Assessment of glomerular filtration rate in cancer patients

A thesis submitted by

Verônica Torres da Costa e Silva

In partial fulfillment of the requirements for the degree of

Master of Science

in

Clinical and Translational Science

Tufts University

Graduate School of Biomedical Sciences

February 2023

Advisor: Lesley A. Inker, MD, MS

Abstract

Current guidelines recommend estimating GFR using creatinine (eGFRcr) with the CKD-EPI equation as the first test for GFR evaluation. The Cockcroft-Gault (CG) equation is still commonly used in oncology practice and clinical trials despite increasing evidence of its greater inaccuracy compared to measured GFR (mGFR), relative to the CKD-EPI equation. Guidelines recommend eGFR using cystatin C (eGFRcys) or both markers (eGFRcr-cys) as a confirmatory test for patients in whom eGFRcr is thought to be inaccurate or in clinical settings in which a highly accurate test is required, as is the case in oncology. However, neither has been carefully evaluated in cancer patients. We compared the performance of the CKD-EPI creatinine and cystatin C equations and other eGFRcr (MDRD, CamGFRv2) to the CG equation in adults with solid tumors. We prospectively recruited 1,200 patients between April 2015 and September 2017 and measured GFR using plasma clearance of ^{51}Cr-EDTA. Bias was defined as the median of the differences between mGFR and eGFR. Accuracy was defined as the percentage of estimates that differed by more than 30% from the measured GFR (1–P_{30}). Mean (SD) age and mGFR were 58.8 (13.2) years and 78.4 (21.7) ml/min/1.73 m^2, respectively. Bias among eGFRcr equations varied from -8.1 to +6.1 ml/min/1.73 m^2. CG was the least accurate of all eGFRcr equations with bias of -8.1 (-9.4 to -6.9) and 1-P_{30} (95% confidence interval) was 24.9 (22.4-27.3)%. CKD-EPI had 1-P_{30} of 19.1 (16.8-21.2)%. eGFRcr-cys had the best performance: bias -2.0 (-2.6 to -1.1) ml/min/1.73m^2 and 1-P_{30} 7.8 (6.3-9.4)%. We conclude that CG equation should not be preferred over CKD-EPI equation, and that eGFRcr-cys can be used as a confirmatory test in adults with solid tumors. A major policy implication would be to adopt general practice guideline-recommended

methods for GFR evaluation in oncology practice.

Table of Contents

List of Tables

List of Figures

List of Copyrighted Materials Used

Antonângelo L, Burdmann EA, Caires RA, Castro G, Costa e Silva VT, Costalonga E, Coura-Filho G, Estevez-Diz MDP, Gil-Jr LA, Inker LA, Levey AS, Marçal L, Mathew P, Miao S, Sapienza MT, Tighiouart H, Zanetta DMT. Estimating Glomerular Filtration Rate from Creatinine and Cystatin C in Adults with Solid Tumors: A Prospective Cross-Sectional Study. *Kidney Int.* 2022;101(3):607-614.

List of Abbreviations

B2M: Beta-2-microglobulin
BMI: Body mass index
BTP: Beta-trace-protein
CAP: College of American Pathologists
CG: Cockfrot-Gault
CKD: Chronic Kidney Disease
CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration
CP: Cystein proteinase
CPI: Cystein proteinase inhibitor
CRP: C-reactive protein
Cys: Cystatin C
DTPA: Diethylenetrtriaminepentaacetate
eClCr: Estimated creatinine clearance
ECOG: Easter Cooperative Oncology Group
EDTA: Ethylenediaminetetraacetic acid
eGFR: Estimated glomerular filtration rate
$eGFR_{B2M}$: Estimated glomerular filtration rate based on the serum beta-2-microglobulin
$eGFR_{B2M\text{-}BTP}$: Estimated glomerular filtration rate based on serum beta-2-microglobulin and serum beta-trace protein
$eGFR_{BTP}$: Estimated glomerular filtration rate based on serum beta-trace protein
eGFRcr: Estimated glomerular filtration rate based on serum creatinine
eGFRcr-cys: Estimated glomerular filtration rate based on serum creatinine and serum cystatin C
eGFRcr-cys-$_{B2M}$: Estimated glomerular filtration rate based on serum creatinine, serum cystatin, and serum beta-2-microglobulin
eGFRcr-cys-$_{BTP}$: Estimated glomerular filtration rate based on serum creatinine, serum cystatin, and serum beta-trace protein
eGFRcr-cys-$_{B2M\text{-}BTP}$: Estimated glomerular filtration rate based on serum creatinine, serum cystatin, serum beta-2-microglobulin, and serum beta-trace protein
eGFRcys: Estimated glomerular filtration rate based on serum cystatin C
FDA: Food Drug Administration
GFR: Glomerular Filtration Rate
IDMS: Isotop dilution mass spectrometry
KDIGO: Kidney Disease Improving Global Outcome
MAPK/ErK: Mitogen activated protein kinase pathway
MDRD: Modification of Diet Renal Disease
mGFR: Measured glomerular filtration rate
NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases
NKDEP: National Kidney Disease Education Program
NIST: National Institute of Standards and Technology
RCT: Randomized clinical trial
S_{B2M}: Serum beta-2-microglobulin
S_{BTP}: Serum beta-trace-protein
Scr: Serum creatinine
Scys: Serum cystatin C

TGF- β: Tumor growth factor beta
US: United States

Chapter 1: Introduction

Glomerular filtration rate (GFR) is generally considered the best overall index of kidney function in health and disease, generally accepted as a measure of the functioning kidney mass[1]. The true GFR cannot be measured directly in humans. Instead, it is assessed from clearance measurements or serum levels of filtration markers, which are exogenous or endogenous low-molecular-weight solutes that are mainly eliminated by the kidneys[2]. Understanding the strengths and limitations that are inherent to each filtration marker is pivotal for optimal decision making.

Several techniques to directly measure GFR based on the serum or urinary clearance of exogenous filtration markers are available in clinical practice, such as ethylenediaminetetraacetic acid (EDTA), iothalamate, diethylenetrtriaminepentaacetate (DTPA) and iohexol, which are commonly used in Europe and South America, although not routinely available in the Unites States (US). Some of these techniques (serum clearance of EDTA and iohexol) are almost unbiased compared to the urinary clearance of inulin, the gold standard for GFR measurement[3].

In clinical practice, GFR is usually estimated through endogenous filtration markers. All endogenous filtration markers are affected by non-GFR determinants which include generation, tubular reabsorption or secretion, and extra-renal elimination[2]. The most commonly used is serum creatinine (Scr) which is derived by the metabolism of phosphocreatine in muscle as well as from dietary meat intake. Creatinine has been used as a filtration marker since 1926 because is not protein-bound, is freely filtered across the glomerulus, the production and excretion are constant in the steady-state, and the assay is inexpensive, reliable and widely available. However, creatinine is also removed from the body via proximal tubular

secretion (10-40% of filtered load) and is affected by drugs that influence tubular secretion (trimetropim, cimetidine, tyrosine kinase inhibitors), and more importantly by diet and muscle mass. These factors limit its accuracy[4].

Estimating equations for GFR are regression equations that estimate the level of measured GFR (mGFR) from plasma concentrations of endogenous filtration markers and demographic and clinical variables as observed surrogates for the unmeasured non-GFR determinants. Estimating equations are primarily used in clinical practice because they provide a more accurate estimate of mGFR than the plasma concentration alone. For creatinine, variables used have included weight, age, sex or race[5]. Although many equations have been developed over the last 40 years, the most commonly Scr-based equations are the Cockroft-Gault (CG)[6], the Modification of Diet Renal Disease (MDRD) Study[7] and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPIcr)[8].

The first equation used in widespread practice was the CG equation. This was developed in 1976, including data from 236 patients (96% men), and estimated creatinine clearance which systematically overestimates the true GFR. The CG is expressed in ml/min, which has an impact when used for the prescription of chemotherapy. It is less accurate in the extremes of age and body size, and it does not use standardized assays (assays traceable to international reference materials)[6]. It continues to be used as regulatory agencies recommended this equation in pharmacokinetic studies in drug development program agencies in 1998[9].

In 1999, the MDRD Study equation was developed, a much more robust model, including 1.628 patients, and estimated the measured GFR. However, the average of the study population was nearly 40 ml/min/1.73m^2. This equation is expressed as ml/min/indexed by body surface area, reducing variation among healthy individuals and

allowing comparisons for normative values[7]. It was recalibrated to standardized assays, and was recommended by the Food and Drug Administration (FDA) in 2010 alongside the CG equation for drug dosing[10]. The MDRD equation provides more accurate GFR estimates than the CG equation in the low GFR range (<60ml/min/1.73m^2) but underestimates measured GFR for individuals who have GFR in the normal range[5].

In 2009, the CKD-EPIcr equation was developed, including more than five thousand patients, using measured GFR as reference. In a similar way to the MDRD equation, is expressed indexed by body surface, and uses standardized assays. The CKD-EPIcr equation provides better estimates than CG in all levels of GFR and better estimates than MDRD equation at higher levels of GFR. In 2012, the nephrology guidelines recommended that GFR estimation based on serum creatinine using the CKD-EPIcr equation should be used as the "first test" for GFR evaluation for routine clinical practice in adults[11].

Other filtration markers not influenced by the non-GFR determinants of Scr, particularly nutrition status, have been assessed in the last ten years. The most widely evaluated is cystatin C (Cys). Cys is a 122-amino acid (nonglycosylated) protein with a molecular weight of 13Kd produced in all nucleated cells. Approximately 99% of the filtered load of Cys is reabsorbed by the proximal tubular cells, where it is almost completely catabolized, with the remainder eliminated largely intact in the urine. The serum level of Cys (Scys) is not influenced by muscle mass or diet[5]. Also, in comparison to Scr, Scys is less affected by age, sex, race, and world region. However, there are important clinical factors that seem to be associated with higher Cys independent of measured GFR such as smoking, inflammation, adiposity, (hyper) thyroid function, and

use of glucocorticoids[12]. Thus, eGFR based in the combination of creatinine and cystatin C is more accurate than eGFR using either alone, reflecting the lesser influence of non-GFR determinants of either marker when both are used[13]. This is the reason why eGFR based on Scys is recommended as a confirmatory test, in combination with Scr (eGFRcr-cys) using the CKD-EPI equations for the overall population[11].

Accurate assessment of GFR in patients with cancer is important to determine eligibility for specific therapies or clinical trials and to adjust dosing of chemotherapy to minimize risks of under treatment and unnecessary systemic and kidney toxicity[14]. Of note, up to 25% of cancer patients have chronic kidney disease (CKD), and two-thirds of them are in the threshold of GFR between 60 and 30 ml/min where the decisions about drug dose, drug selection, and randomized clinical trials (RCTs) are made, and accurate assessment of GFR is herein crucial[15].

Cancer patients were not well represented in the studies in which the eGFR equations described above were derived, and the few equations developed in cancer patients have not been validated in other cancer populations and as of yet, have not been incorporated in clinical practice. Both factors have led to substantial uncertainty in the field, and currently, there are no guidelines recommending the preferred equations for use in patients with cancer[16]. In consequence, many cancer centers worldwide still use the CG equation despite its well-recognized inaccuracy.

A few studies demonstrated that CG should be replaced by the CKD-EPIcr equation in cancer patients as this is associated with more precise estimation of GFR, more precise determination of cancer drug-eligibility, and more accurate dose calculation[17]. A landmark study from Janowitz including 2,471 patients with solid tumors

in England who were scheduled to receive carboplatin, assessed the error (percentage difference) in carboplatin dose calculated using a number of eGFR equations comparing the dose calculated incorporating mGFR[18]. It was observed that CG equation had the highest error in the carboplatin dose with errors greater than 20% in more than 25% of patients. In contrast, only 19% and 14% had errors of greater than 20% with the use of CKD-EPIcr and for the new model, respectively. This study was single center, was restricted to white patients, and Scr assay was not standardized. In subsequent studies, Janowitz's group confirmed the superiority of CKD-EPIcr equation over CG, with now more than 7,000 patients assessed, incorporating multiple centers in United Kingdom (UK), increasing the number of Black patients, and including an adjustment for the standardization of Scr assay[19,20]. However, key limitations remain that these studies are all retrospective, did not collect detailed clinical data, and included mostly European centers.

Cancer patients constitute a heterogeneous population with a wide range of nutritional statuses which will vary by cancer site, clinical stage, and previous or current cancer treatment[21]. Sarcopenia is reported to occur in 16% of patients before cancer treatment to up to 70% of late-stage patients undergoing chemotherapy[22]. Additionally, nutrition status might change during cancer treatment in up to 70% of patients, particularly in patients under chemotherapy that can lose significant amounts of muscle loss in a short period of time[23]. All of these factors will affect creatinine. In this context, Scys could be a useful alternative. However, there is an unresolved debate associated to the reliability of Scys as a filtration marker in patients with cancer. There is a complex, multi-pathway and not completely understood association between Cys and cancer

development, with Cys acting as both tumor promoter or suppressor depending on different cancer sites, cancer stage, and the moment during the course of cancer disease[24]. Only a few clinical studies including a low number of cancer patients (<300) comparing eGFRcys and/or eGFRcr-cys equations to mGFR have been published[25]. Thus, the uncertainty on the use of Cys to estimate mGFR in patients in cancer remains in place.

Herein, this study aimed to evaluate GFR estimating equations compared to mGFR in a large, prospective cohort of patients with solid tumors, using a recommended method for mGFR and standardized assays for Scr and Scys.

Chapter 2: Estimating Glomerular Filtration Rate from Creatinine and Cystatin C in Adults with Solid Tumors: A Prospective Cross-Sectional Study[1]

[1] Verônica T. C. Silva, Luiz A. Gil-Jr, Lesley A. Inker, Renato A. Caires, Elerson Costalonga, George Coura-Filho, Marcelo T. Sapienza, Gilberto Castro, Maria DP. Estevez-Diz MD, Dirce Maria T. Zanetta, Leila Antonângelo, Lia Marçal, Hocine Tighiouart, Shiyuan Miao, Paul Mathew, Andrew S. Levey, Emmanuel A. Burdmann. 2021. *Kidney Int*. 101:607-614. Reprinted here with permission of publisher

2.1. Introduction

Accurate assessment of glomerular filtration rate (GFR) in patients with cancer is important to determine eligibility for specific therapies or clinical trials and to adjust dosing of chemotherapy to minimize risks of under treatment and unnecessary systemic and kidney toxicity. Many cancer centers still use the Cockcroft Gault (CG) equation based on serum creatinine (Scr), although studies in the general population show that it is less accurate than newer equations based on standardized Scr (assays traceable to international reference materials), such as the Modification of Diet in Renal Disease (MDRD) Study and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. Recent studies in patients with solid tumors have shown a potential for error in chemotherapy prescriptions using the CG equation.

Estimated GFR (eGFR) based on Scr (eGFRcr) using the CKD-EPI equation, is recommended as the "first test" for GFR evaluation for routine clinical practice in adults. Patients with cancer were not well represented in the studies in which newer eGFR equations were derived, and for several reasons, the CKD-EPI equation may be less accurate in patients with cancer than in the general population. Creatinine is generated by muscle independent of GFR, thus Scr can be influenced by alterations in diet and nutritional status, which are common in patients with cancer. Serum cystatin C (Scys) is less influenced by these factors than Scr, and eGFR based on Scys is recommended as a confirmatory test, either alone (eGFRcys) or in combination with Scr (eGFRcr-cys) using the CKD-EPI equations. However, Scys may be affected by smoking, inflammation and alterations in fat mass independent of GFR, which are common in patients with cancer.

Limited data are available comparing the performance of GFR estimating equations to measured GFR (mGFR) using validated methods for mGFR and standardized assays for creatinine and cystatin C in patients with cancer. In 2020, a new eGFRcr equation for use with standardized Scr was developed in cancer patients (CamGFRv2), but it has not been validated in an independent study population. This study aimed to evaluate GFR estimating equations compared to mGFR in a large, prospective study of patients with solid tumors, using a recommended method for mGFR and standardized assays for Scr and Scys.

2.2. Methods

2.2.1. Study Population

This study was conducted at the Instituto do Câncer do Estado de São Paulo (ICESP), a cancer hospital in Brazil, part of the University of São Paulo School of Medicine. Patients were enrolled in a prospective cohort (Onco-GFR Study), including mGFR. A detailed description of the full evaluation and eligibility criteria is provided in the Sections 2.5.2.1 and 2.5.2.2. Briefly, adult patients with solid tumors confirmed by histology, ECOG-PS (Eastern Cooperative Oncology Group performance status) ≤ 3, with no recent cancer treatment and no current evidence of risk factors for acute GFR decline, were invited to participate. The current analysis is a cross-sectional evaluation of mGFR and eGFR during the baseline period. The study was approved by the Brazilian Ethics Committee (CEP, number 387/14). All patients gave written informed consent.

2.2.2. Data collection procedures

2.2.2.1. Clinical data

Baseline information included demographics (age, gender, race), comorbid conditions, cancer variables, smoking history, height and weight. Methods of ascertainment and a full description of variables are in the Section 2.5.3.

2.2.2.2. GFR measurement

GFR was measured by plasma clearance of ^{51}Cr-EDTA at the Nuclear Medicine Center (Section 2.5.4). Briefly, blood samples were collected two, four and six hours after administration of 3.7 MBq (100 μCi) of ^{51}Cr-EDTA. GFR was calculated through the slope and intercept of plasma disappearance curve of ^{51}Cr-EDTA with correction of Bröchner-Mortensen, indexed to 1.73 m^2 of body surface area (BSA) using the method of Dubois and Dubois[14].

2.2.2.3. GFR estimating equations

eGFRcr was determined from the 1976 CG, 2006 MDRD, 2009 CKD-EPI and 2020 CamGFRv2 equations. eGFRcys and eGFRcr-cys were determined from the 2012 CKD-EPI equations[15] (Table 2.1). eGFR was indexed for BSA and expressed as ml/min/1.73 m^2.

2.2.2.4. Laboratory tests

All laboratory tests were collected on the day of GFR measurement. Serum samples for creatinine and cystatin C were frozen at – 80°C, and measured at the

University of Minnesota at the end of the study during a single run, using assays traceable to international reference materials. Other analytes were analyzed locally on the day the samples were collected (Section 2.5.5).

2.2.3. Statistical analysis

The main exposure was eGFR equations. The main outcome measures were differences between eGFR and mGFR, ascertained as bias, precision and accuracy. Bias was defined as the median of the differences between mGFR and eGFR (a positive and negative values represent an underestimate and overestimate of mGFR, respectively).

Precision was defined as the interquartile range (IQR) for the differences. Accuracy, which reflects absence of bias and precision, was defined as the percentage of estimates that differed by more than 30% from the measured GFR ($1–P_{30}$) and the root-mean-square error (RMSE) for the regression of mGFR vs. eGFR on the logarithmic scale. Median bias closer to zero and smaller values for IQR, $1\text{-}P_{30}$ and RMSE represent better performance. We emphasized bias because it provides insight into non-GFR determinants of the filtration markers and $1\text{-}P_{30}$ because it represents the percentage of large errors, which can be clinically significant. $1\text{-}P_{30}$ of 10-20% is generally considered adequate for many clinical decisions; $1\text{-}P_{30}$ <10% is considered optimal. Confidence intervals (95%) were calculated by means of bootstrap methods (2000 bootstraps). For the overall population, performance of equations using mGFR as a reference was compared to CG equation (reference equation). For subgroups, we focused primarily on the CKD- EPI equations because they are recommended by current guidelines. For comparisons of newer equations with the CG equation, median bias was compared using

Wilcoxon paired test and 1-P_{30} was compared using McNemar paired test. To account for multiplicity of hypothesis tests for other comparisons, statistical significance was inferred from non-overlapping confidence intervals.

