessment and is not always adopted for use, as in the case of our cohort. Furthermore, previous research has alluded to discordant measures of GFR depending on the filtration marker chosen [35,36]. In a study by Seegmiller and colleagues, iohexol-based measures of GFR were found to be on average 15% lower than iothalamate-based mGFR [37]. In addition, discordance may arise as a result of the different methodologies adopted to measure GFR [38]. Such findings highlight that this gold-standard method is not without its own controversy and call into question the need for utilising this practice where highly accurate measures are not necessarily of primary importance [38]. In our study, all three CKD-EPI formulae performed comparably with a marginally wider range obtained for CKD-EPI CysC. While CKD-EPI SCR/CysC has demonstrated closer associations with mGFR [27], it is worth noting that cystatin C concentrations in this study were not comparable with a normal population in which this formula was designed to perform optimally.

Cystatin C-based eGFR formulae have been advocated to improve the accuracy of GFR estimation (KDIGO) [28], with NICE guidelines [29] also supporting their use most notably within the eGFR range of 45–59 mL/min/1.73 m². In our study, cystatin C based eGFR estimates were discordant when compared with serum creatinine-based estimates CG, MDRD and CKD-EPI, particularly in the range of 45–59 mL/min/1.73 m², with many cystatin C-based estimates higher than their serum creatinine-based estimate. Better concordance between the creatinine-based estimates of GFR may be in part related to the inclusion of creatinine in these formulae. Where cystatin C-based estimates have been advocated in place of serum creatinine within this eGFR range, with MDRD eGFR, more study is required if this is to be advocated in an oncology setting, where specific cancer and treatment confounders are evident. Of note, while sample size was small, cystatin C-based CKD-EPI estimates of GFR were often lower than that generated by serum creatinine-based estimating formulae at eGFR values below 44 mL/min/1.73 m². This comparison highlights the discordance between the formulae which is likely to be potentiated by the use of different biomarkers and their non-GFR determinants which may be very influential in different patient populations, as outlined previously by Meeusen and colleagues [39]. For some measurements, the differences between the formulae observed in evaluating GFR may reflect the influence of elevated cystatin C measures on the estimation of GFR probably related to specific cancer-mediated or features consequent to treatment in oncology patients as cystatin C
levels do not necessarily reflect those of a normal population which CKD-EPI was designed to evaluate.

5. Conclusion

The results in this study demonstrate potential cancer and treatment effects on cystatin C measurement. The comparability of the eGFR derivations CKD-EPI SCr, CKD-EPI CysC and CKD-EPI Cr/CysC was reassuring but our study did not show any additional evidence for the inclusion of cystatin C for estimating GFR in oncology patients.

6. Limitations

The aim of the study was to assess the comparability of estimates of GFR using both creatinine and cystatin C. A limitation is that measured GFR was not performed for comparison in this oncology cohort, although there is evidence that measured GFR is not entirely an optimal/gold standard technique [38]. As muscle mass and body fat are not typically assessed in oncology patients receiving chemotherapy treatment, the data was not available for evaluation in this study.

Declaration of conflicting interests

There are no competing interests.

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Ethical approval

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Guarantor

MCF.

Contributorship

MCF designed research; MJ and CG collected data; MJ analysed data and wrote manuscript; MCF, SD and WT reviewed and edited then manuscript and approved the final version of the manuscript.

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