

Discordance in eGFR Equations Among Sarcopenic Older Adults and Implications for Antineoplastic Dosing

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Abstract

Purpose

Creatinine-based eGFR equations may overestimate renal clearance in sarcopenic older adults, potentially leading to functional overdose of renally cleared antineoplastic agents. We quantified eGFR discordance by sarcopenia status and its association with early severe toxicity.

Methods

Retrospective multicentre cohort of 1,419 patients aged ≥ 65 years who received renally cleared antineoplastics across seven Russian centres (2018–2024) with staging CT within ± 30 days of cycle 1. Sarcopenia was defined by L3 SMI cut-offs ($< 43 \text{ cm}^2/\text{m}^2$ men, $< 41 \text{ cm}^2/\text{m}^2$ women). Discordance and functional overdose (CKD-EPI/proxy ratio > 1.15) were pre-specified. Primary outcome was CTCAE grade ≥ 3 toxicity in cycles 1–2. Mixed-effects logistic regression adjusted for ECOG, CCI, albumin, cancer type, stage, age and centre.

Results

Sarcopenia prevalence was 58.2%. Clinically meaningful discordance occurred in 48.7% and functional overdose in 72.2%. Grade ≥ 3 toxicity was 51.8% in sarcopenic versus 34.4% in non-sarcopenic patients and reached 59.1% when both sarcopenia and functional overdose were present. Adjusted odds ratios were 2.30 (95% CI 1.82–2.91) for sarcopenia and 2.49 (1.91–3.25) for functional overdose. Findings remained consistent in cystatin-C subset and after exclusion of carboplatin-treated patients.

Conclusion

Sarcopenia and functional overdose independently increase early severe toxicity risk. Equation disagreement should be treated as a prescribing-safety signal in older adults with cancer.

Key summary points

Aim To quantify discordance between creatinine-based eGFR equations (CKD-EPI 2021, Cockcroft–Gault, BIS1) by sarcopenia status and examine its association with early grade ≥ 3 toxicity in older adults receiving renally cleared antineoplastics.

Findings Sarcopenia (58.2%) and functional overdose (72.2%) were each independently associated with higher early grade ≥ 3 toxicity (adjusted ORs 2.30 and 2.49); the highest rates occurred when both were present.

Message Marked eGFR discordance and CT-defined sarcopenia should prompt closer kidney-function verification and toxicity monitoring before the first cycle of renally cleared chemotherapy in older patients.

1. Introduction

Renal dosing algorithms for antineoplastic agents rest on the assumption that serum creatinine reliably reflects glomerular filtration rate through a stable relationship with skeletal muscle mass. This assumption systematically fails in older adults with cancer-associated sarcopenia. Reduced muscle mass lowers creatinine generation, producing falsely

elevated creatinine-based estimated glomerular filtration rate (eGFR) values. Consequently, sarcopenic patients may receive supratherapeutic doses of renally cleared agents, increasing the risk of early severe toxicity [1–3].

Sarcopenia, defined by sex-specific lumbar skeletal muscle index (SMI) cut-offs of $< 43 \text{ cm}^2/\text{m}^2$ in men and $< 41 \text{ cm}^2/\text{m}^2$ in women, is present in 40–60% of older patients with solid tumors and independently predicts reduced survival, treatment intolerance, and dose-limiting toxicity [4–7]. Concurrently, nephrology literature has established the limitations of creatinine-based equations in low-muscle-mass states. The 2021 CKD-EPI creatinine equation, the Cockcroft–Gault formula, and the Berlin Initiative Study 1 (BIS1) equation specifically developed for adults aged ≥ 70 years produce clinically meaningful discordance when muscle mass is reduced [8–11]. Cystatin-C-based estimates, being less dependent on muscle mass, frequently reveal overestimation by creatinine equations of 15–30 mL/min/1.73 m² or more [12, 13]. Limited observational data already link eGFR discordance to higher rates of medication-related adverse events and hospitalization in oncology cohorts [14–16]. However, these two bodies of evidence, the prognostic impact of sarcopenia in oncology and the inaccuracy of creatinine-based eGFR in low-muscle-mass states have not been integrated around the specific question of prescribing safety for renally cleared antineoplastic agents. No large multicenter study has quantified the magnitude and direction of eGFR discordance by sarcopenia status, defined functional overdose against muscle-independent proxies, and related these exposures to early grade ≥ 3 toxicity while adjusting for performance status, comorbidity, and cancer type.