Table 2.1: Glomerular filtration rate (GFR) estimating equations.

eGFR filtration markers	Model	Equation
Creatinine	CG	eGFR= (140 – Age) × weight/(72 × Scr) x 0.85 if female Where Scr is serum creatinine
Creatinine	MDRD	eGFR=175 × $Scr^{-1.154}$ × $Age^{-0.203}$ × (0.742 if female) × (1.212 if Black) Where Scr is serum creatinine
Creatinine	CKD-EPI	eGFR= 141 × min(Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1)$^{-1.209}$ × 0.993^{Age} [× 1.018 if female] [× 1.159 if Black] Where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min is the minimum of Scr/κ or 1, and max is the maximum of Scr/κ or 1
Creatinine	CamGFRv2	Squared root of eGFR= 1.66 + 0.0178xAge + 4.77xBSA + 0.302[If sex = male] -0.508[If IDMS] -3.50xlog(SCr)[If IDMS] – 0.738xlog(SCr)^2[If IDMS] + 0.698xlog(SCr)^3[If IDMS]– 4.05x log(SCr)[If non-IDMS] – 1.16x log(SCr)^2[If non-IDMS] + 1.53x log(SCr)^3[If non-IDMS] – 0.028xAgexBSA+ (0.006xAge)[If sex = male] Where Scr is serum creatinine; BSA is body surface area and IDMA is isotope dilution mass spectroscopy
Cystatin C	CKD-EPI	eGFR= 133 × min(Scys/0.8, 1)$^{-0.499}$ × max(Scys/0.8, 1)$^{-1.328}$ × 0.996^{Age} [× 0.932 if female] Where Scys is serum cystatin C, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scys/κ or 1
Creatinine and Cystatin C	CKD-EPI	eGFR= 135 × min(Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1)$^{-0.601}$ × min(Scys/0.8, 1)$^{-0.375}$ × max(Scys/0.8, 1)$^{-0.711}$ × 0.995^{Age} [× 0.969 if female] [× 1.08 if Black] Where Scr is serum creatinine, Scys is serum cystatin C, κ is 0.7 for females and 0.9 for males, α is −0.248 for females and −0.207 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1

Units for eGFR and serum creatinine are mL/min/1.73m2 and mg/dL, respectively. Units for cystatin are mg/L. CG: Cockroft-Gault; MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CamGFRv2: Cambridge glomerular filtration rate version 2. eGFR: estimated glomerular filtration rate; mGFR: measured glomerular filtration rate.

The study was not designed to have sufficient power to detect differences in equation performance between sub-groups. Therefore, we focused on descriptive analyses of median bias among subgroups. Sub-groups were defined by age (<65 or ≥65 years), sex (men or women), body mass index (BMI) (<20, 20-24, 25-29, or ≥30 Kg/m^2), eGFR (≥105, 90-104, 60-89, 45-59 or <45 ml/min per 1.73 m^2), serum albumin (≥4.6, 4.3-4.5 or <4.3 g/dL), C-reactive protein (CRP) (<1.8, 1.8-5.3 or ≥5.4 mg/L), smoking (never, former or current), ECOG-PS (0, 1 or ≥2), distant metastasis (no or yes), and clinical stage (I, II, III, IV or not applicable). Cancer site was classified according to the American Joint Committee on Cancer 8th Edition. In the case of gastrointestinal and hepatobiliary site, we grouped the following sites: upper gastro-intestinal (esophagus, stomach and small intestine), lower gastro-intestinal (appendix, colon/rectum and anus) and hepatobiliary system (liver, intrahepatic bile ducts, gallblader, perihilar bile ducts, distal bile duct, ampulla of vater, exocrine pancreas). For all other sites, the categories presented in this study correspond exactly to those of AJCC system. Race was self-reported by study participants, and race categories (White, Black, Mixed or Asian Participants) were defined by investigators based on the categories used by the IBGE (Brazilian Institute of Geography and Statistics). Race was collected because this variable (categorized as Black vs. non-Black) is used in some of the eGFR equations.

To assess the association of cancer site with Scr and Scys independent of mGFR and other baseline factors, we modeled each filtration marker using linear regression on the logarithmic scale using errors-in-variables regression analysis. We included all variables considered to be clinically relevant. Gastrointestinal site was the reference category. Models were sequentially adjusted for mGFR and mGFR measurement error,

demographic variables (age, sex, and race), laboratory tests (CRP, hemoglobin, serum albumin, urinary albumin/creatinine ratio), BMI, and cancer related variables (ECOG-PS, metastasis and smoking). P value <0.05 in the final model was considered significant.

There were no missing data for these variables. All analysis were performed using R software (version 3.6.2, http://www-r-project.org: Free Software Foundation Inc.) and SAS Enterprise Guide (Version 7.12, Cary, NC).

2.3. Results

2.3.1. Study population

A total of 13,386 patients were screened between April 22th 2015 and September 15th 2017. A total of 1,200 patients agreed to participate and completed the study (Figure 2.1). The final study population had similar age and sex distribution, but higher BMI and lower ECOG-PS than patients screened but not included (Table 2.2).

2.3.2. Baseline characteristics

Mean (SD) age was 58.8±13.2 years, 50.9% were male, and 69.0% were White patients; 70.0% were overweight or obese (BMI ≥25); 50.3% had never smoked and 49.7% were former or current smokers; 48.3% had hypertension and 19.4% had diabetes; median (IQR) Charlson comorbidity index was 1.0 (1.0–3.0) (Table 2.3).

Most participants (84.3%) were new patients (Table 2.4). The most common cancer sites were breast (22.7%), male genital (21.8%) and gastrointestinal (20.9%). Of the total, 51.2% had cancer clinical stage I or II and 14.8% had metastasis at cancer

diagnosis; 94.1% had ECOG-PS levels 0 or 1, and 32.6%, 4.7%, and 3.8% had prior surgery, chemotherapy or radiotherapy, respectively.

Mean (SD) mGFR was 78.5±21.7 ml/min/1.73 m^2, Scr was 0.91±0.37 mg/dL and Scys was 1.10±0.39 mg/L. Most clinical characteristics varied significantly by mGFR category (Table 2.5). Lower mGFR was associated with older age, male sex, higher prevalence of hypertension and diabetes, higher Charlson comorbidity index, lower hemoglobin, lower serum albumin, higher CRP, and higher Scr, Scys, serum urea and urine ACR.

Lower mGFR was related to higher ECOG-PS. There were no differences in clinical stage, metastasis and previous cancer treatment according to mGFR categories (Table 2.6). Clinical characteristics by cancer site are depicted in Table 2.7.

2.3.3. Performance of GFR estimating equations in the overall population

Among eGFRcr equations bias varied from -8.1 to +6.1 ml/min/1.73 m^2 (Table 2.8). CG was the least accurate: 1-P_{30} was 24.9 (22.4-27.3)%. CKD-EPI eGFRcr overerestimated mGFR and 1-P_{30} was 19.1 (16.8-21.2)%. CamGFRv2 underestimated mGFR and 1-P_{30} was 7.2 (5.7–8.7)%. eGFRcys underestimated mGFR by 4.6 (3.7 to 5.5) ml/min/1.73 m^2 and 1-P_{30} was 12.3 (10.3–14.3)%. eGFRcr-cys had the best performance: bias -2.0 (-2.6 to -1.1) ml/min/1.73 m^2 and 1-P_{30} was 7.8 (6.3-9.4)%.

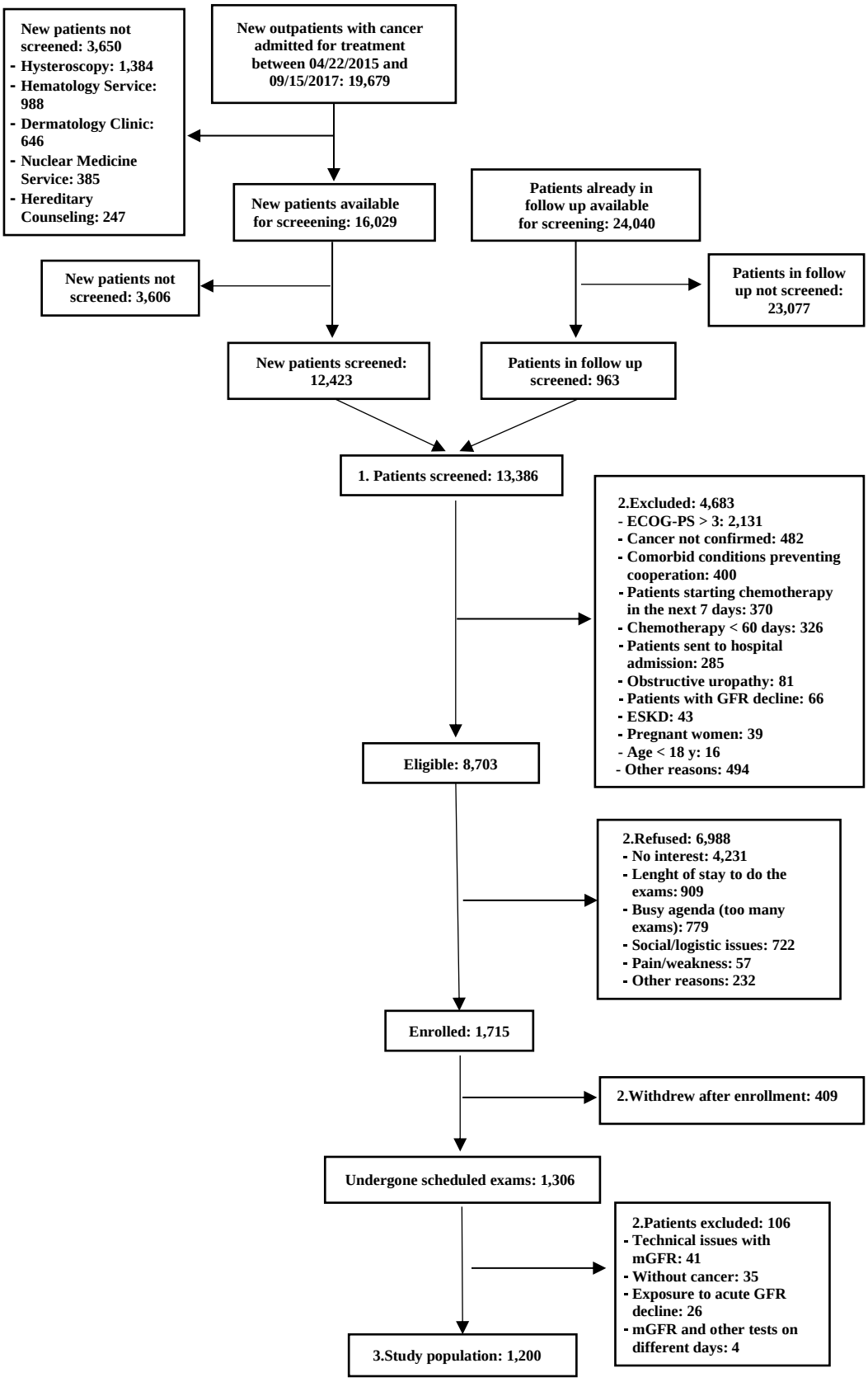
New outpatients with cancer admitted for treatment between 04/22/2015 and 09/15/2017: 19,679
New patients not screened: 3,650
- Hysteroscopy: 1,384
- Hematology Service: 988
- Dermatology Clinic: 646
- Nuclear Medicine Service: 385
- Hereditary Counseling: 247
New patients available for screeening: 16,029
Patients already in follow up available for screening: 24,040
New patients not screened: 3,606
Patients in follow up not screened: 23,077
New patients screened: 12,423
Patients in follow up screened: 963
1. Patients screened: 13,386
2.Excluded: 4,683
- ECOG-PS > 3: 2,131
- Cancer not confirmed: 482
- Comorbid conditions preventing cooperation: 400
- Patients starting chemotherapy in the next 7 days: 370
- Chemotherapy < 60 days: 326
- Patients sent to hospital admission: 285
- Obstructive uropathy: 81
- Patients with GFR decline: 66
- ESKD: 43
- Pregnant women: 39
- Age < 18 y: 16
- Other reasons: 494
Eligible: 8,703
2.Refused: 6,988
- No interest: 4,231
- Lenght of stay to do the exams: 909
- Busy agenda (too many exams): 779
- Social/logistic issues: 722
- Pain/weakness: 57
- Other reasons: 232
Enrolled: 1,715
2.Withdrew after enrollment: 409
Undergone scheduled exams: 1,306
2.Patients excluded: 106
- Technical issues with mGFR: 41
- Without cancer: 35
- Exposure to acute GFR decline: 26
- mGFR and other tests on different days: 4
3.Study population: 1,200

Figure 2.1: Cohort flow diagram. ECOG: Eastern Cooperative Oncology Group performance status; ESKD: end stage kidney disease. 1: screened; 2: screened not included; 3: Study population.

Table 2.2: Characteristics of screened patients who were included versus not included.

	Number	Age (y)	Male (n/%)	Weight (Kg)	BMI (Kg/m^2)	ECOG-PS
1. Screened	13,386	61.8 (52.3 – 70.3)	7,156 (53.4)	65.9 (55 – 77)	25.3 (21.5– 29.4)	1.0 (0.0 – 2.0)
2. Screened not included	12,186	61.4 (51.8 – 69.9)	5569 (45.7)	66 (55.5 – 77.2)	25.5 (21.7 – 29.4)	1.0 (0.0 – 2.0)
3. Study population	1,200	60 (51 – 68)	610 (50.8)	73 (63.3 – 83.3)	27.2 (24.3 – 30.9)	0.0 (0.0 – 1.0)

BMI: body mass index; ECOG-PS: Eastern Cooperative Oncology Group performance status.

2.3.4. Performance of GFR estimating equations in subgroups

Figure 2 shows bias of the CKD-EPI equations across subgroups (Tables 2.9-2.22). For eGFRcr, the overestimation was greater for younger age, women, Black race, lower BMI, and higher ECOG-PS stage. The overestimation for Black race was less if the Black race coefficient was omitted. For eGFRcys, the underestimation was greater for older age, men, higher BMI, current and former smokers, lower albumin, higher CRP, higher ECOG-PS stage, more advanced stages and metastasic disease. For eGFRcr-cys, bias in most subgroups was intermediate between bias for eGFRcr and eGFRcys. Bias was larger for younger age, women, Black patients, and lower BMI. At higher eGFR, all three equations (eGFRcr, eGFRcys and eGFRcr-cys) overestimated mGFR. At lower eGFR, eGFRcr was unbiased, while eGFRcys underestimated mGFR.

Subgroup comparisons for other eGFRcr equations are shown in Tables 2.9-22.

Table 2.3: General characteristics of the overall population (1,200 patients)

Characteristic	**Total**
Participants, n (%)	1,200
Age (y)	58.8 (13.2)
≥ 65 (n, %)	424 (35.3)
Male (%)	611 (50.9)
Race (n, %)	
White patients	828 (69.0)
Black patients	154 (12.8)
Mixed patients	192 (16.0)
Asian patients	26 (2.2)
Weight (Kg)	74.1 (15.9)
Height (cm)	163.0 (9.1)
BSA (m^2)	1.79 (0.20)
BMI (Kg/m^2)(n, %)	27.9 (5.5)
< 20	61 (5.1)
20-24	300 (25.0)
25-29	476 (39.7)
>=30	363 (30.3)
Smoking (n, %)	
Never smoker	604 (50.3)
Former smoker	468 (39.0)
Current smoker	128 (10.7)
Hypertension (n, %)	580 (48.3)
Diabetes (n, %)	233 (19.4)
Charlson	1.0 (1.0 – 3.0)
Hemoglobin (g/dL)	13.5 (1.7)
Albumin (g/dL)	4.4 (0.4)
CRP (mg/L)	3.1 (1.4 – 7.4)
mGFR ml/min/1.73 m^2	78.5 (21.7)
Creatinine (mg/dL)	0.91 (0.37)
Cystatin C (mg/L)	1.10 (0.39)
Urea (mg/dL)	34.6 (14.2)
ACR (mg/g)	6.8 (3.7 - 18.4)

Data are presented as the mean ± SD or median (IQR) and number (n) and proportion (%). mGFR: measured glomerular filtration rate; BSA: body surface area; BMI: body mass index; Charlson: Charlson comorbidity index with no age points; CRP: C reactive protein; ACR: urinary albumin-creatinine ratio. SD: standard deviation; IQR: interquartile range.

2.3.5. Associations of cancer site with serum creatinine and cystatin C

Several cancer sites were significantly associated with Scr and Scys independent of mGFR compared to the reference site (gastrointestinal cancer). After adjustment for

demographic and clinical variables, differences among cancer sites were attenuated corresponding to differences in Scr<7% and Scys<6% compared to the reference site (Figure 2.3 and Tables 2.20-2.21).

Table 2.4: Cancer related characteristics of the overall population (1,200 patients)

Characteristic	**Total**
Participants, n (%)	1,200
Type of consultation, n (%)	
New patients	1,011 (84.3)
Patients in follow up	189 (15.8)
Site (n, %)	
Breast	272 (22.7)
Male Genital Organs	262 (21.8)
Gastrointestinal	251 (20.9)
Head and Neck	109 (9.1)
Urinary Tract	82 (6.8)
Female Reproductive Organs	60 (5.0)
Skin	54 (4.5)
Endocrine System	39 (3.3)
Thorax	34 (2.8)
Bone/Soft Tissue Sarcoma	27 (2.3)
Other	10 (0.8)
Clinical Stage* (n, %)	
1	296 (24.7)
2	318 (26.5)
3	292 (24.3)
4	239 (19.9)
NA	55 (4.6)
Metastasis (n, %)	178 (14.8)
ECOG-PS (n, %)	
0	745 (62.1)
1	384 (32.0)
2 & 3	71 (5.9)
Previous treatment	
Chemotherapy (n, %)	56 (4.7)
Radiotherapy (n, %)	45 (3.8)
Surgery (n, %)	391 (32.6)

Data are presented as the mean ± SD or median (IQR) and number (n) and proportion (%). *: there are 55 patients that cannot be classified according to the TNM stage (NA, not applicable). ECOG: Eastern Cooperative Oncology Group performance status; SD: standard deviation; IQR: interquartile range.

Table 2.5: General characteristics of the overall population (n=1200 patients), stratified by measured glomerular filtration rate (GFR).

Characteristic	**mGFR (ml/min/1.73 m^2)**					
	≥ 105	**104-90**	**89-60**	**59-45**	**< 45**	**P***
Participants, n (%)	133 (11.1)	230 (19.2)	610 (50.8)	147 (12.3)	80 (6.7)	
Age (y)	45.1 (11.5)	52.4 (12.1)	60.3 (11.0)	67.2 (10.6)	72.7 (8.5)	<.0001
≥ 65 (n, %)	6 (4.5)	32 (13.9)	231 (37.9)	90 (61.2)	65 (81.3)	<.0001
Male (%)	51 (38.4)	115 (50.0)	307 (50.3)	82 (55.8)	56 (70.0)	<.0001
Race (n, %)						
White patients	85 (63.9)	152 (66.1)	426 (69.8)	107 (72.8)	58 (72.5)	0.245
Black patients	18 (13.5)	32 (13.9)	81 (13.3)	14 (9.5)	9 (11.3)	
Mixed patients	26 (19.6)	42 (18.3)	90 (14.8)	22 (15.0)	12 (15.0)	
Asian patients	4 (3.0)	4 (1.7)	13 (2.1)	4 (2.7)	1 (1.3)	
Weight (Kg)	75.7 (17.5)	74.4 (16.0)	74.2 (15.7)	71.7 (14.3)	73.7 (16.8)	0.229
Height (cm)	162.8 (9.0)	164.0 (9.2)	162.8 (8.8)	161.4 (9.3)	164.0 (9.8)	0.445
BSA (m^2)	1.80 (0.22)	1.80 (0.21)	1.79 (0.20)	1.75 (0.19)	1.79 (0.22)	0.307
BMI (Kg/m^2)(n, %)	28.5 (5.9)	27.6 (5.2)	28.0 (5.5)	27.5 (5.2)	27.4 (5.7)	0.236
BMI < 20	5 (3.8)	17 (7.4)	27 (4.4)	8 (5.4)	4 (5.0)	0.386
BMI 20-24	32 (24.1)	52 (22.6)	148 (24.3)	41 (27.9)	27 (33.8)	
BMI 25-29	48 (36.1)	96 (41.7)	248 (40.7)	59 (40.1)	25 (31.3)	
BMI >=30	48 (36.1)	65 (28.3)	187 (30.7)	39 (26.5)	24 (30.0)	
Smoking (n, %)						
Never smoker	74 (55.6)	119 (51.7)	304 (49.8)	73 (49.7)	34 (42.5)	0.064
Former smoker	44 (33.1)	85 (37.0)	238 (39.0)	60 (40.8)	41 (51.3)	
Current smoker	15 (11.3)	26 (11.3)	68 (11.2)	14 (9.5)	5 (6.3)	
Hypertension (n, %)	37 (27.8)	70 (30.4)	313 (51.3)	99 (67.4)	61 (76.3)	<.0001
Diabetes (n, %)	16 (12.0)	38 (16.5)	110 (18.0)	36 (24.5)	33 (41.3)	<.0001
Charlson	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	2.0 (1.0, 5.0)	2.5 (1.0, 5.0)	<.0001
Hemoglobin (g/dL)	13.4 (1.6)	13.6 (1.7)	13.6 (1.6)	13.2 (1.8)	12.3 (1.9)	0.0002
Albumin (g/dL)	4.4 (0.4)	4.4 (0.4)	4.4 (0.4)	4.3 (0.4)	4.2 (0.5)	0.014
CRP (mg/L)	3.3 (1.5 - 8.2)	2.6 (1.1 - 5.6)	3.1 (1.3 - 7.3)	3.5 (1.9 - 9.4)	4.1 (2.1 - 11.2)	0.003
mGFR ml/min/1.73 m^2	114.9 (8.2)	96.3 (4.2)	75.6 (8.3)	53.5 (4.1)	34.3 (7.8)	<.0001

Creatinine (mg/dL)	0.69 (0.13)	0.76 (0.16)	0.87 (0.19)	1.08 (0.26)	1.75 (0.82)	<.0001
Cystatin C (mg/L)	0.80 (0.13)	0.88 (0.15)	1.06 (0.20)	1.36 (0.27)	2.07 (0.68)	<.0001
Urea (mg/dL)	26.0 (6.9)	29.2 (8.7)	33.1 (8.9)	40.7 (11.8)	64.5 (26.8)	<.0001
ACR (mg/g)	5.8 (3.7-11.1)	5.5 (3.6 - 11.7)	6.5 (3.6 - 15.0)	9.2 (4.9 - 56.5)	37.8 (11.0 – 188.8)	<.0001

Data are presented as the mean ± SD or median (IQR) and number (n) and proportion (%). *: trend p-values were used to compare variables across ordered categories of mGFR. mGFR: measured glomerular filtration rate; BSA: body surface area; BMI: body mass index; Charlson: Charlson comorbidity index with no age points; CRP: C reactive protein; ACR, urinary albumin-creatinine ratio. SD: standard deviation; IQR: interquartile range.

Table 2.6: Cancer-related variables of the overall population (1200 patients), stratified by measured glomerular filtration rate (GFR).

Characteristic	**mGFR (ml/min/1.73 m^2)**					
	≥ 105	**104-90**	**89-60**	**59-45**	**< 45**	**P***
Participants, n (%)	133 (11.1)	230 (19.2)	610 (50.8)	147 (12.3)	80 (6.7)	
Type of consultation, n (%)						
New patients	116 (87.2)	197 (85.7)	524 (85.9)	120 (81.6)	54 (67.5)	0.001
Patients in follow up	17 (12.8)	33 (14.4)	86 (14.1)	27 (18.4)	26 (32.5)	
Site (n, %)						
Breast	37 (27.8)	55 (23.9)	151 (24.8)	20 (13.6)	9 (11.3)	<.0001
Male Genital Organs	19 (14.3)	43 (18.7)	136 (22.3)	41 (27.9)	23 (28.8)	
Gastrointestinal	23 (17.3)	53 (23.0)	123 (20.2)	34 (23.1)	18 (22.5)	
Head and Neck	10 (7.5)	17 (7.4)	60 (9.8)	17 (11.6)	5 (6.3)	
Urinary Tract	5 (3.8)	12 (5.2)	35 (5.7)	18 (12.2)	12 (15.0)	
Female Reproductive Organs	10 (7.5)	11 (4.8)	32 (5.3)	5 (3.4)	2 (2.5)	
Skin	10 (7.5)	12 (5.2)	24 (3.9)	1 (0.7)	7 (8.8)	
Endocrine System	8 (6.0)	11 (4.8)	17 (2.8)	1 (0.7)	2 (2.5)	
Thorax	5 (3.8)	5 (2.2)	16 (2.6)	7 (4.8)	1 (1.3)	
Bone/Soft Tissue Sarcoma	5 (3.8)	7 (3.0)	13 (2.1)	1 (0.7)	1 (1.3)	
Other	1 (0.8)	4 (1.7)	3 (0.5)	2 (1.4)	0 (0.0)	
Clinical Stage** (n, %)						
1	41 (30.8)	55 (23.9)	159 (26.1)	26 (17.7)	15 (18.8)	0.063
2	34 (25.6)	57 (24.8)	163 (26.7)	43 (29.3)	21 (26.3)	
3	30 (22.6)	64 (27.8)	145 (23.8)	32 (21.8)	21 (26.3)	
4	24 (18.1)	41 (17.8)	112 (18.4)	41 (27.9)	21 (26.3)	
NA	4 (3.0)	13 (5.7)	31 (5.1)	5 (3.4)	2 (2.5)	

Metastasis (n, %)	17 (12.8)	34 (14.8)	80 (13.1)	32 (21.8)	15 (18.8)	0.073
ECOG-PS (n, %)						
0	96 (72.2)	166 (72.2)	388 (63.6)	71 (48.3)	24 (30.0)	<.0001
1	33 (24.8)	54 (23.5)	189 (31.0)	65 (44.2)	43 (53.8)	
2 & 3	4 (3.0)	10 (4.4)	33 (5.4)	11 (7.5)	13 (16.3)	
Previous treatment						
Chemotherapy (n, %)	9 (6.8)	7 (3.0)	23 (3.8)	11 (7.5)	6 (7.5)	0.351
Radiotherapy (n, %)	5 (3.8)	12 (5.2)	18 (3.0)	8 (5.4)	2 (2.5)	0.658
Surgery (n, %)	41 (30.8)	83 (36.1)	192 (31.5)	46 (31.3)	29 (36.3)	0.971

Data are presented as the mean ± SD or median (IQR) and number (n) and proportion (%). * trend p-values were used to compare variables across ordered categories of mGFR. ** there are 55 patients that cannot be classified according to the TNM stage (NA, not applicable). ECOG-PS: Eastern Cooperative Oncology Group performance status.

Table 2.7: Patient's characteristics according to cancer site (part 1)

Parameter	Breast	Male Genital Organs	Gastrointestinal	Head and Neck	Urinary Tract	Female Reproductive Organs	P
Participants, n (%)	272 (22.7)	262 (21.8)	251 (20.9)	109 (9.1)	82 (6.8)	60 (5.0)	
Age (y)	55.3 (12.2)	63.4 (12.7)	59.9 (12.8)	58.4 (13.0)	62.3 (12.3)	54.0 (11.5)	<.0001
≥ 65 (n, %)	56 (20.6)	145 (55.3)	90 (35.9)	36 (33.0)	35 (42.7)	11 (18.3)	<.0001
Male (n, %)	3 (1.1)	262 (100.0)	139 (55.4)	78 (71.6)	54 (65.9)	0 (0.0)	<.0001
Race (n, %)							
White patients	173 (63.6)	168 (64.1)	170 (67.7)	81 (74.3)	66 (80.5)	42 (70.0)	0.035
Black patients	38 (14.0)	41 (15.7)	32 (12.8)	13 (11.9)	6 (7.3)	10 (16.7)	
Mixed patients	54 (19.9)	48 (18.3)	40 (15.9)	14 (12.8)	8 (9.8)	8 (13.3)	
Asian patients	7 (2.6)	5 (1.9)	9 (3.6)	1 (0.9)	2 (2.4)	0 (0.0)	
Weight (Kg)	73.0 (15.1)	78.2 (14.7)	69.1 (14.3)	71.2 (17.4)	75.7 (13.4)	76.8 (17.7)	<.0001
Height (cm)	158.1 (7.3)	168.4 (7.3)	162.9 (9.6)	165.0 (8.6)	164.0 (9.0)	157.9 (5.9)	<.0001
BSA (m^2)	1.74 (0.18)	1.88 (0.19)	1.74 (0.21)	1.77 (0.21)	1.82 (0.18)	1.77 (0.18)	<.0001
BMI (Kg/m^2)(n, %)	29.2 (5.5)	27.5 (4.5)	26.0 (4.5)	26.2 (6.1)	28.1 (4.4)	30.9 (7.4)	<.0001
BMI (n, %)							
< 20	10 (3.7)	6 (2.3)	24 (9.6)	12 (11.0)	0 (0.0)	3 (5.0)	<.0001
20-24	49 (18.0)	66 (25.2)	82 (32.7)	35 (32.1)	21 (25.6)	9 (15.0)	
25-29	107 (39.3)	121 (46.2)	99 (39.4)	42 (38.5)	33 (40.2)	18 (30.0)	
≥ 30	106 (39.0)	69 (26.3)	46 (18.3)	20 (18.4)	28 (34.2)	30 (50.0)	
Smoking (%)							
Never smoker	166 (61.0)	112 (42.8)	126 (50.2)	36 (33.0)	33 (40.2)	35 (58.3)	<.0001
Former smoker	85 (31.3)	124 (47.3)	102 (40.6)	45 (41.3)	38 (46.3)	20 (33.3)	
Current smoker	21 (7.7)	26 (9.9)	23 (9.2)	28 (25.7)	11 (13.4)	5 (8.3)	
Hypertension (n, %)	118 (43.4)	159 (60.7)	116 (46.2)	41 (37.6)	45 (54.9)	27 (45.0)	0.0003
Diabetes (n, %)	48 (17.7)	56 (21.4)	55 (21.9)	13 (11.9)	16 (19.5)	16 (26.7)	0.568
Charlson	1.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)	2.0 (1.0 - 7.0)	1.0 (1.0 - 2.0)	1.0 (1.0 - 3.0)	1.0 (1.0 - 2.0)	<.0001
Hemoglobin (g/dL)	13.3 (1.1)	14.4 (1.5)	12.8 (1.9)	13.7 (1.6)	13.1 (2.1)	12.5 (1.5)	<.0001
Albumin (g/dL)	4.5 (0.3)	4.5 (0.4)	4.2 (0.5)	4.4 (0.3)	4.3 (0.4)	4.4 (0.4)	<.0001
CRP (mg/L)	2.9 (1.4 - 5.6)	2.2 (1.0 - 5.6)	3.5 (1.7 - 8.0)	3.9 (1.9 - 12.2)	4.0 (1.7 - 11.8)	3.6 (2.0 - 12.3)	<.0001
mGFR (ml/min/1.73 m^2)	82.6 (20.3)	75.0 (21.4)	77.4 (21.2)	78.8 (20.5)	67.0 (22.6)	82.5 (21.6)	<.0001
mGFR (ml/min/1.73 m^2)(n, %)							
< 45	9 (3.3)	23 (8.8)	18 (7.2)	5 (4.6)	12 (14.6)	2 (3.3)	0.000
45-59	20 (7.4)	41 (15.7)	34 (13.6)	17 (15.6)	18 (22.0)	5 (8.3)	

60-89	151 (55.5)	136 (51.9)	123 (49.0)	60 (55.1)	35 (42.7)	32 (53.3)	
90-104	55 (20.2)	43 (16.4)	53 (21.1)	17 (15.6)	12 (14.6)	11 (18.3)	
≥ 105	37 (13.6)	19 (7.3)	23 (9.2)	10 (9.2)	5 (6.1)	10 (16.7)	
Creatinin (mg/dL)	0.75 (0.18)	1.09 (0.36)	0.89 (0.40)	0.90 (0.22)	1.15 (0.63)	0.78 (0.29)	<.0001
Cystatin C (mg/L)	0.96 (0.27)	1.16 (0.42)	1.14 (0.39)	1.08 (0.27)	1.34 (0.56)	1.03 (0.36)	<.0001
Urea (mg/dL)	31.3 (10.3)	38.3 (15.9)	32.9 (13.7)	34.0 (11.6)	42.3 (20.7)	33.4 (13.5)	<.0001
ACR (mg/g)	6.3 (4.0 - 13.7)	6.7 (3.5 - 23.3)	6.0 (3.6 - 11.0)	7.1 (3.7 - 15.4)	19.9 (6.5 - 158.5)	9.4 (5.0 - 30.1)	<.0001
Type of consultation (n, %)							
New patients	226 (83.1)	214 (81.7)	221 (88.1)	97 (89.0)	64 (78.1)	47 (78.3)	0.142
Patients in follow up	46 (16.9)	48 (18.3)	30 (12.0)	12 (11.0)	18 (22.0)	13 (21.7)	
Clinical Stage (n, %)							
1	72 (26.5)	39 (14.9)	40 (15.9)	30 (27.5)	28 (34.2)	25 (41.7)	<.0001
2	98 (36.0)	88 (33.6)	66 (26.3)	13 (11.9)	11 (13.4)	12 (20.0)	
3	55 (20.2)	86 (32.8)	73 (29.1)	16 (14.7)	18 (22.0)	17 (28.3)	
4	24 (8.8)	47 (17.9)	69 (27.5)	46 (42.2)	14 (17.1)	5 (8.3)	
NA*	23 (8.5)	2 (0.8)	3 (1.2)	4 (3.7)	11 (13.4)	1 (1.7)	
Metastasis (n, %)	24 (8.8)	31 (11.8)	69 (27.5)	7 (6.4)	12 (14.6)	5 (8.3)	<.0001
ECOG-PS (n, %)							
0	208 (76.5)	185 (70.6)	105 (41.8)	63 (57.8)	44 (53.7)	32 (53.3)	<.0001
1	57 (21.0)	69 (26.3)	125 (49.8)	39 (35.8)	29 (35.4)	26 (43.3)	
2 & 3	7 (2.6)	8 (3.1)	21 (8.4)	7 (6.4)	9 (11.0)	2 (3.3)	
Previous treatment							
Chemotherapy (n, %)	25 (9.2)	5 (1.9)	11 (4.4)	5 (4.6)	1 (1.2)	4 (6.7)	0.004
Radiotherapy (n, %)	26 (9.6)	2 (0.8)	4 (1.6)	6 (5.5)	0 (0.0)	3 (5.0)	<.0001
Surgery (n, %)	98 (36.0)	57 (21.8)	110 (43.8)	17 (15.6)	33 (40.2)	28 (46.7)	<.0001

Data are presented as the mean ± SD or median (IQR) and number (n) and proportion (%); BSA: body surface area; BMI: body mass index; Charlson: Charlson comorbidity index with no age points; CRP: C reactive protein; mGFR: measured glomerular filtration rate; ACR, urinary albumin-creatinine ratio. SD: standard deviation; IQR: interquartile range. *NA: not applicable (patients that cannot be classified according to the TNM stage). ECOG-PS: Eastern Cooperative Oncology Group performance status.

Table 2.8: Patient's characteristics according to cancer site (part 2)

Parameter	Skin	Endocrine System	Thorax	Bone and Soft Tissue Sarcoma	Other	P
Participants, n (%)	54 (4.5)	39 (3.3)	34 (2.8)	27 (2.3)	10 (0.8)	
Age (y)	57.7 (16.0)	52.1 (13.1)	63.1 (10.0)	49.9 (15.1)	46.8 (10.3)	<.0001
≥ 65 (n, %)	19 (35.2)	8 (20.5)	18 (52.9)	6 (22.2)	0 (0.0)	<.0001
Male (n, %)	29 (53.7)	6 (15.4)	20 (58.8)	14 (51.9)	6 (60.0)	<.0001
Race (n, %)						
White patients	49 (90.7)	32 (82.1)	24 (70.6)	16 (59.3)	7 (70.0)	0.035
Black patients	1 (1.9)	2 (5.1)	4 (11.8)	4 (14.8)	3 (30.0)	
Mixed patients	4 (7.4)	5 (12.8)	4 (11.8)	7 (25.9)	0 (0.0)	
Asian patients	0 (0.0)	0 (0.0)	2 (5.9)	0 (0.0)	0 (0.0)	
Weight (Kg)	79.2 (17.3)	78.6 (18.4)	70.7 (19.2)	79.7 (17.9)	72.9 (14.8)	<.0001
Height (cm)	163.6 (9.4)	157.9 (7.6)	161.7 (10.3)	165.0 (9.2)	166.7 (6.6)	<.0001
BSA (m^2)	1.85 (0.22)	1.79 (0.22)	1.74 (0.26)	1.86 (0.21)	1.81 (0.20)	<.0001
BMI (Kg/m^2)(n, %)	29.5 (5.8)	31.4 (6.2)	26.7 (5.2)	29.3 (6.5)	26.1 (4.1)	<.0001
BMI (n, %)						
< 20	2 (3.7)	0 (0.0)	3 (8.8)	0 (0.0)	1 (10.0)	<.0001
20-24	11 (20.4)	5 (12.8)	11 (32.4)	9 (33.3)	2 (20.0)	
25-29	16 (29.6)	14 (35.9)	13 (38.2)	8 (29.6)	5 (50.0)	
≥ 30	25 (46.3)	20 (51.3)	7 (20.6)	10 (37.0)	2 (20.0)	
Smoking (%)						