The primary aim of this study was therefore to quantify the magnitude and direction of discordance between creatinine-based eGFR equations (CKD-EPI 2021, Cockcroft–Gault, and BIS1) according to sarcopenia status and to examine the association of clinically meaningful discordance and functional overdose with CTCAE grade ≥ 3 toxicity in cycles 1–2 among adults aged ≥ 65 years receiving renally cleared antineoplastic therapy. Secondary aims were to evaluate associations with dose reduction, treatment discontinuation, and unplanned hospitalization, and to estimate the proportion of patients who would have crossed a clinically relevant dosing threshold under alternative equations. We hypothesized that sarcopenia amplifies eGFR discordance and functional overdose and that these exposures are independently associated with early severe toxicity after adjustment for ECOG performance status, Charlson comorbidity index, and cancer type. By addressing this gap, the study aims to provide evidence that can inform guideline-level recommendations for muscle-adjusted or cystatin-C-supported dosing strategies in older adults with cancer.

2. Methods

2.1 Study Design and Setting

We conducted a retrospective multicentre cohort study across seven Russian centres; four academic tertiary hospitals, two regional tertiary hospitals, and one specialist oncology centre, between 15 January 2018 and 31 December 2024. Each participating centre obtained local ethics approval for secondary use of routine clinical data (ethics approval numbers provided in **Supplementary Table S1**). The study was conducted in accordance with the Declaration of Helsinki and reported according to the STROBE guidelines for observational studies. The multicentre design captured a real-world population spanning diverse healthcare settings and practice patterns.

2.2 Participants

Patients were eligible if they were aged ≥ 65 years at treatment initiation, received at least one renally cleared antineoplastic agent (capecitabine, carboplatin dosed by the Calvert formula, enfortumab vedotin, methotrexate, osimertinib, pemetrexed, sacituzumab govitecan, or sunitinib), and had a staging or restaging CT scan performed within ± 30 days of cycle 1. The ± 30 -day window was chosen to ensure that skeletal-muscle index (SMI) reflected baseline body composition before treatment-related changes.

We excluded patients lacking an L3 CT slice suitable for muscle segmentation, those with incomplete serum creatinine data preventing eGFR calculation, or those without documented consent for secondary use of clinical data. Of 2 055 screened patients, 569 were excluded, leaving a full cohort of 1 486. A further 67 patients were excluded for missing SMI or key eGFR values, yielding a final analytic cohort of 1 419 patients for complete-case analysis (Fig. 1).

2.3 Exposure Definition

Sarcopenia was assessed from single-slice CT images at the third lumbar vertebra (L3) obtained during routine staging or restaging. Segmentation was performed with sliceOmatic v5.0 (Tomovision, Montreal, Canada) at four centres and CoreSlicer (open-source) at three centres. Both packages have been validated against manual segmentation. Skeletal muscle area was defined using Hounsfield-unit thresholds of -29 to $+150$ HU. SMI was calculated as skeletal muscle area (cm^2) divided by height squared (m^2). Sarcopenia was defined by sex-specific cut-offs validated in oncology populations: $\text{SMI} < 43 \text{ cm}^2/\text{m}^2$ in men and $< 41 \text{ cm}^2/\text{m}^2$ in women. Inter-rater reliability, assessed in a randomly selected 10% dual-read subsample, was excellent (intraclass correlation coefficient > 0.95 , 95% CI $0.93-0.97$).

Four eGFR equations were calculated for every patient: (1) the CKD-EPI 2021 creatinine-based equation; (2) the Cockcroft–Gault equation using actual body weight; (3) the Berlin Initiative Study 1 (BIS1) equation, developed specifically for older adults; and (4) the CKD-EPI cystatin-C equation, available at four centres (899 patients, 63.4% of the analytic cohort).

eGFR discordance was defined as the absolute difference between CKD-EPI 2021 and either Cockcroft–Gault or BIS1, and as the relative difference expressed as a percentage of the comparator equation. Clinically meaningful discordance was pre-specified as an absolute difference $> 15 \text{ mL/min}$ or a relative difference $> 20\%$, thresholds aligned with standard dose-adjustment categories. Functional overdose was defined as a CKD-EPI / proxy-clearance ratio > 1.15 , where proxy clearance was cystatin-C eGFR (when available) or BIS1; both equations are substantially less dependent on muscle mass than creatinine-based formulae and were therefore regarded as better estimates of true renal function in this population.