Never smoker	37 (68.5)	29 (74.4)	7 (20.6)	18 (66.7)	5 (50.0)	<.0001
Former smoker	15 (27.8)	9 (23.1)	18 (52.9)	8 (29.6)	4 (40.0)	
Current smoker	2 (3.7)	1 (2.6)	9 (26.5)	1 (3.7)	1 (10.0)	
Hypertension (n, %)	24 (44.4)	24 (61.5)	12 (35.3)	10 (37.0)	4 (40.0)	0.0003
Diabetes (n, %)	10 (18.5)	7 (18.0)	6 (17.7)	4 (14.8)	2 (20.0)	0.568
Charlson	1.0 (1.0 - 2.0)	1.0 (1.0 - 2.0)	2.5 (2.0 - 7.0)	1.0 (1.0 - 7.0)	1.5 (1.0 - 7.0)	<.0001
Hemoglobin (g/dL)	13.9 (1.7)	13.7 (1.1)	13.0 (1.8)	13.7 (1.6)	13.8 (1.1)	<.0001
Albumin (g/dL)	4.4 (0.3)	4.5 (0.4)	4.1 (0.5)	4.5 (0.3)	4.3 (0.3)	<.0001
CRP (mg/L)	3.1 (1.7 - 7.4)	2.8 (1.4 - 7.1)	15.9 (1.7 - 39.5)	2.3 (1.1 - 7.6)	3.1 (1.6 - 6.6)	<.0001
mGFR (ml/min/1.73 m^2)	80.6 (25.2)	86.5 (20.2)	79.6 (23.7)	86.2 (22.7)	83.1 (20.3)	<.0001
mGFR (ml/min/1.73 m^2)(n, %)						
< 45	7 (13.0)	2 (5.1)	1 (2.9)	1 (3.7)	0 (0.0)	0.000
45-59	1 (1.9)	1 (2.6)	7 (20.6)	1 (3.7)	2 (20.0)	
60-89	24 (44.4)	17 (43.6)	16 (47.1)	13 (48.2)	3 (30.0)	
90-104	12 (22.2)	11 (28.2)	5 (14.7)	7 (25.9)	4 (40.0)	
≥ 105	10 (18.5)	8 (20.5)	5 (14.7)	5 (18.5)	1 (10.0)	
Creatinin (mg/dL)	0.97 (0.50)	0.79 (0.20)	0.86 (0.22)	0.92 (0.26)	0.91 (0.21)	<.0001
Cystatin C (mg/L)	1.16 (0.54)	1.00 (0.33)	1.18 (0.33)	1.07 (0.36)	1.17 (0.56)	<.0001
Urea (mg/dL)	36.3 (18.4)	32.3 (9.6)	31.8 (11.2)	33.1 (10.1)	32.9 (7.4)	<.0001
ACR (mg/g)	6.4 (3.1 - 11.8)	6.8 (3.9 - 13.5)	6.6 (3.6 - 15.0)	9.3 (3.6 - 32.9)	4.4 (3.1 - 4.8)	<.0001
Type of consultation (n, %)						
New patients	48 (88.9)	32 (82.1)	32 (94.1)	21 (77.8)	9 (90.0)	0.142
Patients in follow up	6 (11.1)	7 (18.0)	2 (5.9)	6 (22.2)	1 (10.0)	
Clinical Stage (n, %)						
1	22 (40.7)	24 (61.5)	6 (17.7)	9 (33.3)	1 (10.0)	<.0001
2	19 (35.2)	1 (2.6)	4 (11.8)	5 (18.5)	1 (10.0)	
3	4 (7.4)	12 (30.8)	7 (20.6)	4 (14.8)	0 (0.0)	
4	7 (13.0)	2 (5.1)	16 (47.1)	6 (22.2)	3 (30.0)	
NA*	2 (3.7)	0 (0.0)	1 (2.9)	3 (11.1)	5 (50.0)	
Metastasis (n, %)	4 (7.4)	0 (0.0)	15 (44.1)	8 (29.6)	3 (30.0)	<.0001
ECOG-PS (n, %)						
0	37 (68.5)	31 (79.5)	16 (47.1)	20 (74.1)	4 (40.0)	<.0001
1	12 (22.2)	7 (18.0)	11 (32.4)	6 (22.2)	3 (30.0)	
2 & 3	5 (9.3)	1 (2.6)	7 (20.6)	1 (3.7)	3 (30.0)	
Previous treatment						
Chemotherapy (n, %)	1 (1.9)	0 (0.0)	1 (2.9)	3 (11.1)	0 (0.0)	0.004
Radiotherapy (n, %)	1 (1.9)	0 (0.0)	0 (0.0)	3 (11.1)	0 (0.0)	<.0001
Surgery (n, %)	18 (33.3)	8 (20.5)	3 (8.8)	16 (59.3)	3 (30.0)	<.0001

Data are presented as the mean ± SD or median (IQR) and number (n) and proportion (%); BSA: body surface area; BMI: body mass index; Charlson: Charlson comorbidity index with no age points; CRP: C reactive protein; mGFR: measured glomerular filtration rate; ACR, urinary albumin-creatinine ratio. SD: standard deviation; IQR: interquartile range. *NA: not applicable (patients that cannot be classified according to the TNM stage). ECOG-PS: Eastern Cooperative Oncology Group performance status.

Table 2.9**:** Performance of GFR estimating equations in the total cohort.

Filtration marker (eGFR)	**Equation**	**Bias (median) (ml/min/1.73 m^2)**	**Precision (IQR) (ml/min/1.73 m^2)**	**Accuracy (1-P_{30}) (%)**	**Accuracy (RMSE)**
Creatinine (eGFRcr)	CG	-8.1 (-9.4 to -6.7)	24.2 (22.4 – 25.8)	24.9 (22.4 – 27.3)	0.239 (0.229 – 0.249)
Creatinine (eGFRcr)	MDRD	-4.8 (-6.0 to -3.6)[a]	20.0 (18.5 – 21.6)	18.2 (16.0 – 20.3)[a]	0.213 (0.204 – 0.223)
Creatinine (eGFRcr)	CKD-EPI	-8.1 (-8.9 to -7.1)[a]	18.4 (17.1 – 19.6)	19.1] (16.8 – 21.2)[a]	0.206 (0.197-0.215)
Creatinine (eGFRcr)	CamGFRv 2	6.1 (5.3 – 6.9) [a]	17.2 (16.0 – 18.1)	7.2 (5.7 – 8.7) [a]	0.185 (0.178 – 0.193)
Cystatin C (eGFRcys)	CKD-EPI	4.6 (3.7 to 5.5)[a]	17.5 (16.3 – 19.2)	12.3 (10.3 – 14.3)[a]	0.215 (0.204 – 0.225)
Creatinine-Cystatin C (eGFRcr-cys)	CKD-EPI	-2.0 (-2.6 to -1.1)[a]	15.9 (14.7 – 16.8)	7.8 (6.3 – 9.4)[a]	0.165 (0.157 – 0.172)

Data are presented with 95% confidence intervals. Bias was calculated as the median value of (mGFR-eGFR). IQR is the interquartile range of the difference between mGFR and eGFR. 1-P_{30} is the percentage of estimates that differed by more than 30% from the measured GFR. RMSE is the root mean squared error for the regression of log mGFR on log eGFR. To convert GFR from ml/min per 1.73 m^2 to ml/s per 1.73 m^2, multiply by 0.0167. a: $p < 0.001$ compared to CG. eGFR: estimated glomerular filtration rate; mGFR: measured glomerular filtration rate. CG: Cockcroft-Gault; MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CamGFRv2: Cambridge GFR version 2.

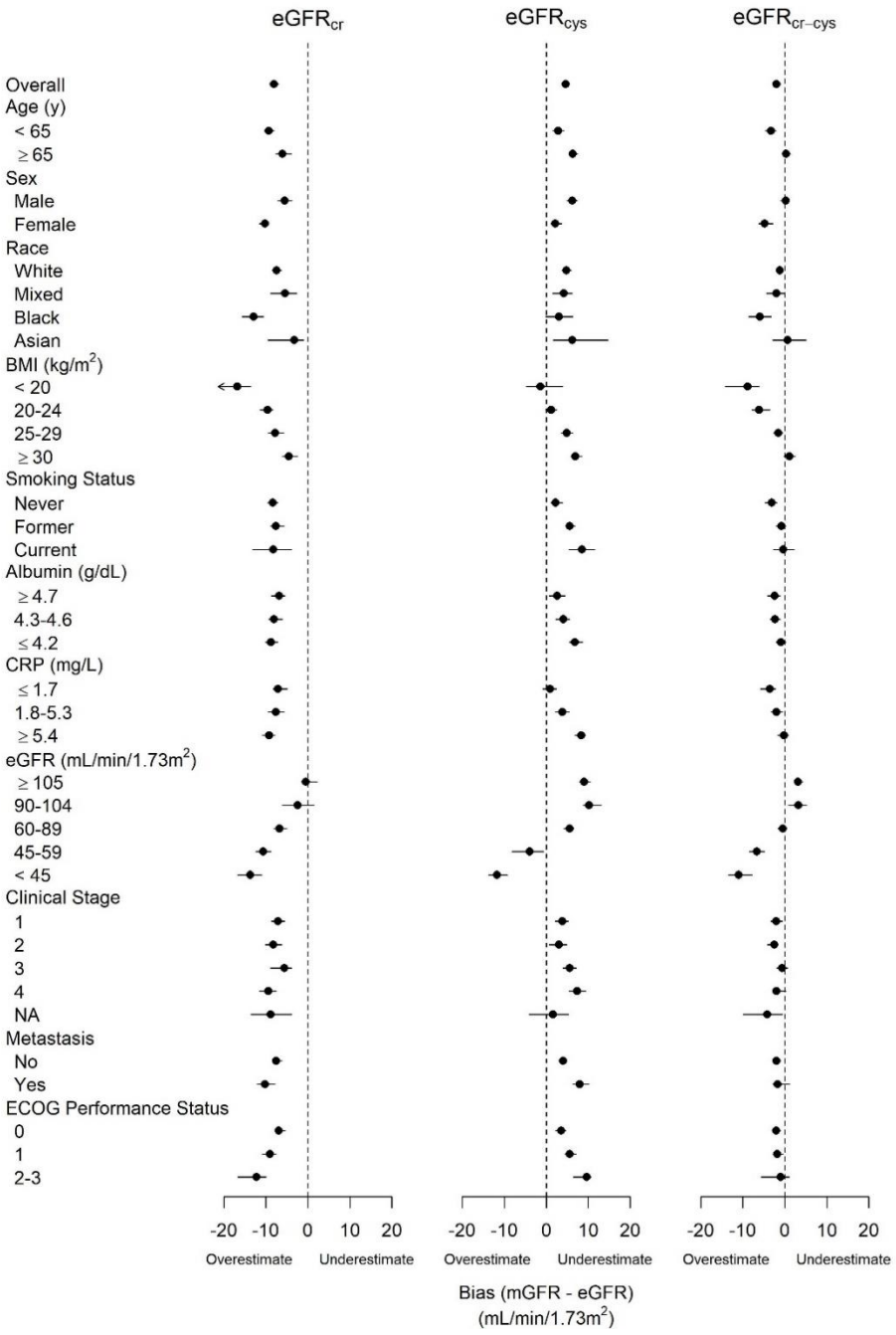

Figure 2.2**:** Bias of CKD-EPI equations by sub-groups. Bias was calculated as the median value of (mGFR-eGFR). Data are presented with 95% confidence intervals. Sample sizes are detailed in Tables S6-S16. BMI: body mass index; CRP: C reactive protein; eGFR: estimated glomerular filtration rate; mGFR: measured glomerular filtration rate; ECOG: Eastern Cooperative Oncology Group.

Table 2.10: Comparison of the median bias in eGFR for the CG, MDRD, CamGFRv2 and CKD-EPI equations by sub-groups of age.

Filtration marker (eGFR)	**Equation**	**Age (years)**	
		<65	**≥ 65**
		N=776	N=424
Creatinine (eGFRcr)	CG	-13.1 (-15.9 to -11.7)	0.8 (-0.8 to 1.9)
Creatinine (eGFRcr)	MDRD	-4.1 (-5.6 to -2.8)	-6.3 (-8.1 to -4.2)
Creatinine (eGFRcr)	CKD-EPI	-9.3 (-10.3 to -8.1)	-6.0 (-7.6 to -3.9)
Creatinine (eGFRcr)	CamGFRv2	7.0 (5.9 to 8.2)	4.8 (2.9 to 5.9)
Cystatin C (eGFRcys)	CKD-EPI	2.8 (1.5 to 4.2)	6.3 (5.4 to 7.4)
Creatinine-Cystatin C (eGFRcr-cys)	CKD-EPI	-3.3 (-4.6 to -2.2)	0.3 (-0.5 to 1.3)

Non-overlapping confidence intervals were considered to represent differences. Bias was calculated as mGFR-eGFR. Units for GFR and bias are ml/min/1.73 m^2. To convert GFR from mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.0167. CG: Cockcroft-Gault; MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CamGFRv2: Cambridge GFR version 2.

Table 2.11: Comparison of the median bias in eGFR for the CG, MDRD, CamGFRv2 and CKD-EPI equations by sub-groups of sex.

Filtration marker (eGFR)	**Equation**	**Sex**	
		Male	**Female**
		N=610	N=590
Creatinine (eGFRcr)	CG	-1.6 (-3.0 to -0.5)	-16.5 (-18.3 to -14.7)
Creatinine (eGFRcr)	MDRD	-4.1 (-5.6 to -2.5)	-5.8 (-7.3 to -3.8)
Creatinine (eGFRcr)	CKD-EPI	-5.5 (-7.1 to -3.8)	-10.2 (-11.5 to -9.3)
Creatinine (eGFRcr)	CamGFRv2	6.8 (5.7 to 8.5)	5.4 (4.1 to 6.7)
Cystatin C (eGFRcys)	CKD-EPI	6.2 (5.0 to 7.3)	2.1 (1.1 to 3.7)
Creatinine-Cystatin C (eGFRcr-cys)	CKD-EPI	0.2 (-0.9 to 0.8)	-4.8 (-6.2 to -2.9)

Non-overlapping confidence intervals were considered to represent differences. Bias was calculated as mGFR-eGFR. Units for GFR and bias are ml/min/1.73 m^2. To convert GFR from mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.0167. CG: Cockcroft-Gault; MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CamGFRv2: Cambridge GFR version 2.

Table 2.12: Comparison of the median bias in eGFR for the CG, MDRD, CamGFRv2 and CKD-EPI equations by race.

Filtration marker (eGFR)	**Equation**	**Race**			
		White patients	**Mixed patients**	**Black patients**	**Asian patients**
		N=828	N=192	N=154	N=26
Creatinine (eGFRcr)	CG	-9.1 (-10.1 to -7.3)	-10.9 (-14.2 to -8.5)	-1.9 (-4.6 to 0.5)	6.9 (-7.0 to 11.1)
Creatinine (eGFRcr)	MDRD	-4.1 (-5.5 to -2.7)	-2.5 (-5.7 to 0.0)	-12.1 (-14.2 to -8.8)	-2.1 (-11.6 to 1.8)
Creatinine (eGFRcr)	CKD-EPI	-7.4 (-8.5 to -6.3)	-5.4 (-8.9 to -2.7)	-12.9 (-15.7 to -10.5)	-3.2 (-9.5 to -0.9)
Creatinine (eGFRcr)	CamGFRv2	5.3 (4.1 to 6.1)	7.0 (5.0 to 9.5)	9.6 (7.8 to 11.5)	11.2 (5.3 to 16.0)
Cystatin C (eGFRcys)	CKD-EPI	4.8 (3.7 to 5.9)	4.2 (1.5 to 6.2)	3.0 (-0.2 to 6.3)	6.2 (1.6 to 14.7)
Creatinine-Cystatin C (eGFRcr-cys)	CKD-EPI	-1.2 (-2.1 to -0.4)	-2.0 (-4.4 to -0.2)	-6.0 (-8.6 to -3.2)	0.7 (-2.9 to 5.1)

Non-overlapping confidence intervals were considered to represent differences. Bias was calculated as mGFR-eGFR. Units for GFR and bias are ml/min/1.73m^2. To convert GFR from mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.0167. Bias for Black patients not including the race coefficient was for MDRD 2.99 (0.93 to 5.07); for eGFRcr.CKD-EPI 0.31 (-3.43 to 1.84) and for eGFRcr-cys CKD-EPI was 0.51 (-1.55 to 2.22). CG: Cockcroft-Gault; MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CamGFRv2: Cambridge GFR version 2.

Table 2.13: Comparison of the median bias in eGFR for the CG, MDRD, CamGFRv2 and CKD-EPI equations by sub-groups of body mass index (BMI).

Filtration marker (eGFR)	**Equation**	**BMI (Kg/m^2)**			
		BMI < 20	**BMI 20-24**	**BMI 25-29**	**BMI ≥ 30**
		N=61	N=300	N=476	N=363
Creatinine (eGFRcr)	CG	-3.2 (-7.0 to 1.4)	-2.1 (-3.6 to -0.4)	-7.3 (-9.3 to -6.0)	-16.1 (-18.9 to -12.2)
Creatinine (eGFRcr)	MDRD	-19.7 (-24.8 to -13.8)	-7.9 (-9.4 to -5.5)	-4.4 (-6.3 to -2.3)	-0.7 (-2.5 to 1.0)
Creatinine (eGFRcr)	CKD-EPI	-16.8 (-21.4 to -13.6)	-9.6 (-11.4 to -8.3)	-7.8 (-9.4 to -5.8)	-4.5 (-6.0 to -2.5)
Creatinine (eGFRcr)	CamGFRv2	1.5 (-2.7 to 4.7)	5.2 (3.4 to 6.9)	6.8 (6.0 to 8.3)	6.6 (5.0 to 8.6)
Cystatin C (eGFRcys)	CKD-EPI	-1.4 (-4.8 to 3.9)	1.2 (-0.2 to 2.5)	4.9 (3.5 to 6.3)	6.9 (5.9 to 8.4)
Creatinine-Cystatin C (eGFRcr-cys)	CKD-EPI	-8.9 (-14.2 to -6.1)	-6.1 (-7.8 to -3.6)	-1.5 (-2.6 to -0.6)	1.1 (-0.2 to 2.4)

Non-overlapping confidence intervals were considered to represent differences. Bias was calculated as mGFR-eGFR. Units for GFR and bias are ml/min/1.73 m^2. To convert GFR from mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.0167. BMI: body mass index. CG: Cockcroft-Gault; MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CamGFRv2: Cambridge GFR version 2.

Table 2.14: Comparison of the median bias in eGFR for the CG, MDRD, CamGFRv2 and CKD-EPI) equations by sub-groups of smoking status.

Filtration marker (eGFR)	**Equation**	**Smoking status**		
		Never smoker	**Former smoker**	**Current smoker**
		N=604	N=468	N=128
Creatinine (eGFRcr)	CG	-10.0 (-11.2 to -8.3)	-6.6 (-8.8 to -4.3)	-3.7 (-8.9 to -0.7)
Creatinine (eGFRcr)	MDRD	-5.2 (-6.4 to -3.2)	-4.0 (-6.1 to -2.5)	-8.0 (-11.2 to -2.2)
Creatinine (eGFRcr)	CKD-EPI	-8.3 (-9.6 to -7.2)	-7.6 (-8.9 to -5.7)	-8.2 (-13.1 to -3.9)
Creatinine (eGFRcr)	CamGFRv2	5.8 (4.6 to 7.2)	6.2 (5.1 to 7.3)	7.6 (4.6 to 9.7)
Cystatin C (eGFRcys)	CKD-EPI	2.2 (1.1 to 3.9)	5.6 (4.6 to 6.8)	8.5 (5.4 to 11.5)
Creatinine-Cystatin C (eGFRcr-cys)	CKD-EPI	-3.1 (-4.7 to -1.9)	-0.8 (-2.1 to 0.2)	-0.4 (-2.7 to 2.2)

Non-overlapping confidence intervals were considered to represent differences. Bias was calculated as mGFR-eGFR. Units for GFR and bias are ml/min/1.73 m^2. To convert GFR from mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.0167. CG: Cockcroft-Gault; MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CamGFRv2: Cambridge GFR version 2.

Table 2.15: Comparison of the median bias in eGFR for the CG, MDRD, CamGFRv2 and CKD-EPI equations by sub-groups of serum albumin level.

Filtration marker (eGFR)	**Equation**	**Serum albumin (g/dL)**		
		≥4.6	**4.3 – 4.5**	**< 4.3**
		N=398	N=417	N=385
Creatinine (eGFRcr)	CG	-7.1 (-9.1 to -4.3)	-9.2 (-10.5 to -6.8)	-8.0 (-10.3 to -6.3)
Creatinine (eGFRcr)	MDRD	-2.7 (-4.3 to -1.6)	-5.8 (-7.7 to -3.2)	-7.3 (-9.0 to -4.7)
Creatinine (eGFRcr)	CKD-EPI	-6.8 (-8.7 to -5.4)	-8.1 (-9.3 to -6.0)	-8.8 (-10.1 to -7.2)
Creatinine (eGFRcr)	CamGFRv2	7.6 (6.2 to 9.1)	5.6 (3.6 to 6.7)	5.3 (3.7 to 6.8)
Cystatin C (eGFRcys)	CKD-EPI	2.6 (0.7 to 4.5)	4.1 (2.2 to 5.6)	6.8 (5.5 to 8.7)
Creatinine-Cystatin C (eGFRcr-cys)	CKD-EPI	-2.4 (-4.1 to -1.1)	-2.3 (-3.5 to -1.1)	-0.9 (-2.1 to 0.2)

Non-overlapping confidence intervals were considered to represent differences. Bias was calculated as mGFR-eGFR. Units for GFR and bias are ml/min/1.73 m^2. To convert GFR from mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.0167. CG: Cockcroft-Gault; MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CamGFRv2: Cambridge GFR version 2.

Table 2.16: Comparison of the median bias in eGFR for the CG, MDRD, CamGFRv2 and CKD-EPI equations by sub-groups of serum C reactive protein (CRP) level.

Filtration marker (eGFR)	**Equation**	**C Reactive Protein (mg/dL)**		
		< 1.8	**1.8 – 5.3**	**≥ 5.4**
		N=385	N=415	N=400
Creatinine (eGFRcr)	CG	-4.1 (-6.7 to -2.0)	-9.4 (-11.1 to -7.0)	-9.4 (-10.9 to -7.5)
Creatinine (eGFRcr)	MDRD	-2.8 (-4.7 to -1.2)	-5.3 (-6.6 to -3.2)	-6.6 (-8.2 to -4.5)
Creatinine (eGFRcr)	CKD-EPI	-7.1 (-8.3 to -4.9)	-7.6 (-9.5 to -5.7)	-9.2 (-10.8 to -7.9)
Creatinine (eGFRcr)	CamGFRv2	7.7 (6.6 to 9.6)	5.8 (5.0 to 7.3)	4.5 (2.6 to 6.1)
Cystatin C (eGFRcys)	CKD-EPI	0.9 (-0.9 to 2.4)	3.8 (2.2 to 5.4)	8.3 (6.8 to 9.3)
Creatinine-Cystatin C (eGFRcr-cys)	CKD-EPI	-3.6 (-5.9 to -2.2)	-2.0 (-3.2 to -0.6)	-0.2 (-1.7 to 0.8)

Non-overlapping confidence intervals were considered to represent differences. Bias was calculated as mGFR-eGFR. Units for GFR and bias are ml/min/1.73 m^2. To convert GFR from mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.0167. CG: Cockcroft-Gault; MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CamGFRv2: Cambridge GFR version 2.

Table 2.17: Comparison of the median bias in eGFR for the CG, MDRD, CamGFRv2 and CKD-EPI equations by sub-groups of eGFR.

Filtration marker (eGFR)	**Equation**	**eGFR**				
		≥ 105	**104-90**	**89-60**	**59-45**	**< 45**
Creatinine (eGFRcr)	CG	-27.0 (-29.9 to -24.3)	-11.3 (-13.8 to -9.3)	-2.0 (-3.3 to -0.9)	3.1 (1.3 to 4.9)	0.6 (-0.7 to 2.6)
Creatinine (eGFRcr)	MDRD	-22.0 (-24.2 to -20.1)	-8.8 (-11.7 to -6.6)	-1.5 (-2.3 to 0.0)	-0.5 (-3.5 to 2.4)	-0.7 (-2.0 to 3.1)
Creatinine (eGFRcr)	CKD-EPI	-13.7 (-16.7 to -11.0)	-10.6 (-12.4 to -8.8)	-6.7 (-8.1 to -5.1)	-2.4 (-6.0 to 1.5)	-0.5 (-1.4 to 2.2)
Creatinine (eGFRcr)	CamGFRv2	5.0 (-8.5 15.5)	8.9 (4.1 to 12.5)	6.8 (5.9 to 7.8)	4.8 (2.5 to 6.2)	2.0 (0.4 to 4.2)
Cystatin C (eGFRcys)	CKD-EPI	-11.7 (-13.8 to -9.3)	-4.0 (-8.2 to -0.6)	5.6 (4.2 to 6.5)	10.2 (8.8 to 13.0)	9.0 (7.9 to 10.4)
Creatinine-Cystatin C (eGFRcr-cys)	CKD-EPI	-11.0 (-13.5 to -7.8)	-6.7 (-8.4 to -4.8)	-0.5 (-1.6 to 0.2)	3.2 (0.9 to 5.2)	3.1 (2.3 to 4.2)

Non-overlapping confidence intervals were considered to represent differences. Bias was calculated as mGFR-eGFR. Units for GFR and bias are ml/min/1.73 m^2. To convert GFR from mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.0167.*: For eGFRcr, the number of participants are: <45 (56); 45-59 (95); 60-89 (459); 90-104 (373); ≥ 105 (217). For eGFRcys, the number of participants are: <45 (136); 45-59 (215); 60-89 (502); 90-104 (188); ≥ 105 (159). For eGFRcr-cys, the number of participants are: <45 (78); 45-59 (144); 60-89 (529); 90-104 (628); ≥ 105 (181). For MDRD, the number of participants are: <45 (53); 45-59 (117); 60-89 (576); 90-104 (247); ≥ 105 (207). For CG, the number of participants are: <45 (69); 45-59 (119); 60-89 (469); 90-104 (213); ≥ 105 (330). For CamGFRv2, the number of participants are: <45 (74); 45-59 (155); 60-89 (841); 90-104 (117); ≥ 105 (13). GFR: glomerular filtration rate. CG: Cockcroft-Gault; MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CamGFRv2: Cambridge GFR version 2.

Table 2.18: Comparison of the median bias in eGFR for the CG, MDRD, CamGFRv2 and CKD-EPI equations by sub-groups of clinical stage.

Filtration marker (eGFR)	**Equation**	**Clinical Stage**				
		I	**II**	**III**	**IV**	**NA**
		N=296	N=318	N=292	N=239	N=55
Creatinine (eGFRcr)	CG	-9.5 (-12.9 to -6.2)	-9.3 (-10.9 to -7.1)	-6.8 (-10.0 to -3.3)	-6.5 (-8.6 to -4.5)	-9.4 (-15.5 to -3.5)
Creatinine (eGFRcr)	MDRD	-2.5 (-4.5 to -1.0)	-4.4 (-7.5 to -2.3)	-4.4 (-7.6 to -2.3)	-8.8 (-11.3 to -6.2)	-3.1 (-9.0 to 0.6)
Creatinine (eGFRcr)	CKD-EPI	-7.1 (-8.7 to -5.5)	-8.2 (-10.0 to -6.4)	-5.6 (-8.9 to -3.8)	-9.4 (-11.5 to -7.5)	-8.9 (-13.5 to -3.8)
Creatinine (eGFRcr)	CamGFRv2	6.1 (5.2 to 7.8)	6.5 (4.9 to 7.8)	7.6 (5.5 to 9.6)	4.1 (1.5 to 6.1)	6.7 (0.7 to 9.2)
Cystatin C (eGFRcys)	CKD-EPI	3.8 (2.1 to 5.2)	2.9 (0.6 to 4.6)	5.6 (4.0 to 7.2)	7.3 (5.4 to 9.4)	1.6 (-4.1 to 5.3)
Creatinine-Cystatin C (eGFRcr-cys)	CKD-EPI	-2.1 (-3.4 to -0.6)	-2.5 (-4.4 to -1.4)	-0.7 (-2.0 to 0.7)	-2.0 (-2.9 to 0.2)	-4.2 (-9.9 to -0.6)

Non-overlapping confidence intervals were considered to represent differences. Bias was calculated as mGFR-eGFR. Units for GFR and bias are ml/min/1.73 m^2. To convert GFR from mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.0167. NA: not applicable (patients that can't be classified according to the TNM stage). CG: Cockcroft-Gault; MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CamGFRv2: Cambridge GFR version 2.

Table 2.19: Comparison of the median bias in eGFR for the CG, MDRD, CamGFRv2 and CKD-EPI equations by the presence of metastasis.

Filtration marker (eGFR)	**Equation**	**Metastasis**	
		No	**Yes**
		N=1022	N=178
Creatinine (eGFRcr)	CG	-8.2 (-9.5 to -6.7)	-7.6 (-10.8 to -4.6)
Creatinine (eGFRcr)	MDRD	-4.3 (-5.5 to -2.9)	-8.1 (-11.2 to -5.3)
Creatinine (eGFRcr)	CKD-EPI	-7.5 (-8.4 to -6.2)	-10.2 (-12.0 to -7.9)
Creatinine (eGFRcr)	CamGFRv2	6.6 (5.7 to 7.5)	3.5 (1.4, 5.5)
Cystatin C (eGFRcys)	CKD-EPI	4.0 (3.1 to 4.9)	8.0 (6.4 to 10.1)
Creatinine-Cystatin C (eGFRcr-cys)	CKD-EPI	-2.0 (-2.8 to -1.1)	-1.7 (-2.8 to 1.1)

Non-overlapping confidence intervals were considered to represent differences. Bias was calculated as mGFR-eGFR. Units for GFR and bias are ml/min/1.73 m^2. To convert GFR from mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.0167. CG: Cockcroft-Gault; MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CamGFRv2: Cambridge GFR version 2.

Table 2.20: Comparison of the median bias in eGFR for the CG, MDRD, CamGFRv2 and CKD-EPI equations by sub-groups of ECOG-PS.

Filtration marker (eGFR)		**ECOG-PS**		
		0	**1**	**2&3**
		N=745	N=384	N=71
Creatinine (eGFRcr)	CG	-8.9 (-10.1 to -7.0)	-6.1 (-8.8 to -4.4)	-11.1 (-13.6 to -6.9)
Creatinine (eGFRcr)	MDRD	-2.8 (-4.2 to -2.0)	-7.4 (-9.1 to -5.8)	-13.8 (-18.9 to -7.6)
Creatinine (eGFRcr)	CKD-EPI	-6.9 (-7.8 to -5.4)	-9.0 (-10.8 to -7.6)	-12.2 (-16.7 to -9.9)
Creatinine (eGFRcr)	CamGFRv2	7.8 (6.9, 9.1)	3.4 (2.1, 5.4)	0.4 (-2.4, 4.5)
Cystatin C (eGFRcys)	CKD-EPI	3.5 (2.2 to 4.6)	5.6 (4.5 to 7.1)	9.6 (6.4 to 10.6)
Creatinine-Cystatin C (eGFRcr-cys)	CKD-EPI	-2.1 (-2.9 to -1.1)	-1.8 (-2.8 to -0.5)	-1.0 (-5.7 to 1.1)

Non-overlapping confidence intervals were considered to represent differences. Bias was calculated as mGFR-eGFR. Units for GFR and bias are ml/min/1.73 m^2. To convert GFR from mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.0167. ECOG-PS: Eastern Cooperative Oncology Group performance status. CG: Cockcroft-Gault; MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CamGFRv2: Cambridge GFR version 2.

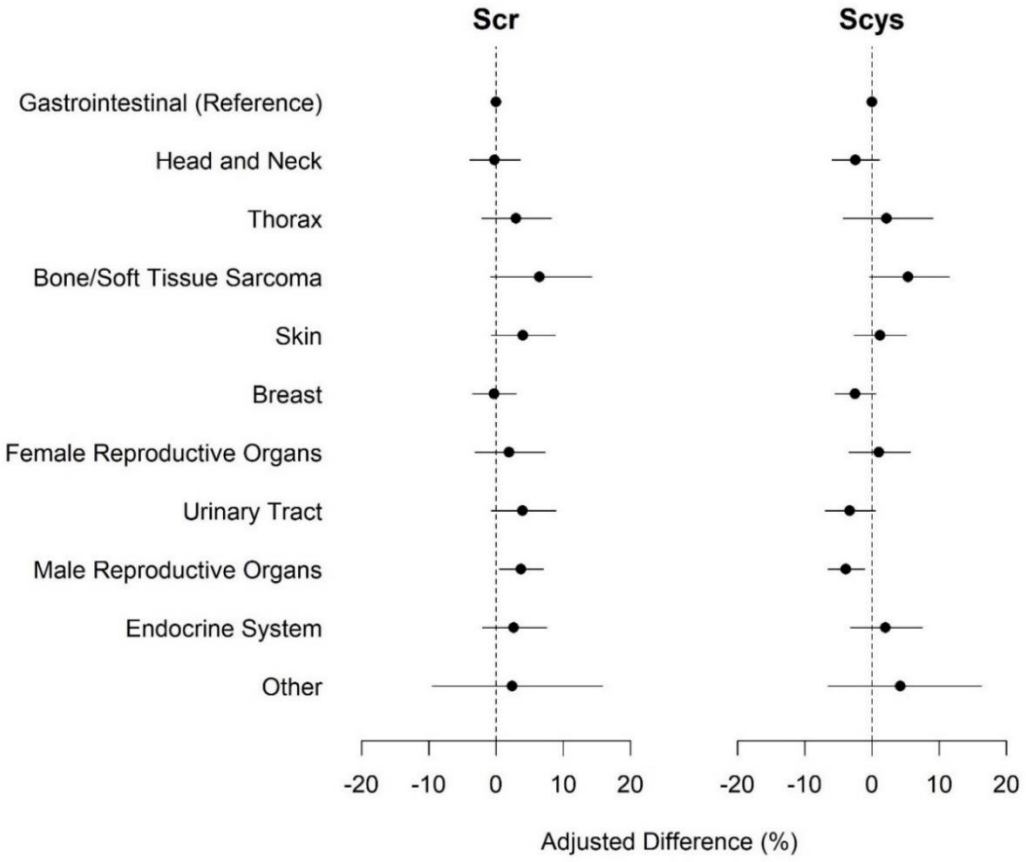

Figure 2.3: Association of cancer site with serum concentrations of creatinine (Scr) and cystatin C (Scys). Data shown are the adjusted percent change difference in Scr and Scys for each cancer site (using gastrointestinal site as reference) assessed by linear regression performed on the logarithmic scale. The model for Scr was adjusted for mGFR, mGFR measurement error, age, sex and race, BMI, CRP, Hb, ACR, and ECOG-PS. The model for Scys was adjusted for mGFR, mGFR measurement error, age, sex and race, BMI, CRP, Alb, ACR, smoking status and metastasis. Model coefficients were converted to percent differences by the following formula: percent difference = 100*[exp(beta coefficient)-1]. mGFR: measured glomerular filtration rate; BMI: body mass index; CRP: C-reactive protein; Hb: hemoglobin; ACR: urinary albumin/creatinine ratio and ECOG-PS: Eastern Cooperative Oncology Group performance status.

Table 2.21: Multivariate linear regression models for serum creatinine (Scr).

	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**
Intercept	3.07 (2.85, 3.29)	4.84 (4.42, 5.26)	4.40 (3.94, 4.86)	4.47 (4.00, 4.94)	4.50 (4.05, 4.94)
Log mGFR (ml/min/1.73m^2)	-0.75 (-0.80, -0.70)	-0.87 (-0.92, -0.82)	-0.91 (-0.96, -0.86)	-0.92 (-0.97, -0.86)	-0.91 (-0.97, -0.86)
Cancer Site					
Head and Neck	0.06 (0.01, 0.10)	0.01 (-0.03, 0.05)	0.00 (-0.04, 0.03)	-0.01 (-0.04, 0.03)	0.00 (-0.04, 0.04)
Thorax	0.00 (-0.08, 0.08)	0.02 (-0.04, 0.08)	0.02 (-0.03, 0.07)	0.03 (-0.02, 0.08)	0.03 (-0.02, 0.08)
Bone/Soft Tissue Sarcoma	0.14 (0.06, 0.23)	0.11 (0.04, 0.18)	0.06 (-0.01, 0.13)	0.06 (-0.01, 0.13)	0.06 (-0.01, 0.13)
Skin	0.08 (0.01, 0.15)	0.09 (0.04, 0.13)	0.04 (-0.01, 0.08)	0.04 (-0.01, 0.08)	0.04 (-0.01, 0.08)
Breast	-0.08 (-0.12, -0.05)	0.05 (0.01, 0.08)	0.00 (-0.03, 0.03)	0.00 (-0.04, 0.03)	0.00 (-0.04, 0.03)
Female Reproductive Organs	-0.07 (-0.12, -0.02)	0.05 (0.00, 0.10)	0.02 (-0.03, 0.07)	0.02 (-0.03, 0.07)	0.02 (-0.03, 0.07)
Urinary Tract	0.10 (0.04, 0.16)	0.07 (0.02, 0.12)	0.04 (-0.01, 0.08)	0.04 (-0.01, 0.08)	0.04 (-0.01, 0.09)
Endocrine System	0.00 (-0.06, 0.06)	0.09 (0.04, 0.13)	0.03 (-0.02, 0.07)	0.03 (-0.02, 0.07)	0.03 (-0.02, 0.07)
Other	0.12 (0.02, 0.22)	0.03 (-0.08, 0.15)	0.01 (-0.12, 0.13)	0.02 (-0.10, 0.15)	0.02 (-0.10, 0.15)
Male Genital Organs	0.19 (0.16, 0.23)	0.08 (0.05, 0.12)	0.04 (0.01, 0.07)	0.04 (0.00, 0.07)	0.04 (0.00, 0.07)
Log Age (y)		-0.28 (-0.34, -0.22)	-0.31 (-0.37, -0.25)	-0.30 (-0.36, -0.24)	-0.30 (-0.36, -0.24)
Women (vs men)	-	-0.26 (-0.29, -0.24)	-0.25 (-0.28, -0.22)	-0.25 (-0.28, -0.22)	-0.25 (-0.28, -0.22)
Race (vs White)					
Black patients	-	0.09 (0.06, 0.11)	0.09 (0.06, 0.12)	0.09 (0.06, 0.12)	0.09 (0.06, 0.12)
Mixed patients	-	0.00 (-0.02, 0.03)	0.01 (-0.02, 0.03)	0.01 (-0.02, 0.03)	0.01 (-0.02, 0.03)
Asian patients	-	0.03 (-0.03, 0.08)	0.06 (0.01, 0.11)	0.06 (0.01, 0.11)	0.06 (0.01, 0.11)
BMI (Kg/m^2)(vs 20-24)					
<20	-	-	-0.08 (-0.12, -0.05)	-0.08 (-0.12, -0.04)	-0.08 (-0.12, -0.04)
25-29	-	-	0.04 (0.02, 0.06)	0.04 (0.02, 0.06)	0.04 (0.02, 0.06)
≥30	-	-	0.09 (0.06, 0.11)	0.09 (0.06, 0.11)	0.08 (0.06, 0.11)
Log CRP (mg/L)	-	-	-0.01 (-0.02, 0.00)	-0.01 (-0.02, 0.00)	-0.01 (-0.02, 0.00)
Log Alb (g/dL)	-	-	0.06 (-0.07, 0.18)	0.04 (-0.09, 0.16)	-
Log Hb (g/dL)	-	-	0.24 (0.14, 0.33)	0.22 (0.13, 0.31)	0.23 (0.15, 0.32)
Log ACR (mg/g)	-	-	0.00 (-0.01, 0.01)	0.00 (-0.01, 0.01)	0.00 (0.00, 0.01)
Smoking status (vs never smoker)					
Current	-	-	-	0.01 (-0.02, 0.05)	-
Previous	-	-	-	0.00 (-0.02, 0.02)	-
ECOG-PS (vs category 0)					
1	-	-	-	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)
2&3	-	-	-	-0.08 (-0.12, -0.03)	-0.08 (-0.12, -0.04)
Metastasis (vs no)	-	-	-	0.00 (-0.02, 0.03)	-
R^2	0.703	0.823	0.857	0.859	0.859

Cells report intercept, beta coefficients and R^2. Model 1: cancer sites adjusted for mGFR; model 2: cancer sites adjusted for mGFR, age, sex and race; model 3: cancer sites adjusted for mGFR, age, sex and race, BMI, CRP, Alb, Hb and ACR; model 4: cancer sites adjusted for mGFR, age, sex and race, BMI, CRP, Alb, Hb, ACR, smoking status, ECOG and metastasis; model 5 (significant variables): cancer sites adjusted for mGFR, mGFR measurement error, age, sex and race, BMI, CRP, Hb, ACR, and ECOG. a: $p < 0.0001$; b: $p < 0.001$; c: $p < 0.01$; d: $p < 0.05$. The regression was performed on the logarithmic scale; beta-coefficients can be converted to percent difference in Scr by the following formula: percent difference = 100*[exp(beta coefficient)-1]. The reference categories were: men, White, BMI 20-24, ECOG 0, metastasis "no" and never smoker. P value <0.05 in the final model was considered significant. mGFR: measured glomerular filtration rate; BMI: body mass index; CRP: C-reactive protein; Alb: albumin; Hb: hemoglobin; ACR: urinary albumin-creatinine ratio and ECOG-PS: Eastern Cooperative Oncology Group performance status.