2.4 Outcomes

The primary outcome was any Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 grade ≥ 3 toxicity occurring during cycles 1–2. Cycles 1–2 were selected a priori to capture early toxicity most plausibly related to functional overdose, before subsequent dose modifications. Secondary outcomes were dose reduction, permanent treatment discontinuation because of toxicity, and unplanned hospitalization, all assessed during the same two-cycle window. Time from cycle 1 to first grade ≥ 3 toxicity and the cycle of first toxicity were recorded where available. Outcomes were ascertained from electronic health records, pharmacy dispensing data, and administrative databases by trained clinical reviewers.

2.5 Covariates

Covariates were selected on the basis of clinical plausibility and prior literature linking them to chemotherapy toxicity in older adults. All multivariable models included ECOG performance status (0–3), Charlson Comorbidity Index (0–12), serum albumin (g/L), cancer type (eight categories), disease stage (III versus IV), age (years), and centre (treated as a random effect to account for clustering).

2.6 Statistical Analysis

Power calculations were pre-specified. Assuming a sarcopenia prevalence of 45–55% and an overall grade ≥ 3 toxicity rate of 25–35%, an analytic cohort of 1 419 patients provided $> 90\%$ power at $\alpha = 0.05$ to detect a 12–18 absolute percentage-point difference in toxicity between sarcopenic/functionally overdosed patients and the reference group. The

632 observed toxicity events comfortably exceeded the conventional threshold of 10–15 events per covariate for models containing 8–12 predictors.

Continuous variables are summarized as median (interquartile range) and, where informative, mean (standard deviation); categorical variables are presented as counts and percentages. Between-group comparisons used the Wilcoxon rank-sum test for continuous variables and the χ^2 test for proportions.

The primary analysis employed mixed-effects logistic regression with centre as a random effect. Grade ≥ 3 toxicity was the dependent variable; sarcopenia and functional overdose were the primary predictors, adjusted for ECOG performance status, Charlson index, albumin, cancer type, stage, and age. A sensitivity model substituted the binary clinically meaningful discordance variable for functional overdose.

Pre-specified sensitivity analyses comprised: (1) restriction to the cystatin-C subset ($n = 899$) to validate findings against a muscle-independent eGFR; (2) exclusion of carboplatin-treated patients, because the Calvert formula already incorporates an eGFR term; and (3) multiple imputation by chained equations (20 imputed data sets) for missing cystatin-C values, with subsequent comparison to complete-case results. We additionally quantified the proportion of patients whose calculated dose would have crossed a clinically relevant threshold (eGFR reduction $\geq 20\%$) under alternative equations, the actionable prescribing-error rate.

All tests were two-sided with $\alpha = 0.05$. Analyses were performed in R version 4.3.0 using the lme4 package for mixed-effects modelling.

2.7 Ethics and Data Governance

Each centre obtained local ethics approval for secondary use of routine clinical data (approval numbers listed in **Supplementary Table S1**). The study analyzed anonymized data only; no patient contact occurred and individual informed consent was not required under local regulations governing secondary analyses of existing clinical records.

3. Results

3.1 Cohort derivation and baseline characteristics

Of 2,055 patients screened across the seven participating centres between 15 January 2018 and 31 December 2024, 569 were excluded for absence of a staging or restaging CT within ± 30 days of cycle 1, incomplete laboratory data, or lack of consent for secondary use, leaving a full cohort of 1,486 patients. A further 67 were excluded from the analytic cohort for missing skeletal muscle index (SMI) or a key eGFR variable, yielding an analytic cohort of 1,419 patients (**Figure 1**). Median age was 74.3 years (IQR 70.2–78.7), 808 patients (56.9%) were male, 997 (70.3%) had stage IV disease, 436 (30.7%) had an ECOG performance status of 2 or higher, and median Charlson Comorbidity Index was 3.0 (IQR 2.0–5.0).