Table 2.22: Multivariate linear regression models for serum cystatin C (Scys).

	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**
Intercept	3.80 (3.63, 3.96)	3.99 (3.65, 4.34)	4.01 (3.62, 4.39)	4.04 (3.64, 4.44)	4.24 (3.86, 4.63)
Log mGFR (ml/min/1.73m^2)	-0.86 (-0.90, -0.83)	-0.87 (-0.91, -0.82)	-0.88 (-0.92, -0.83)	-0.88 (-0.93, -0.83)	-0.87 (-0.91, -0.82)
Cancer Site					
Head and Neck	-0.01 (-0.05, 0.03)	-0.02 (-0.06, 0.01)	-0.02 (-0.06, 0.01)	-0.03 (-0.06, 0.01)	-0.03 (-0.06, 0.01)
Thorax	0.07 (0.00, 0.14)	0.07 (0.00, 0.13)	0.04 (-0.03, 0.10)	0.02 (-0.05, 0.08)	0.02 (-0.04, 0.09)
Bone/Soft Tissue Sarcoma	0.04 (-0.01, 0.10)	0.05 (-0.01, 0.10)	0.05 (-0.01, 0.10)	0.05 (-0.01, 0.11)	0.05 (0.00, 0.11)
Skin	0.01 (-0.03, 0.06)	0.01 (-0.03, 0.05)	-0.01 (-0.04, 0.03)	0.00 (-0.03, 0.04)	0.01 (-0.03, 0.05)
Breast	-0.08 (-0.11, -0.06)	-0.03 (-0.06, 0.00)	-0.03 (-0.06, 0.00)	-0.03 (-0.06, 0.00)	-0.03 (-0.06, 0.01)
Female Reproductive Organs	-0.03 (-0.07, 0.02)	0.03 (-0.02, 0.07)	0.01 (-0.04, 0.05)	0.01 (-0.03, 0.06)	0.01 (-0.04, 0.06)
Urinary Tract	0.00 (-0.04, 0.04)	-0.01 (-0.05, 0.03)	-0.03 (-0.07, 0.01)	-0.03 (-0.07, 0.01)	-0.03 (-0.07, 0.01)
Endocrine System	-0.02 (-0.07, 0.04)	0.02 (-0.04, 0.08)	0.00 (-0.05, 0.06)	0.02 (-0.04, 0.07)	0.02 (-0.03, 0.07)
Other	0.06 (-0.06, 0.18)	0.05 (-0.08, 0.18)	0.03 (-0.09, 0.15)	0.03 (-0.08, 0.14)	0.04 (-0.07, 0.15)
Male Genital Organs	-0.01 (-0.03, 0.02)	-0.05 (-0.08, -0.02)	-0.05 (-0.08, -0.02)	-0.04 (-0.07, -0.02)	-0.04 (-0.07, -0.01)
Log Age (y)		-0.03 (-0.08, 0.02)	-0.07 (-0.11, -0.02)	-0.07 (-0.12, -0.02)	-0.06 (-0.11, -0.01)
Women (vs men)	-	-0.10 (-0.13, -0.08)	-0.10 (-0.12, -0.07)	-0.09 (-0.12, -0.07)	-0.10 (-0.13, -0.08)
Race (vs white)					
Black patients	-	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.01)	-0.01 (-0.04, 0.01)	-0.02 (-0.04, 0.01)
Mixed patients	-	-0.02 (-0.04, 0.01)	-0.02 (-0.05, 0.00)	-0.03 (-0.05, 0.00)	-0.03 (-0.05, 0.00)
Asian patients	-	0.02 (-0.03, 0.07)	0.05 (-0.01, 0.10)	0.05 (-0.01, 0.11)	0.05 (-0.01, 0.11)
BMI (Kg/m^2)(vs 20-24)					
<20	-	-	-0.03 (-0.06, 0.01)	-0.04 (-0.08, 0.00)	-0.04 (-0.08, -0.01)
25-29	-	-	0.05 (0.03, 0.07)	0.05 (0.03, 0.07)	0.05 (0.03, 0.08)

≥30	-	-	0.07 (0.05, 0.10)	0.08 (0.06, 0.11)	0.09 (0.06, 0.11)
Log CRP (mg/L)	-	-	0.02 (0.02, 0.03	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)
Log Alb (g/dL)	-	-	-0.24 (-0.36, -0.12)	-0.24 (-0.35, -0.12)	-0.16 (-0.27, -0.05)
Log Hb (g/dL)	-	-	0.17 (0.09, 0.25)	0.16 (0.08, 0.24)	-
Log ACR (mg/g)	-	-	0.01 (0.00, 0.01)	0.00 (0.00, 0.01)	0.00 (0.00, 0.01)
Smoking status (vs never smoker)					
Current	-	-	-	0.08 (0.05, 0.11)	0.08 (0.05, 0.11)
Previous	-	-	-	0.02 (0.00, 0.04)	0.02 (0.00, 0.04)
ECOG-PS (vs category 0)					
1	-	-	-	0.00 (-0.02, 0.02)	-
2&3	-	-	-	0.01 (-0.03, 0.04)	-
Metastasis (vs no)	-	-	-	0.03 (0.01, 0.06)	0.03 (0.00, 0.06)
R^2	0.813309	0.828755	0.860515	0.867276	0.864231

Cells report intercept, beta-coefficients and R^2. Model 1: cancer sites adjusted for mGFR; model 2: cancer sites adjusted for mGFR, age, sex and race; model 3: cancer sites adjusted for mGFR, age, sex and race, BMI, CRP, Alb, Hb and ACR; model 4: cancer sites adjusted for mGFR, mGFR measurement error, age, sex and race, BMI, CRP, Alb, Hb, ACR, smoking status, ECOG and metastasis; model 5 (significant variables): cancer sites adjusted for mGFR , age, sex and race, BMI, CRP, Alb, ACR, smoking status and metastasis. a: $p < 0.0001$; b: $p < 0.001$; c: $p < 0.01$; d: $p < 0.05$. The regression was performed on the logarithmic scale; beta-coefficients can be converted to percent difference in Scys by the following formula: percent difference = 100*[exp(beta coefficient)-1]. The reference categories were: men, White, BMI 20-24, ECOG 0, metastasis "no" and never smoker. P value <0.05 in the final model was considered significant. mGFR: measured glomerular filtration rate; BMI: body mass index; CRP: C-reactive protein; Alb: albumin; Hb: hemoglobin; ACR: urinary albumin-creatinine ratio and ECOG-PS: Eastern Cooperative Oncology Group performance status.

2.4. Discussion

Inaccurate estimates of kidney function can lead to inappropriate exclusion from life-saving cancer therapy whereas inappropriate inclusion can expose patients to disproportionate treatment-related toxicity. In this study, we report the performance of GFR estimating equations using Scr and Scys compared to mGFR in a large population with solid tumors (primarily early-stage disease), which appears generally representative of cancer patients in Brazil in terms of primary cancer site by sex. We used a reference method for mGFR (plasma clearance of ^{51}Cr-EDTA), and standardized assays for Scr and Scys, and their relationships to a large number of prospectively-collected variables. CG was least accurate of all the equations that we evaluated. We found variable bias among equations based on Scr. Using guideline-recommended CKD-EPI equations, eGFRcr overestimated mGFR, eGFRcys underestimated mGFR, and eGFRcr-cys had minimal bias [-2.0 (-2.6 to -1.1) ml/min/1.73m^2] and optimal 1-P_{30} [7.8 (6.3–9.4)%]. The recently described CamGFRv2 equation performed well in our study population. Bias of eGFRcr and eGFRcys varied across subgroups defined by clinical and demographic characteristics, but no cancer site had a large effect on Scr or Scys independent of mGFR and demographic or clinical characteristics. Our findings are novel and have important policy implications for the estimation of GFR in patients with cancer.

Currently, GFR evaluation is not standardized in clinical oncology practice; treatment protocols use Scr, estimated creatinine clearance (eClcr) using the CG equation, and eGFRcr using the MDRD Study or CKD-EPI equations. It has been estimated that a threshold of Scr or eClcr with the CG equation, alone or in combination are the most commonly used criteria in cancer clinical trials, often in a logically

inconsistent manner. Indeed, only 2% of all cancer clinical trials and 14% of cancer clinical trials in the setting of decreased kidney function utilize an estimation of the GFR. The CG equation was developed in 1976 and eClcr using this equation was recommended for use in pharmacokinetic studies in drug development programs by regulatory agencies in 1998. It remains commonly used for the prescription of cancer chemotherapy, despite increasing evidence of its limitations (Table 2.22).

Table 2.23: Comparison between the CG and CKD-EPI equations.

eGFR equation	**CG**	**CKD-EPI**	**Comment**
Year	1976	2009	
Development Population N Male African-American	 249 100% 0% (presumed)	 8,254 55.6% 32%	CG equation was developed in a small non-representative study population
Reference Measure	Urinary creatinine clearance (24 hour sample)	mGFR (urinary clearance of iothalamate)	eClcr systematically overestimates mGFR because of clearance of creatinine by secretion in addition to clearance by glomerular filtration. Urinary clearance of iothalamate is accepted as a reference method for mGFR
Creatinine assay	Not traceable to IDMS reference material	Traceable to IDMS reference material	CG equation systematically overestimates mClcr because it was derived by an older creatinine assay method, which overestimates Scr compared to current international IDMS-traceable reference methods, and it cannot be re-expressed for use with current assays. Drug dosing recommendations based on prior pharmacokinetic studies are not applicable to current eClcr.
Performance compared to mGFR* Median Bias ml/min/1.73 m2 1-P_{30} (%)	 -8.0 (-8.7, -7.2) 37.5 (35.9, 39.0)	 2.6 (2.2, 3.0) 16.0 (14.8, 17.1)	CG equation is not as accurate in estimating mGFR as CKD-EPI equation. CKD-EPI equation is recommended for routine clinical practice.

*Using CKD-EPI 2009 external validation dataset, see ref 23. CG: Cockroft-Gault; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; mGFR: measured glomerular filtration rate; eClcr: estimated creatinine clearance; mClcr: measured creatinine clearance; IDMS: isotope dilution mass spectroscopy.

Updated draft guidance from regulatory agencies in 2020 recommends eGFR using the MDRD or CKD-EPI equations for pharmacokinetic studies for drug development programs. Our data on equation performance, along with these updated guidelines, should encourage the oncology community to incorporate newer equations that enable more accurate GFR estimation into clinical practice and research.

Janowitz and colleagues reported that the CKD-EPI equation was the least biased and most accurate among existing eGFRcr equations in two large studies of patients with solid tumors, and proposed new equations that enable use of non-calibrated or calibrated serum creatinine and performed better than the CKD-EPI equation in their study populations. In our study, CamGFRv2 was more accurate than CKD-EPI but had opposite bias (underestimation vs. overestimation of mGFR). In principle, clinical laboratories should report eGFR for all patients using a single GFR estimating equation for each filtration marker or combination of filtration markers whenever the filtration marker is measured. Of note, CamGFRv2 did not perform as well as CKD-EPI in a diverse study population (Abstract submitted to the American Society of Nephrology Meeting, 2021), thus it would not be suitable to replace CKD-EPI for use in general clinical practice, and we would not recommend it specifically for cancer patients, because using different equations for different subgroups of the population is not practical since each patient belongs to more than one subgroup.

The cause of overestimation of mGFR by eGFRcr by all equations other than CamGFRv2 in our study is not clear, but may be due in part to differences in mGFR methods. Urinary clearance of iothalamate (the method used to develop the MDRD and CKD-EPI equations) exceeds urinary inulin clearance (the classical method for mGFR),

whereas plasma clearance of ^{51}Cr-EDTA (the method used in this study and in CamGFR) is not reported to differ systematically from the urinary inulin clearance. The difference may also be due in part to non-GFR determinants of Scr. Systematic overestimation of mGFR in our study may reflect a higher prevalence of decreased muscle mass due to malnutrition and chronic illness related to cancer. Our observation of larger overestimation of mGFR in subgroups with lower BMI and more advanced disease (higher ECOG-PS, presence of metastasis) are consistent with this hypothesis. Alternatively, systematic overestimation of mGFR may reflect lower muscle mass in the Brazilian population compared to North American and European populations in which the equations were developed. This has not been consistently observed in studies comparing mGFR with eGFR equations in Brazilian study populations with and without CKD and no serious comorbidity. However, most of the studies included a small number of participants or were restricted to certain geographic areas[25,26,27,28]. Noteworthy, we observed larger overestimation in Blacks patients consistent with poor fit in Brazil of the African-American race coefficient derived in North America.

The cause of underestimation of mGFR by eGFRcys is also not clear. Our observation that eGFRcys underestimation of mGFR was larger in subgroups with higher BMI, current smokers, lower serum albumin, higher CRP, and higher ECOG-PS suggests non-GFR determinants of Scys as the cause. We did not observe a large independent association of cancer site with Scys independent of mGFR. Thus, possibly, systematic underestimation of mGFR by eGFRcys in our study represents the higher prevalence of these conditions related to cancer, rather than related to cancer per se. Studies in populations with and without cancer will be necessary to evaluate this hypothesis.

eGFRcr-cys had minimal bias and optimal accuracy in the overall study population and in most sub-groups. It has been well-documented that the use of multiple non-correlated endogenous filtration markers (such as creatinine and cystatin C) tends to cancel bias and to improve precision compared to each marker alone, due to weaker associations with the non-GFR factors affecting each marker ("panel eGFR"). The clinical implication is that when there is concern about bias in eGFRcr, confirmatory testing can be performed using cystatin C to determine eGFRcr-cys. mGFR can also be considered in certain sub-groups in which decision making may require more accurate GFR evaluation, such as patients who are old and frail, with sarcopenia or extremes of weight or clinical suspicion of very low GFR. There is encouraging data demonstrating that a panel of filtration markers including additional low molecular weight proteins or metabolites can further increase accuracy of eGFR, but these markers have not been assessed in cancer patients.

The most significant limitation of our study is that patients may have had better clinical performance status, less advanced cancer, lower prevalence of comorbid diseases including CKD, and better nutritional status compared to the general population of patients with cancer treated in our hospital. Although the study population was large, we may not have had sufficient power to identify informative subgroups regarding equation performance. Finally, our study was performed at a single center, and the results may not be generalizable to other centers. Confirmation in other centers and in patients with more advanced cancer and with lower GFR would be appropriate.

In conclusion, CG was the least accurate of the eGFRcr equations that we evaluated, and it should not be preferred over CKD-EPI equation, which is recommended

by current guidelines for the adult general population. Using the CKD-EPI equations, eGFRcr overestimated mGFR, eGFRcys underestimated mGFR, and eGFRcr-cys had minimal bias and best accuracy, confirming eGFRcr-cys as a confirmatory test, as in the general population. A major policy implication is that standardization of methods for GFR estimation in patients with cancer, using methods recommended for the general population, can improve communication and may improve outcomes in oncology practice and research.

2.5. Supplementary material

2.5.1 Supplementary study conduct

The Onco-GFR study was conducted at the Instituto do Câncer do Estado de São Paulo (ICESP), a tertiary academic hospital in Brazil exclusively devoted to the care of patients with cancer. The study is comprised of patients newly evaluated for treatment as well as patients already in follow-up. New patients were sequentially screened at the time of the first institutional consultation. Patients in follow-up were recruited from selected clinics as described below, as long as they were not in current or recent (in the last 60 days) cancer treatment. Eligible patients were invited to participate. In the case of acceptance, informed consent was signed and the exams necessary to the project were scheduled. Patients underwent collection of serum blood and urine samples, measurement of glomerular filtration rate (GFR), and nutritional evaluation. A geriatric evaluation was performed in elderly patients (≥60 years). Image exams and chemotherapy data (regimens, side effects, clinical outcomes) were also recorded. A multidisciplinary research team included nephrologists, oncologists, geriatrics, clinical pathologists,

nuclear medicine physicians, radiologists, nutritionists, pharmacists and nurses. Patients were followed until the end of treatment (death, palliative care or discharge).

2.5.2. Supplementary inclusion and exclusion criteria and recruitment strategy

2.5.2.1. Inclusion criteria:

1. Patients in treatment for cancer at the Instituto do Câncer do Estado de São Paulo (ICESP).
2. Malignant tumor confirmed by histology sample (with the exception of hepatocellular carcinoma which was included based on standard criteria).
3. Signed informed consent.

2.5.2.2 Exclusion criteria:

1. Age under 18 years old.
2. Benign tumor.
3. Hematological malignancy (such as myeloma, leukemia, lymphoma).
4. Eastern Cooperative Oncology Group performance status (ECOG-PS) >3.
5. Chronic kidney disease on kidney replacement therapy.
6. Pregnant and nursing women.
7. Patients admitted at the Nuclear Medicine Service (logistic reasons) and Dermatology Clinic (mostly superficial skin cancer).
8. Patients exposed to systemic chemotherapy or pelvic radiotherapy in the last 60 days before measured GFR and the laboratory study exams.

9. Patients with suspected or confirmed obstructive uropathy or other circumstances associated with the risk of acute GFR decline before performing measured GFR and study laboratory exams, decided by the investigator.

10. Comorbid conditions precluding cooperation with the study, as estimated by the investigator (such as severe congestive heart failure, oxygen-dependent lung disease, severe motor deficit).

11. Patients starting chemotherapy in the next seven days.

12. Patients requiring hospital admission.

2.5.2.3. Recruitment strategy

New patients were recruited from the following clinics: Clinical Oncology, Hepatology, Endocrinology, Urology, Abdominal Surgery, Mastology, Gynecology, Neurosurgery, Thoracic Surgery, Head and Neck Surgery, Plastic Surgery, Surgery for Soft Tissue Sarcomas, Otorhinolaryngology. Patients in follow-up were recruited from all but the following clinics: Neurosurgery, Otorhinolaryngology, and Plastic Surgery. Patients from the following clinics were not recruited: Hematology Clinic (exclusion criteria), Nuclear Medicine Service, Dermatology Clinic, Hereditary Counseling Clinic and Hysteroscopy Clinic (mostly benign cases).

2.5.3. Supplementary baseline data and definitions

2.5.3.1. Baseline clinical data

Baseline information that was collected at the time of recruitment included: demographic variables (age, gender, race), cancer variables (previous cancer treatment,

clinical performance status assessed by ECOG and Karnofsky index, tumor site, TNM and stage for each tumor), comorbid conditions (described below), drugs under use, smoking and drinking history, family income and education level (degree and years at school). Arterial blood pressure was measured twice.

2.5.3.2. Comorbid conditions and definitions used on the study

1. Race: self-assigned. Mixed race refers to mixed Black and White.

2. Tumor stage: based on the TNM system (8ª edition of American Joint Committee on Cancer /Cancer Stage Manual). Cancer variables were ascertained at the time of admission and on additional exams or procedures performed in sequence and were reviewed by two oncologists. Clinical stage was determined based on disease extension at the time of cancer diagnosis.

3. Systemic arterial hypertension: blood pressure > 140 x 90 mmHg or the use of medication to reduce blood pressure, according to definition of the 8th Joint National Committee.

4. Diabetes mellitus: use of insulin or drugs to reduce blood glycemia. End organ damage was defined as the presence of retinopathy, neuropathy or kidney disease.

5. Heart failure: ejection fraction under 55%, recorded by echocardiogram.

6. Coronary heart disease: previous acute myocardial infarction, unstable or stable angina.

7. Cerebrovascular disease: history of transient ischemic attacks or stroke (presence of permanent neurological damage or image from central nervous system confirming the event). Sequel was considered as any permanent deficit in consequence of this event.

8. Peripheral vascular disease: history of intermittent claudication or any confirmatory exam (doppler ultrasound, angiography).

9. Arrhythmia: chronic atrial fibrillation or flutter or ventricular arrhythmia requiring chronic treatment.

10. Dementia: chronic cognitive deficit diagnosed by a neurologist.

11. Connective tissue disease: diagnose of any rheumatologic disease such as systemic lupus erythematous, rheumatoid arthritis, polymyositis.

12. Peptic ulcer disease: history of gastritis, esophagitis or ulcer requiring treatment.

13. Dyslipidemia: use of statins to reduce cholesterol levels.

14. Hypothyroidism: chronic use of thyroid hormones.

15. Hyperthyroidism: confirmed by an endocrinologist.

16. Depression or other psychiatric disorder (such as bipolar disorder, schizophrenia): confirmed by a psychiatrist.

17. Kidney stones: confirmed by image exams (ultrasound or tomography).

18. Transplantation: history of transplantation of organs other than the kidney.

19. Recurrent urinary tract infection: more than two episodes (confirmed by urine culture) in six months or three episodes in one year.

20. Chronic obstructive pulmonary disease and asthma: defined by current guidelines.

21. Chronic liver disease: cirrhosis confirmed by liver biopsy, portal hypertension or hepatic encephalopathy.

22. AIDS (acquired immunodeficiency syndrome): defined by current guidelines.

23. Charlson comorbidity index: applied as proposed original definitions without age points.

24. Smoking status: classified as current smoker (any consumption of tobacco at the time of recruitment); former smoker (previous consume of tobacco, with no consume in the last 30 days before recruitment) and never smoker (never consumed tobacco). For all categories, the amount of pack-years of tobacco was recorded.

25. Alcohol consumption: classified as social drinking (drinking doesn't disrupt patient's life or create serious physical, mental or personal problems) and alcohol use disorder (any other alcohol consumption that is not considered to be social drinking). In this last case, the type and amount of alcohol consumption was recorded.

2.5.4. Supplementary methods for GFR Measurement

2.5.4.1. Methods to avoid acute GFR decline

Measured GFR (mGFR) was scheduled up to 60 days after recruitment, and timed to avoid exposure to acute GFR decline (medications, contrasted exams, surgeries, hospital admission or visit to the emergency room). When mGFR was scheduled, patients were advised to avoid nonsteroidal anti-inflammatory drugs and to avoid changes in medications in use, particularly renin-angiotensin blocking agents, diuretics and other medications used to treat hypertension. Patients were contacted by phone a few days before the exam to confirm the attendance and check if the instructions were followed. A screening query was performed at this moment (phone call) and a few days later when patients arrived to collect blood samples and perform the mGFR. A specific form was fulfilled and reviewed by the principal investigator. Data recorded were:

1. Use of antibiotics in the last two weeks: name of drug, period of use, and dose.

2. Use of non-hormonal anti-inflammatory drugs in the last two weeks: name of drug, period of use, and dose.

3. Emergency department visit in the last two weeks: reason for the visit, period of stay, and medications used.

4. Surgery or hospital admission in the last three weeks: type of surgery, reason of admission/, length of stay, and day of discharge.

5. Contrast exam (iodinated) in the last 7 days: day of exam was recorded.

6. Magnetic resonance with gadolinium in the last 7 days: day of exam was recorded.

7. Urinary symptoms in the last four weeks: hematuria, dysuria, change in urine output.

8. Change in anti-hypertensive medication in the last four weeks.

9. Medications in use with special attention to immunosuppresive, and antiretroviral therapy.

If items 3 or 4 were detected during the phone call or during the mGFR visit, the exams were rescheduled, upon confirmation by the principal investigator. If item 5 was detected, mGFR was performed if patients had eGFR > 60ml/min/1.73 m^2 (based on CKD-EPI equation considering baseline serum creatinine) with no diabetes or other causes for acute GFR decline (items 1 to 4). Baseline serum creatinine was defined as serum creatinine recorded up to 90 days before mGFR procedure.

2.5.4.2. Technical procedure

Patients were recommended to avoid extreme exercise the day before GFR visit, and instructed to fast for three hours and to drink 300 ml of water about one hour prior to radiopharmaceutical administration. During the six hours of the exam, the patients were

free to eat except to avoid red meat, and were instructed to drink water as usual for their daily routine. Patients had both their height and weight measured.

Two syringes containing about 3.7 MBq of ^{51}Cr-EDTA (IPEN – São Paulo, Brazil) were prepared containing at least 1 mL of solution and weighed in an analytical balance (Quimis® Q500L210C). The content of one of the syringes was injected in a volumetric balloon containing 1000 mL of distilled water and the solution was homogenized 20 times before samples extraction. After 15 minutes two standard samples of 2 mL of the homogenized solution were pipetted.

The solution of the other syringe was administered intravenously, followed by 10 mL of saline flush prepared in a separated third syringe to guarantee that all of the ^{51}Cr-EDTA was administered. Both ^{51}Cr-EDTA syringes were weighed after administration of its content in the same analytical balance, and the value obtained after subtraction of the weight of each syringe before and after administration was considered the ^{51}Cr-EDTA injected mass for both volumetric balloon and the patient.

The site of ^{51}Cr-EDTA administration was monitored for radioactivity to guarantee that all the radiopharmaceutical solution was completely injected in the vascular compartment using a pancake surface (IEN SPQ-7026®) monitoring Geiger-Muller probe (IEN MIR-7026®).

Blood samples were collected after 2, 4 and 6 hours after ^{51}Cr-EDTA administration in a different limb from the infusion limb, in tubes containing 0.2 mL of heparin to avoid blood coagulation. During each draw the first 3 mL of blood were discarded and then 10 mL of blood were collected. Each tube was centrifuged at 1000 g for 10 minutes to obtain 2 mL of plasma.

All samples obtained from both volumetric balloon and patient were then counted for 5 minutes in a radiation well counter using the chromium-51 photo peak of 320 keV as center and with a window of 10% spread from photo peak center. Background radiation was counted for 5 minutes and was discounted from each sample counts and final counts were divided by the volume to obtain results in counts/mL units.

Weight and height were used to determine BSA. The time of each sample extraction was subtracted from injection time obtaining the injection-sample time interval in minutes. Using each sample counts and injection-sample time interval in an Excel® spreadsheet, an exponential decay curve was plotted and slope and intercept of the curve were determined.

^{51}Cr-EDTA concentration volume conversion factor was determined multiplying balloon standard samples counts by the balloon total volume and then multiplying by the weight difference from the standard syringes before and after ^{51}Cr-EDTA in the balloon.

The initial distribution volume of ^{51}Cr-EDTA was determined by dividing the concentration volume conversion factor by the curve intercept, and finally multiplying patient´s initial distribution volume by the curve slope is determined the raw glomerular filtration rate in mL/min.

GFR was indexed for 1.73 m^2 body surface area (BSA) according to the equation:

Indexed GFR = non-indexed GFR * 1.73 m2/BSA.

The final GFR was obtained after Brochner-Mortensen correction using the following equation:

Indexed GFR = (1.0004*indexed GFR) – (0.00146*(indexed GFR))^2

Two members of the research team were present during the mGFR procedure to ensure proper data collection. All data related to the mGFR procedure was collected (including height, weight, time of infusion, time of sample collection, infusion site counts) in a working form, as well as any clinical occurrence during the exam, such as pain, nausea, particularly if requiring medication. These records (working form) were completed by the working team members and reviewed by both the nuclear medicine physician and the principal investigator twice. All mGFR results were reviewed by two independent nuclear medicine physicians, as usually done in routine assistance. In addition, all exams and technical records were carefully reviewed by the nuclear medicine physician on the research team, including plotting of patient samples counts per time decay on graphics, checking for consistency of the plotted curves and estimated distribution volume of each patient. If a major issue was identified by the research team, the mGFR procedure was canceled and rescheduled.

2.5.5. Supplementary laboratory tests

Serum creatinine and cystatin C were measured using the Roche Cobas 6000 Chemistry analyzer (Roche Diagnostics, Indianapolis, IN). The creatinine assay was calibrated using the Roche enzymatic method traceable to IDMS (isotope dilution mass spectrometry) reference method. The cystatin C assay was calibrated using the turbidimetric assay (Gentian AS, Moss, Norway), traceable to the International Federation of Clinical Chemistry Working Group for Standardization of Serum Cystatin C and the Institute of Reference Materials and Measurements certified reference materials.

Serum urea, albumin, hemoglobin, C-reactive protein and urinary albumin/creatinine ratio were analyzed locally. Serum urea was measured by ultra-violet kinetic models, serum albumin was performed through the colorimetric method, and C reactive protein was performed by immunoturbidimetry. Untimed urine samples were collected on site between 07:00 and 10:00 AM (first morning urine if possible). Urine albumin concentration was measured on a nephelometric analyzer, urine creatinine concentration was measured by Jaffe reaction. Hemoglobin was measured by cyanide-free SLS-methodology using Sysmex XT-2000 analyzer (Sysmex Corp., Kobe, Japan). The remaining tests were measured using Cobas 8000 Modular P Chemistry Analyzer (Roche Instrument Center, Rotkreuz, Switzerland). Urine albumin/creatinine ratio (UACR) was obtained by dividing urine albumin concentration by urine creatinine concentration. For non-detectable values for urine albumin concentration (lower limit of detection was 3.00 mg/L; 284 participants), we imputed a value of 2.99 mg/L, and used the imputed values for the computation of UACR. Extra samples of blood and urine were collected and stored for future exams.

2.6. Student contribution

All the work presented in this Thesis was done by the student responsible the project.

Chapter 3: Discussion

In this study, we report the performance of GFR estimating equations based on Scr and Scys compared to mGFR in a large population with solid tumors, primarily with early-stage disease. The population was generally representative of cancer patients in Brazil in terms of primary cancer site by sex[26]. We used plasma clearance of ^{51}Cr-EDTA, an accepted reference method for mGFR, and standardized assays for Scr and Scys, and a large number of prospectively-collected variables. We found that there was variable bias among equations based on Scr, with CG the least accurate of all the equations that we evaluated. Using guideline-recommended CKD-EPI equations, eGFRcr overestimated mGFR, eGFRcys underestimated mGFR, and eGFRcr-cys had minimal bias [-2.0 (-2.6 to -1.1) ml/min/1.73m^2] and optimal 1-P_{30} [7.8 (6.3–9.4]. Bias of eGFRcr and eGFRcys varied across subgroups defined by clinical and demographic characteristics, but no cancer site had a large effect on Scr or Scys independent of mGFR and demographic or clinical characteristics.

3.1. Why assess glomerular filtration rate in patients with cancer?

An accurate assessment of GFR is a fundamental aspect of cancer care and research. First, GFR is used to decide upon eligibility for, and adjust the dosing of chemotherapy, so to minimize the risks of undertreatment and unnecessary kidney and systemic toxicity. Inaccurate estimates of GFR can lead to inappropriate exclusion from life-saving cancer therapy whereas inappropriate inclusion can expose patients to disproportionate or severe toxicity[27]. Data from a landmark multicenter study, including nearly five thousand patients with solid tumors in France demonstrated that 80% of them

received chemotherapy as part of their treatment. More importantly, 80% of treated patients received at least one drug requiring adjustment for GFR[28]. However, currently, GFR evaluation is not standardized in clinical oncology practice. Treatment protocols use Scr, estimated creatinine clearance (eClcr) using the CG equation, and eGFRcr using the MDRD Study or CKD-EPIcr equations. Second, assessment of GFR is used to determine eligibility in RCTs. Overestimates of GFR can lead to inappropriate inclusion in trials, thus potentially overestimating risk of toxicity from the novel drug. Underestimates of GFR may prevent individual patients who have failed conventional therapy from being considered from novel, potentially life-saving therapies. Third, accurate assessment of GFR may lead to more confidence in inclusion of patients with CKD in RCTs in general[17]. There has always been concern about enrolling patients even with mild decreases in GFR, as defined by the FDA as creatinine clearance between 50-79 ml/min in phase 1 RCTs, considering the risk for major toxicity and concerns that the intervention could worsen their kidney disease and lower their GFR. In consequence, currently, around 85% of RCTs exclude patients with chronic kidney disease[29]. This barrier persists even for RCTs evaluating therapy without any kidney clearance nor significant likelihood of nephrotoxicity (e.g. immunotherapies, hormonal therapies) and therefore it is not known how to optimally treat patients with CKD and cancer[17]. Accurate assessment of GFR could increase eligibility in RCT improve access to potential beneficial anti-cancer treatment.

The lack of uniformity in assess GFR for eligibility also contributes to the uncertainty when evaluating GFR in RCTs. It has been estimated that a threshold of Scr or eClcr with the CG equation, alone or in combination are the most commonly used

criteria in cancer clinical trials, often in a logically inconsistent manner. In a random sample of more than four hundred cisplatin trials (phase one to three) registered at the clinical trials platform by December 2017, thresholds to define decreased GFR for trial eligibility were quite diverse[30]. Serum creatinine alone was used in 22%, a composite of creatinine or estimated creatinine clearance in 24%, and estimated creatinine clearance in 15%. Only 6% used estimated GFR. One-third of trials did not articulate a specific threshold for kidney function.

3.2. The performance of eGFRcr equations

In our study, most eGFRcr equations overestimated mGFR, with a variation in magnitude of the overestimation that ranged from -8.1 to -4.6 ml/min/1.73 m^2. There are prior studies including up to 300 patients with solid tumors, and using plasma clearance of exogenous filtration markers demonstrating bias for CG and CKD-EPIcr varying between 17.6 to 4.3, and 4.5 to -0.5 ml/min, respectively[31,32]. There are a number of potential sources of error that could explain why differences in accuracy can observed in validation populations compared to the population in which the equation was derived[5]. Most common errors are systematic differences between the development and validation populations such as different frequency of race/ethinicity groups, extremes of body size, differences in nutrition status, in methods used for the assessment of mGFR, in assays for endogenous filtration markers (use or not of standardized assays), and in the relationship of surrogates for the non- GFR determinants of the filtration markers to the underlying physiological processes. Bias reflects systematic errors among populations.

The cause of overestimation of mGFR by eGFRcr in our study is not clear, but may be due in part to differences in mGFR methods or consequence of non-GFR determinants. Urinary clearance of iothalamate is thought to possibly result in higher values compared to plasma clearance of ^{51}Cr-EDTA (the method used in this study)[33]. Thus, the differences in these two methodologies could have led to the observed overestimate for the MDRD and CKD-EPIcr equations. Alternatively, the difference may be due in part to non-GFR determinants of Scr. Systematic overestimation of mGFR in our study may reflect a higher prevalence of decreased muscle mass due to malnutrition and chronic illness related to cancer. Our observation of larger overestimation of mGFR in subgroups with lower body mass (BMI) and more advanced disease (higher Eastern Cooperative Oncology Group performance status [ECOG-PS], presence of metastasis) are consistent with this hypothesis. Of note, several series have demonstrated large bias for eGFRcr equations, particularly CG, in the elderly[34], and in patients with comorbid conditions such as heart failure[35], liver disease[36], morbid obesity, and malnutrition[37]. Alternatively, systematic overestimation of mGFR may reflect lower muscle mass in the Brazilian population compared to North American and European populations in which the equations were developed. This has not been consistently observed in studies comparing mGFR with eGFR equations in Brazilian study populations with and without CKD and no serious comorbidity[38,39]. However, most of the studies included a small number of participants or were restricted to certain geographic areas.

3.3. The role of standardized assays from creatinine measurement

Variation in creatinine assays can lead to important variation in assessment of GFR using creatinine as a filtration marker[4]. As a consequence, the use of standardized creatinine in equations that were developed for non- standardized creatinine assays can cause unpredictable bias and inflate error in eGFRcr estimation. This is the case for CG, which was the least accurate of all assessed equations (1-P30 was 24.9 [22.4 – 27.3%]) in our study. The CG equation was developed in 1976 based on non-standardized assays, which are 10 to 20% higher compared to the standardized ones, currently in use[4]. This might help to explain the poor performance of CG equation in these studies, including ours, and highlight the clinical impact of standardized assays.

Our study was the largest series to date assessing eGFRcr equations using standardized assays, reinforcing the reliability of our results and its implications for oncology practice. Variation in creatinine assays can lead to inconsistency in development and implementation of drug dosing recommendations. That because using non-standardized creatinine methods obtained results that were dependent upon the particular creatinine method used in a given study. Thus, incorporating results from the pharmacokinetic studies into recommended drug dosages on the US FDA drug labels led to inconsistent translation into clinical practice due to the variability among creatinine methods used in different laboratories[40]. To overcome these inconsistencies, in 2005, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) National Kidney Disease Education Program (NKDEP), in collaboration with the National Institute of Standards and Technology (NIST) and College of American Pathologists (CAP), established a creatinine-standardization program through the isotope dilution

mass spectrometry (IDMS)-traceable method. Standardized assays are currently recommended and are adopted by most laboratories worldwide[41]. The effect of standardization varied among clinical laboratories, but on average has led to lower values for serum creatinine and higher values for eGFR using creatinine as a filtration marker than before standardization. Although the impact of standardized assays was not largely assessed in cancer treatment, a few studies have been demonstrating that when incorporated into the CG equation, IDMS creatinine assay increases carboplatin dose calculated through the Calvert equation in approximately 10%[42]. This observation led the National Cancer Institute to issue an Information Letter in 2010 recommending that all clinical trial protocols be amended so that estimates of GFR, based on IDMS-creatinine, would be capped at 125 mg/mL to prevent overdosing.