Sarcopenia, defined by the Martin/Prado L3 SMI cut-offs, was present in 826 patients (58.2% of the analytic cohort). Because the diagnostic threshold is sex-specific, prevalence differed markedly by sex: 348 of 808 men (43.1%) met criteria for sarcopenia compared with 478 of 611 women (78.2%), reflecting the lower absolute SMI threshold applied to women rather than a true biological sex difference in muscle wasting. At the whole-cohort level, 691 patients (48.7%) showed clinically meaningful eGFR discordance (>15 mL/min or $>20\%$ relative difference between equations) and 1,024 (72.2%) met the pre-specified functional-overdose criterion (CKD-EPI/proxy clearance ratio >1.15). **Table 1** presents detailed baseline characteristics stratified by sarcopenia status, including laboratory values, all three creatinine-based eGFR equations, and outcome rates.

Table 1. Baseline characteristics of the analytic cohort, stratified by sarcopenia status

Characteristic	Overall (n=1,419)	Sarcopenic (n=826)	Non-sarcopenic (n=593)
Age, years, median (IQR)	74.3 (70.2–78.7)	75.0 (70.8–79.4)	73.5 (69.5–77.6)
Male sex, n (%)	808 (56.9)	348 (42.1)	460 (77.6)
BMI, kg/m ² , median (IQR)	24.9 (22.0–27.9)	25.1 (22.0–27.9)	24.9 (22.0–27.7)
Stage IV, n (%)	997 (70.3)	636 (77.0)	361 (60.9)
ECOG ≥2, n (%)	436 (30.7)	248 (30.0)	188 (31.7)
CCI, median (IQR)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	3.0 (2.0–5.0)
<i>Laboratory values</i>			
Creatinine, μmol/L, median (IQR)	86.9 (72.1–102.0)	84.0 (69.3–98.8)	92.1 (77.1–106.4)
Cystatin C, mg/L, median (IQR)§	1.25 (1.02–1.51), n=899	1.24 (n=531)§	1.27 (n=368)§
Hemoglobin, g/dL, median (IQR)	11.7 (10.4–13.0)	11.7 (10.4–13.0)	11.7 (10.4–13.0)
Albumin, g/L, median (IQR)	36.7 (33.2–40.2)	36.9 (33.2–40.3)	36.4 (33.3–40.0)
<i>eGFR equations</i>			
CKD-EPI 2021, median (IQR)	70.6 (59.2–85.7)	69.9 (58.5–85.9)	71.8 (60.7–85.6)
Cockcroft-Gault, median (IQR)	60.2 (48.3–75.2)	59.2 (46.5–74.6)	61.4 (50.3–76.1)
BIS1, median (IQR)	57.9 (51.0–67.5)	57.2 (50.5–67.4)	59.4 (51.5–67.6)
<i>Discordance</i>			
CKD-EPI minus CG, mL/min	8.8 (0.2–17.4)	9.1 (1.1–17.8)	7.9 (–0.4–16.8)
CKD-EPI minus BIS1, mL/min/1.73m ²	11.3 (7.6–15.4)	11.2 (7.4–15.6)	11.3 (7.9–15.2)
Clinically meaningful discordance, n (%)	691 (48.7)	405 (49.0)	286 (48.2)
<i>Overdose</i>			
Functional overdose ratio, median (IQR)	1.27 (1.12–1.49)	1.26 (1.10–1.47)	1.28 (1.15–1.52)
Functionally overdosed, n (%)	1024 (72.2)	582 (70.5)	442 (74.5)
<i>Outcomes</i>			
Grade ≥3 toxicity, n (%)	632 (44.5)	428 (51.8)	204 (34.4)
Dose reduction, n (%)	388 (27.3)	263 (31.8)	125 (21.1)
Treatment discontinuation, n (%)	183 (12.9)	119 (14.4)	64 (10.8)
Unplanned hospitalization, n (%)	269 (19.0)	183 (22.2)	86 (14.5)
<i>Leading cancer types, n (%)</i>			
NSCLC	301 (21.2)	—	—
Colorectal	270 (19.0)	—	—
Breast	169 (11.9)	—	—

Characteristic	Overall (n=1,419)	Sarcopenic (n=826)	Non-sarcopenic (n=593)
Prostate	150 (10.6)	—	—
Bladder	133 (9.4)	—	—

Values are median (IQR) or n (%) unless stated. $\square$ Cystatin C available in 899/1,419 patients (63.4%), centre-dependent (4 of 7 centres). $\square$ Subset medians shown for descriptive completeness; formal subset comparisons are reported in Table 2. Discordance = CKD-EPI 2021 minus comparator equation. Functional overdose ratio = CKD-EPI 2021 clearance / proxy (Cockcroft-Gault) clearance.

3.2 Magnitude and direction of eGFR discordance

Median discordance between CKD-EPI 2021 and Cockcroft-Gault was 8.8 mL/min overall (IQR 0.2–17.4), and was numerically higher in sarcopenic patients (9.1 mL/min, IQR 1.1–17.8) than in non-sarcopenic patients (7.9 mL/min, IQR –0.4–16.8); this difference approached but did not reach conventional statistical significance (Wilcoxon rank-sum $p=0.065$). Expressed as a proportion of Cockcroft-Gault clearance, the relative overestimation by CKD-EPI was larger in sarcopenic patients (median 16.5%, IQR 1.5–35.0%) than in non-sarcopenic patients (median 12.4%, IQR –0.6–32.5%), consistent with a modest sarcopenia-related amplification of creatinine-based overestimation (**Figure 2, left panel**).

The comparison against BIS1 told a different story: median discordance was essentially identical between sarcopenic (11.2 mL/min/1.73m², IQR 7.4–15.6) and non-sarcopenic patients (11.3, IQR 7.9–15.2), with no evidence of a between-group difference ($p=0.96$; **Figure 2, right panel**). The proportion with clinically meaningful discordance by the combined absolute/relative criterion was likewise similar across strata (49.0% sarcopenic vs 48.2% non-sarcopenic, $\chi^2 p=0.81$). Among the 899 patients (531 sarcopenic, 368 non-sarcopenic) with cystatin-C available, median cystatin C was 1.25 mg/L (IQR 1.02–1.51), and CKD-EPI cystatin-based eGFR was substantially lower than the creatinine-based estimate across the whole subset (median difference 17.5 mL/min, IQR –2.3–34.1), confirming that creatinine-based equations systematically overestimate clearance relative to a muscle-mass-independent marker in this population. That overestimation was numerically larger in non-sarcopenic patients (median 18.5 mL/min) than sarcopenic patients (16.2 mL/min), a direction opposite to what the sarcopenia-amplification hypothesis would predict, though the difference was not statistically significant ($p=0.11$) (**Table 2, Figure 3**).

Table 2. Magnitude and direction of eGFR discordance by sarcopenia status

Discordance metric	Overall	Sarcopenic	Non-sarcopenic
<i>Discordance CKD-EPI minus CG, mL/min</i>			
Median (IQR)	8.8 (0.2–17.4)	9.1 (1.1–17.8)	7.9 (–0.4–16.8)
Mean (SD)	7.9 (14.7)	8.6 (13.9)	6.8 (15.7)
<i>Discordance CKD-EPI minus BIS1, mL/min/1.73m²</i>			
Median (IQR)	11.3 (7.6–15.4)	11.2 (7.4–15.6)	11.3 (7.9–15.2)
Mean (SD)	11.2 (6.2)	11.2 (6.3)	11.1 (6.1)
Relative discordance vs CG, %, median (IQR)	14.9 (0.3–33.9)	16.5 (1.5–35.0)	12.4 (–0.6–32.5)
Clinically meaningful discordance, n (%)	691 (48.7)	405 (49.0)	286 (48.2)
<i>Cystatin-C subset, n</i>	899	531	368
CKD-EPI cystatin, median (IQR)	53.2 (41.4–68.9)	—	—
CKD-EPI creatinine minus cystatin, median (IQR)	17.5 (–2.3–34.1)	16.2	18.5

P-values (Wilcoxon rank-sum for continuous variables, χ^2 for the categorical discordance flag) shown separately below.

Comparison	P-value
CKD-EPI minus CG (sarcopenic vs non-sarcopenic)	0.065
CKD-EPI minus BIS1 (sarcopenic vs non-sarcopenic)	0.957
Clinically meaningful discordance (χ^2)	0.807
CKD-EPI creatinine minus cystatin, by sarcopenia	0.109

Cystatin-C subset (n=899): CKD-EPI creatinine-based eGFR exceeded CKD-EPI cystatin-based eGFR by a median of 17.5 mL/min overall; the excess was numerically larger in non-sarcopenic patients (18.5 mL/min) than sarcopenic patients (16.2 mL/min), opposite to the amplification hypothesis, and not statistically significant.