3.4. Cystatin C as a filtration marker

3.4.1. Concepts on cystatin C physiology and physiopathologic pathways

Cys C is a naturally occurring inhibitor of lysosomal cysteine proteinases (CP), such as cathepsins B, H, K, L, and S. Cys C belongs to the type 2 cystatin superfamily of CP inhibitors (CPI) including cystatins C, D, E/M, F, G, S, SN, and SA[43]. Under normal physiology, Cys main activity is to protect against tissue injury caused by CP release in the course of an insult. However, Cys also operates through other routes other than the CP pathway and modulates other physiological functions, such as cell proliferation, differentiation, and migration, immune modulation, neuroprotection, and bone remodeling[44]. In malignancy, Cys has been shown to be extensively expressed in cells and tissues of various solid tumors[45,] and clinical studies have demonstrated higher Scys

levels in cancer patients compared to non-cancer patients although these studies did not adjust confounding factors such as age and GFR[46]. In a cancer setting, Cys exerts a series of complex effects, including paths beyond its role as CPI. As a tumor suppressor, Cys acts counter-balancing the effects of CP, which are up-regulated in tumor cells and tissues in order to degrade the extracellular matrix protein and promote cell invasion, angiogenesis, and metastasis[24]. Cys also may antagonize paths that lead to tumor growth such as tumor growth factor beta (TGF-β) receptor and signaling, and androgen receptors MAPK/ErK (mitogen activated protein kinase pathway). Several experimental and clinical studies demonstrated an association between down-regulation of Cys in the cancer intracellular space and/or tissue and more aggressive tumors. Conversely, Cys has been described as a tumor promoter through several mechanisms, such as compensatory up-regulation of other cathepsins, inhibition of apoptosis, and impairment of anti-tumor immune response, apart from promoting bone metastasis[24]. Clinical observations have suggested that Cys could be used as a biomarker for cancer detection, and clinical response due to a significant association between increased Scys level to larger tumor size, and reduced survival, although this association was demonstrated for only certain cancer sites[47].

Considering these conflicting results mostly based in experimental studies, the utility of Scys as filtration marker has been assessed in a few clinical studies. Initially, a few studies including less than 300 patients compared eGFRcys equations to CrCl or eGFRcr equations in patients with solid tumors, demonstrating conflicting results[48,49,50]. Of note, these studies lacked a more reliable standard for GFR assessment, such as mGFR, and did not used standardized assays, and this issued remained inconclusive.

More recently, a few small series (<300 patients) have been published assessing eGFR equations combing Scr and Scys in patients with solid tumors, using mGFR as reference[25], although our study represents the largest series published so far. Of note, the impact of known GFR determinants of Scys such as fat mass, corticosteroid exposure, smoking, and hyperthyroidism is not well known in studies including cancer patients and their impact in clinical practice is difficult to estimate[51,52,53,54,]. Corticosteroids are frequently part of chemotherapy regimens, but Scys is expected to be more useful in scenarios where decisions upon drug dosage is yet to be made. So, the real impact of these non-GFR determinants seems to be unknown and in the cancer population.

3.4.2. The performance of the eGFRcys equation

We found that eGFRcys underestimated mGFR by 4.6 (3.7 to 5.5) ml/min/1.73 m^2 with 1-P_{30} indicating large errors of 12.3 (10.3–14.3)%. Larger underestimation was observed in subgroups with higher BMI, current smokers, lower serum albumin, higher C-reactive protein (CRP), and higher ECOG-PS, suggesting the impact of these elements linked to chronic inflammation as non-GFR determinants of Scys , and the cause of the overestimate[55,56,57,58,59]. We did not observe a large independent association of cancer site with Scys independent of mGFR. Thus, possibly, systematic underestimation of mGFR by eGFRcys in our study represents the higher prevalence of these conditions related to cancer, rather than related to cancer per se. This hypothesis confronts the concept currently in place that Scys is not a reliable filtration marker in patients with cancer in consequence of the direct impact that cancer cells might increase Scys level.

3.5. The performance of the eGFRcr-cys equation

In our study, eGFRcr-cys had minimal bias [-2.0 (-2.6 to -1.1) ml/min/1.73m^2] and optimal 1-P_{30} [7.8 (6.3–9.40]. It has been well-documented, in the overall population, that the use of multiple non-correlated endogenous filtration markers (such as creatinine and cystatin C) tends to cancel bias and to improve precision compared to each marker alone, due to weaker associations with the non-GFR factors affecting each marker ("panel eGFR")[60]. Our study is the only series confirming this effect in patients with solid tumors that used standardized assays for Scr and Scys coupled with a robust methodology of GFR measurement. Although the clinical use of Cys as a filtration marker in patients with cancer has been discouraged for several years, our data suggests that Cys can be used as a confirmatory test, in association with Scr, and is particularly useful in a few sub-groups such as those in the extremes of weight.

3.6. Implications

Our findings are novel and have important policy implications for the estimation of GFR in patients with cancer, particularly in the scenario of drug dosing. eClcr using the CG equation was recommended for use in pharmacokinetic studies in drug development programs by regulatory agencies in 1998[21]. It remains commonly used for the prescription of cancer chemotherapy, despite increasing evidence of its limitations[7,8,9,22]. Updated draft guidance from regulatory agencies in 2020 recommends eGFR using the MDRD or CKD-EPIcr equations for pharmacokinetic studies for drug development programs[23]. Our data on equation performance, along with these updated guidelines, should encourage the oncology community to similarly update their

recommendations. A practical approach would be to use a more general recommendation to use the most accurate method to estimate GFR in the patient, consistent with the Kidney Disease Improving Global Outcomes (KDIGO) controversies conference on use of GFR in drug dosing[61]. Finally, our data suggest that the mistrust for the use of Cys as filtration marker should be re-assessed and cancer centers can incorporate eGFRcr-cys equations in clinical care and research.

3.7. Study limitations

The most significant limitation of our study is that patients may have had better clinical performance status, less advanced cancer, lower prevalence of comorbid diseases including CKD, and better nutritional status compared to the general population of patients with cancer treated in our hospital. Although the study population was large, we may not have had sufficient power to identify informative subgroups regarding equation performance. Finally, our study was performed at a single center, and the results may not be generalizable to other centers. Confirmation in other centers and in patients with more advanced cancer and with lower GFR would be appropriate.

3.8. Future steps

There are important future steps that it can be envisioned considering the data presented. Firstly, like Cys, novel filtration markers such as beta-2-microglobulin (B2M) and beta-trace protein (BTP), are not largely influenced by age, sex, race, muscle mass and nutrition status. eGFR models incorporating these biomarkers and not including race were recently developed by the CKD-EPI research group and assessed in a large group of

non-cancer patients[62]. The models were: $eGFR_{B2M,}$ eGFR based on the serum level of B2M (S_{B2M}); $eGFR_{BTP}$, eGFR based on the serum level of BTP (S_{BTP}); eGFRcr-cys-$_{B2M,}$ eGFR based on Scr, Scys, and S_{B2M}; eGFRcr-cys-$_{BTP}$, eGFR based on Scr, Scys, and S_{BTP}; eGFRcr-cys-$_{B2M-BTP}$ or 4-marker panel, eGFR based on Scr, Scys, S_{2BM}, and S_{BTP}. It was demonstrated that 4-marker panel eGFR was not superior, but similar to 2012 eGFRcr-cys. Adding B2M and/or BTP to eGFRcr-cys might add the advantage to compensate for known and unknown non-GFR determinants of each of these filtration markers providing more accurate eGFR models. Noteworthy, B2M assay is cheap, robust, and largely available, which can be a useful alternative when Cys is not readily available. However, eGFR equations incorporating B2M and BTP to eGFRcr or eGFRcr-cys have never been assessed in cancer patients. Another important step would be to evaluate the impact of more accurate equations on clinical outcomes. Although our study and other series demonstrated that robust eGFR equations are associated with more accurate GFR estimates, it is yet to be proved that these errors are associated with relevant clinical events such as higher toxicity in patients receiving chemotherapy, CKD development and progression, sepsis, hospital admission, and survival.

In conclusion, CG was the least accurate of the eGFRcr equations that we evaluated, and it should not be preferred over CKD-EPI equation, which is recommended by current guidelines for the adult general population. Using the CKD-EPI equations, eGFRcr overestimated mGFR, eGFRcys underestimated mGFR, and eGFRcr-cys had minimal bias and best accuracy, confirming eGFRcr-cys as a confirmatory test, as in the general population.

Chapter 4: Bibliography

1. Benzing T, Salant D. Insights into Glomerular Filtration and Albuminuria. *N Engl J Med*. 2021;384(15):1437-1446.
2. Levey AS, Grams ME, Inker LA. Uses of GFR and Albuminuria Level in Acute and Chronic Kidney Disease. *N Engl J Med*. 2022;386(22):2120-2128.
3. Soveri I, Berg UB, Björk J, et al. Measuring GFR: A systematic review. *Am J Kidney Dis*. 2014;64(3):411-424.
4. Levey AS, Inker LA. Assessment of Glomerular Filtration Rate in Health and Disease : A State of the Art Review. 2017;102(3):405-419.
5. Levey AS, Coresh J, Tighiouart H, et al. Measured and estimated glomerular filtration rate: current status and future directions. *Nat Rev Nephrol*. 2020;16(1):51-64.
6. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.
7. Levey AS, Bosch JP, Lewis JB, et al. A More Accurate Method To Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation. *Ann Intern Med*. 1999;130(6):461-470.
8. Levey AS, Stevens LA, Schimd CH et al: A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med* 150:604–613, 2009.
9. US Department of Health and Human Services, F.D.A. Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing and Labeling. Silver Spring, MD: Center for Drug Evaluation and Research (CDER), 1998.
10. Revised Draft Guidance for Industry on Pharmacokinetics in Patients With Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling; Availability. https://www.federalregister.gov/documents/2010/03/22/2010-6171/revised-draft-guidance-for-industry-on-pharmacokinetics-in-patients-with-impaired-renal. Accessed October 17, 2022.
11. Kidney Disease: Improving global outcomes (KDIGO) CKDWork Group: KDIGO 2012 clinical practice guidelineforthe evaluation and management of chronic kidney disease. *Kidney Int Suppl* 3:1–150, 2013.
12. Stevens LA, Schmid CH, Greene T, et al. Factors other than glomerular filtration rate affect serum cystatin C levels. *Kidney Int*. 2009;75(6):652-660.
13. Inker LA, Schmid CH, Tighiouart H, et al. Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. *N Engl J Med*. 2012;367(1):20-29.
14. Malyszko J, Lee MW, Capasso G, et al. How to assess kidney function in oncology patients. *Kidney Int*. 2020;97(5):894-903.
15. Casal MA, Nolin TD, Beumer JH. Estimation of kidney function in oncology implications for anticancer drug selection and dosing. *Clin J Am Soc Nephrol*. 2019;14(4):587-595.
16. Sprangers B, Abudayyeh A, Latcha S, et al. How to determine kidney function in cancer patients? *Eur J Cancer*. 2020;132:141-149.
17. Sprangers B, Perazella MA, Lichtman SM, et al. Improving Cancer Care for Patients With CKD: The Need for Changes in Clinical Trials. *Kidney Int Reports*.

2022;7(9):1939-1950.
18. Janowitz T, Williams EH, Marshall A, et al. New model for estimating glomerular filtration rate in patients with cancer. *J Clin Oncol*. 2017;35(24):2798-2805.
19. Williams EH, Connell CM, Weaver JMJ, et al. Multicenter validation of the CamGFR model for estimated glomerular filtration rate. *JNCI Cancer Spectr*. 2019;3(4):4-7.
20. Williams EH, Flint TR, Connell CM, et al. CamGFR v2: A new model for estimating the glomerular filtration rate from standardized or non-standardized creatinine in patients with cancer. *Clin Cancer Res*. 2021;27(5):1381-1390.
21. Torres da Costa e Silva V, Costalonga EC, Coelho FO, et al. Assessment of Kidney Function in Patients With Cancer. *Adv Chronic Kidney Dis*. 2018;25(1):49-56.
22. Villaseñor A, Ballard-Barbash R, Baumgartner K, et al. Prevalence and prognostic effect of sarcopenia in breast cancer survivors: the HEAL Study. *J Cancer Surviv*. 2012;6(4):398.
23. Stene GB, Helbostad JL, Amundsen T, et al. Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer. *Acta Oncol*. 2015;54(3):340-348.
24. Leto G, Crescimanno M, Flandina C. On the role of cystatin C in cancer progression. *Life Sci*. 2018;202(March):152-160.
25. Chancharoenthana W, Wattanatorn S, Vadcharavivad S, et al. Agreement and Precision Analyses of Various Estimated Glomerular Filtration Rate Formulae in Cancer Patients. *Sci Rep*. 2019;9(1):1-10.
26. INCA. www.inca.gov.br/numeros-de-cancer.
27. McMahon BA, Rosner MH. GFR Measurement and Chemotherapy Dosing in Patients with Kidney Disease and Cancer. *Kidney360*. 2020;1(2):141-150.
28. Launay-Vacher V, Oudard S, Janus N, et al. Prevalence of Renal Insufficiency in cancer patients and implications for anticancer drug management: the renal insufficiency and anticancer medications (IRMA) study. *Cancer*. 2007;110(6):1376-1384.
29. Kitchlu A, Shapiro J, Amir E, et al. Representation of patients with chronic kidney disease in trials of cancer therapy. *JAMA - J Am Med Assoc*. 2018;319(23):2437-2439.
30. Wang E, Paulus JK, Hackenyos D, et al. Imprecise Kidney Function Thresholds in Cancer Clinical Trials and the Potential for Harm. *JNCI Cancer Spectr*. 2018;2(4):4-6.
31. Shepherd STC, Gillen G, Morrison P, et al. Performance of formulae based estimates of glomerular filtration rate for carboplatin dosing in stage 1 seminoma. *Eur J Cancer*. 2014;50(5):944-952.
32. Craig AJ, Samol J, Heenan SD, et al. Overestimation of carboplatin doses is avoided by radionuclide GFR measurement. *Br J Cancer*. 2012;107(8):1310.
33. Stevens LA, Levey AS. Measured GFR as a confirmatory test for estimated GFR. *J Am Soc Nephrol*. 2009;20(11):2305-2313.
34. Verhave JC, Fesler P, Ribstein J, et al. Estimation of renal function in subjects with normal serum creatinine levels: influence of age and body mass index. *Am J Kidney Dis*. 2005;46(2):233-241.

35. Jonsson A, Viklund I, Jonsson A, et al. Comparison of creatinine-based methods for estimating glomerular filtration rate in patients with heart failure. *ESC Hear Fail*. 2020;7(3):1150-1160.
36. Beben T, Rifkin DE. GFR Estimating Equations and Liver Disease. *Adv Chronic Kidney Dis*. 2015;22(5):337-342.
37. Kittiskulnam P, Tiskajornsiri K, Katavetin P, et al. The failure of glomerular filtration rate estimating equations among obese population. *PLoS One*. 2020;15(11).
38. Soares A, Eyff T, Campani R, et al. Performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study Equations in Healthy South Brazilians. *AJKD*. 2010;55(6):1162-1163.
39. Veronese FV, Gomes EC, Chanan J, et al. Performance of CKD-EPI equation to estimate glomerular filtration rate as compared to MDRD equation in South Brazilian individuals in each stage of renal function. 2014;52(12):1747-1754.
40. Miller WG, Myers GL, Ashwood ER, et al. Creatinine measurement: state of the art in accuracy and interlaboratory harmonization. *Arch Pathol Lab Med*. 2005;129(3):297-304.
41. Myers GL, Miller WG, Coresh J, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. *Clin Chem*. 2006;52(1):5-18.
42. McLean L, Whittle JR, Graham J, et al. Carboplatin dosing in the era of IDMS-creatinine; the Cockroft-Gault formula no longer provides a sufficiently accurate estimate of glomerular filtration rate for routine use in clinical care. *Gynecol Oncol*. 2020;157(3):793-798.
43. Zi M, Xu Y. Involvement of cystatin C in immunity and apoptosis. *Immunol Lett*. 2018;196:80.
44. Mussap M, Plebani M. Biochemistry and clinical role of human cystatin C. *Crit Rev Clin Lab Sci*. 2004;41(5-6):467-550.
45. Kos J, Werle B, Lah T, Brunner N. Cysteine proteinases and their inhibitors in extracellular fluids: Markers for diagnosis and prognosis in cancer. *International Journal of Biological Markers*. 2000;15:84-89.
46. Yan Y, Zhou K, Wang L, et al. Clinical significance of serum cathepsin B and cystatin C levels and their ratio in the prognosis of patients with esophageal cancer. *Onco Targets Ther*. 2017;10:1947-1954.
47. Keppler D. Towards novel anti-cancer strategies based on cystatin function. *Cancer Lett*. 2006;235(2):159-176.
48. Štabuc B, Vrhovec L, Štabuc-Šilih M, Cizej TE. Improved prediction of decreased creatinine clearance by serum cystatin C: use in cancer patients before and during chemotherapy. *Clin Chem*. 2000;46(2):193-197.
49. Bodnar L, Wcislo GB, Smoter M, et al. Cystatin C as a parameter of glomerular filtration rate in patients with ovarian cancer. *Kidney Blood Press Res*. 2010;33(5):360-367.
50. Jones M, Denieffe S, Griffin C, et al. Evaluation of cystatin C in malignancy and comparability of estimates of GFR in oncology patients. *Pract Lab Med*. 2017;8(June 2016):95-104.

51. Pricker M, Wiesli P, Brändle M, et al. Impact of thyroid dysfunction on serum cystatin C. *Kidney Int*. 2003;63(5):1944-1947.
52. Carter Y, Sippel RS, Chen H. Hypothyroidism after a cancer diagnosis: etiology, diagnosis, complications, and management. *Oncologist*. 2014;19(1):34-43.
53. Risch L, Huber AR. Glucocorticoids and increased serum cystatin C concentrations. *Clin Chim Acta*. 2002;320(1-2):133-134.
54. Bjarnadóttir M, Grubb A, Ólafsson Í. Promoter-mediated, dexamethasone-induced increase in cystatin C production by HeLa cells. *Scand J Clin Lab Invest*. 1995;55(7):617-623.
55. Stevens LA, Schmid CH, Greene T, et al. Factors other than glomerular filtration rate affect serum cystatin C levels. *Kidney Int*. 2009;75(6):652-660.
56. Galteau MM, Guyon M, Gueguen R, et al. Determination of serum cystatin C: biological variation and reference values. *Clin Chem Lab Med*. 2001;39(9):850-857.
57. White CA, Akbari A, Doucette S, et al. Effect of clinical variables and immunosuppression on serum cystatin C and beta-trace protein in kidney transplant recipients. *Am J Kidney Dis*. 2009;54(5):922-930.
58. Rokadia HK, Agarwal S. Serum cystatin C and emphysema: results from the National Health and Nutrition Examination Survey (NHANES). *Lung*. 2012;190(3):283-290.
59. Muntner P, Winston J, Uribarri J, et al. Overweight, Obesity, and Elevated Serum Cystatin C Levels in Adults in the United States. *Am J Med*. 2008;121(4):341-348.
60. Inker LA, Levey AS, Coresh J. Estimated Glomerular Filtration Rate From a Panel of Filtration Markers — Hope for Increased Accuracy Beyond Measured Glomerular Filtration Rate ? *Adv Chronic Kidney Dis*. 2017;25(1):67-75.
61. Matzke GR, Aronoff GR, Atkinson AJ, et al. Drug dosing consideration in patients with acute and chronic kidney disease-a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2011;80(11):1122-1137.
62. Inker LA, Couture SJ, Tighiouart H, et al. A New Panel-Estimated GFR, Including β2-Microglobulin and β-Trace Protein and Not Including Race, Developed in a Diverse Population. *Am J Kidney Dis*. 2021;77(5):673-683.