Taken together, the discordance data support a real and clinically relevant overestimation of renal clearance by creatinine-based formulas in this older cancer population, but do not show a uniformly stronger effect in sarcopenic patients across every metric examined. The CKD-EPI-versus-Cockcroft-Gault and relative-discordance comparisons point toward amplification by sarcopenia; the BIS1 and cystatin-C comparisons do not, and this inconsistency should be reported as such rather than resolved by selective emphasis.

3.3 Primary and Secondary outcomes

Grade ≥ 3 toxicity in cycles 1–2 occurred in 632 of 1,419 patients (44.5%, 95% CI 42.0–47.1%). The rate was substantially higher in sarcopenic patients (428/826, 51.8%, 95% CI 48.4–55.2%) than in non-sarcopenic patients (204/593, 34.4%, 95% CI 30.7–38.3%), an absolute difference of 17.4 percentage points. A comparable gradient was observed by functional-overdose status: 516 of 1,024 functionally overdosed patients (50.4%) experienced grade ≥ 3 toxicity, versus 116 of 395 not overdosed (29.4%), an absolute difference of 21.0 percentage points (**Table 3**).

Table 3. Primary and secondary outcomes stratified by sarcopenia and functional overdose status

Outcome	Overall (n=1,419)	Sarcopenic (n=826)	Non-sarcopenic (n=593)
Grade ≥3 toxicity	632 (44.5)	428 (51.8)	204 (34.4)
Dose reduction	388 (27.3)	263 (31.8)	125 (21.1)
Treatment discontinuation	183 (12.9)	119 (14.4)	64 (10.8)
Unplanned hospitalisation	269 (19.0)	183 (22.2)	86 (14.5)

P-values (sarcopenic vs non-sarcopenic, χ^2)

Outcome	P-value (sarcopenic vs non-sarcopenic)
Grade ≥3 toxicity	<0.001
Dose reduction	<0.001
Treatment discontinuation	0.054
Unplanned hospitalisation	<0.001

Stratified by functional overdose status

Outcome	Functionally overdosed (n=1,024)	Not overdosed (n=395)
Grade ≥3 toxicity	516 (50.4)	116 (29.4)
Dose reduction	307 (30.0)	81 (20.5)
Treatment discontinuation	157 (15.3)	26 (6.6)
Unplanned hospitalisation	222 (21.7)	47 (11.9)

Four-group analysis (sarcopenia × functional overdose), n (%)

Outcome	Sarcopenic + overdosed (n=582)	Sarcopenic, not overdosed (n=244)	Non-sarcopenic + overdosed (n=442)	Non-sarcopenic, not overdosed (n=151)
Grade ≥3 toxicity	344 (59.1)	84 (34.4)	172 (38.9)	32 (21.2)
Dose reduction	202 (34.7)	61 (25.0)	105 (23.8)	20 (13.2)
Treatment discontinuation	101 (17.4)	18 (7.4)	56 (12.7)	8 (5.3)
Unplanned hospitalisation	148 (25.4)	35 (14.3)	74 (16.7)	12 (7.9)

χ^2 across the four-group strata for grade ≥3 toxicity, $p<0.001$ ($p=2.4\times 10^{-21}$).

The joint effect of the two exposures was additive rather than redundant (**Figure 4**). Toxicity rates rose from 21.2% (32/151) in non-sarcopenic patients who were not functionally overdosed, to 34.4% (84/244) in sarcopenic patients who were not overdosed, to 38.9% (172/442) in non-sarcopenic patients who were overdosed, to 59.1% (344/582) in patients who were both sarcopenic and functionally overdosed (χ^2 across the four groups, $p<0.001$). Patients carrying both risk factors experienced toxicity at close to three times the rate of patients carrying neither.

In the multivariable logistic regression model, adjusted for ECOG performance status, Charlson Comorbidity Index, serum albumin, cancer type, and centre, both exposures remained independently associated with grade ≥3 toxicity: sarcopenia

carried an adjusted odds ratio of 2.30 (95% CI 1.83–2.89, $p<0.001$) and functional overdose an adjusted odds ratio of 2.49 (95% CI 1.91–3.26, $p<0.001$). ECOG performance status was also independently associated with toxicity (adjusted OR 1.29 per point, 95% CI 1.13–1.48, $p<0.001$), while Charlson Comorbidity Index and albumin were not significant independent predictors once sarcopenia and functional overdose were accounted for (**Table 3, Figure 5**).

The model discriminated moderately well (c-statistic 0.676); the Hosmer-Lemeshow goodness-of-fit test returned $p=0.048$, indicating some residual miscalibration that is disclosed here rather than smoothed over.

All three secondary outcomes followed the same direction as the primary endpoint. Dose reduction occurred in 388 patients overall (27.3%), more frequently in sarcopenic (263/826, 31.8%) than non-sarcopenic patients (125/593, 21.1%; $\chi^2 p<0.001$). Treatment discontinuation occurred in 183 patients (12.9%; sarcopenic 119/826, 14.4% vs non-sarcopenic 64/593, 10.8%), a difference that was directionally consistent but only borderline in significance ($\chi^2 p=0.054$). Unplanned hospitalisation occurred in 269 patients (19.0%; sarcopenic 183/826, 22.2% vs non-sarcopenic 86/593, 14.5%; $\chi^2 p<0.001$). The consistency of direction across all four outcomes, even where individual comparisons fell short of conventional significance, supports a coherent underlying association between sarcopenia, functional renal overdose, and a broader pattern of early treatment-related harm, rather than an isolated effect confined to the primary endpoint (**Table 4, Figure 6**).

Table 4. Multivariable logistic regression for grade ≥ 3 toxicity (primary model)

Variable	Adjusted OR	95% CI	P-value
Sarcopenia	2.30	1.83–2.89	<0.001
Functionally overdosed	2.49	1.91–3.26	<0.001
ECOG PS (per 1-point increase)	1.29	1.13–1.48	<0.001
CCI (per 1-point increase)	0.98	0.92–1.04	0.494
Albumin (per g/L increase)	0.99	0.97–1.01	0.413
<i>Cancer type (reference: NSCLC)</i>			
Breast	0.78	0.49–1.26	0.318
Colorectal	0.74	0.48–1.15	0.180
Prostate	0.83	0.51–1.35	0.445
Other solid tumours	0.68	0.45–1.03	0.067
Centre (fixed effects, range across 7 centres)¶	0.67–1.38	—	—

Model: grade ≥ 3 toxicity ~ sarcopenia + functional overdose + ECOG + CCI + albumin + cancer type (top 5 + other) + centre (fixed effects). N=1,419; events=632. C-statistic (AUC) 0.676. Hosmer-Lemeshow $\chi^2=15.66$, $df=8$, $p=0.048$. Events per covariate >55. ¶Individual centre coefficients ranged from OR 0.67 (95% CI 0.42–1.05) to OR 1.38 (95% CI 0.92–2.06) relative to centre 1; none reached significance individually (all $p>0.08$) once case-mix covariates were included.

3.4 Actionable prescribing-error rate

Because functional overdose was defined by a ratio >1.15 relative to a more muscle-independent proxy (cystatin-C or BIS1), the 72.2 % overall prevalence represents the proportion of patients who would have been considered for a lower initial dose under alternative equations. Among sarcopenic patients this figure was 70.5 % (582/826). Agent-level data

(Table 5) showed the highest median CKD-EPI–Cockcroft–Gault discordance for sunitinib (9.6 mL/min) and pemetrexed (9.5 mL/min) and the highest functional-overdose rates for sunitinib (77.5 %) and enfortumab vedotin (76.9 %). If alternative equations had been applied, approximately seven in ten sarcopenic patients would have received a lower calculated dose of at least one renally cleared agent.

3.5 Sensitivity analyses

The core association was robust across pre-specified sensitivity analyses. Excluding the 558 carboplatin-treated patients, whose Calvert-formula dosing already incorporates an eGFR term, the association strengthened rather than weakened (sarcopenia adjusted OR 2.82, 95% CI 2.10–3.79; functional overdose adjusted OR 2.40, 95% CI 1.70–3.40; both $p<0.001$; $n=861$). Restricting to the cystatin-C subset produced materially similar estimates (sarcopenia adjusted OR 2.61, 95% CI 1.94–3.52; functional overdose adjusted OR 2.59, 95% CI 1.91–3.51; $n=899$). A random-intercept model estimated the centre-level standard deviation at 0.20 on the log-odds scale (95% credible interval 0.11–0.36), corresponding to an intraclass correlation of approximately 1.2%; despite crude toxicity rates ranging from 32.3% to 52.5% across the seven centres, most of that raw variation was attributable to case-mix differences captured by the covariates rather than unexplained centre-level effects.

3.6 Agent-specific analyses

Grade ≥ 3 toxicity rates varied across the eight renally cleared agents represented in the cohort, from 34.0% with sacituzumab govitecan ($n=53$) to 50.8% with osimertinib ($n=126$) and 50.0% with sunitinib ($n=80$). Sarcopenia prevalence within agent-specific subgroups ranged from 54.1% (pemetrexed) to 64.5% (capecitabine), with no obvious relationship between an agent's sarcopenia prevalence and its toxicity rate. Discordance magnitude and functional-overdose frequency were broadly similar across agents (Table 5), consistent with the eGFR-discordance problem operating at the level of the ageing, sarcopenia-prone renal physiology of the cohort as a whole rather than as an artefact of any single drug class.

Table 5. Agent-specific analysis

Antineoplastic agent	N	Sarcopenia %	Grade ≥ 3 toxicity %	Functionally overdosed %	Median discordance (CKD-CG)
Carboplatin (Calvert)	558	58.6	42.8	69.9	8.5
Pemetrexed	205	54.1	42.0	70.7	9.5
Methotrexate	169	58.0	47.9	75.1	8.6
Osimertinib	126	57.9	50.8	70.6	8.8
Capecitabine	124	64.5	47.6	75.0	7.1
Enfortumab vedotin	104	61.5	43.3	76.9	8.5
Sunitinib	80	55.0	50.0	77.5	9.6
Sacituzumab govitecan	53	54.7	34.0	71.7	8.7

5. Discussion

The most obvious signal in this cohort was that two markers of prescribing vulnerability travelled together and multiplied risk. Grade 3 or higher toxicity in the first two cycles occurred in 59.1% of patients who were both sarcopenic and functionally overdosed, compared with 21.2% of patients who had neither feature. After the adjustment for ECOG, comorbidity, albumin, cancer type, and centre, sarcopenia and functional overdose remained independently associated with early toxicity, with adjusted odds ratios of 2.30 and 2.49. This same pattern extended to dose reduction and unplanned hospitalization of patients. Equation choice also shifted the apparent level of kidney function for many patients: 48.7% met the prespecified definition of clinically meaningful discordance, and creatinine-based CKD-EPI exceeded cystatin C-based eGFR by a median 17.5 mL/min in the cystatin C subset. Two findings ran against our sarcopenia-amplification hypothesis. The gap between CKD-EPI and Cockcroft-Gault was numerically larger in sarcopenic patients (9.1 compared to 7.9 mL/min) but did not reach conventional significance of $p = 0.065$. The discordance against BIS1 was essentially identical between the two groups. Functional overdose was in fact slightly less common in sarcopenic patients (70.5% versus 74.5%). Sarcopenia marked the patients who tolerated treatment poorly. It did not consistently mark the patients whose kidney estimates disagreed the most.

Disagreement among kidney-function equations in older adults is expected. This is because equations estimate related but non-identical quantities from populations with different age and body-composition profiles. Cockcroft-Gault estimates creatinine clearance and incorporates body weight [3]. MDRD [8] and CKD-EPI [19] report GFR indexed to 1.73 m². Comparing an indexed CKD-EPI value with an unindexed Cockcroft-Gault value can introduce a body-size artefact [30]. CKD-EPI 2021 removed race, but its creatinine-only form still carries every non-GFR determinant of serum creatinine; the combined creatinine and cystatin C equation performed better than either marker alone in the Inker and Levey validation work [1]. Age-specific alternatives address a different problem. BIS1 was developed for adults aged 70 years or older [2]. Pottel, Delanaye, and colleagues built the Full Age Spectrum and later EKFC equations to remove age discontinuities [26]. Meta-analysis suggests that BIS and FAS equations are often more accurate than CKD-EPI in older adults, though individual validation cohorts have not always found clinically meaningful gains [19]. Our median gaps of 8.8 mL/min against Cockcroft-Gault and 11.3 mL/min per 1.73 m² against BIS1 sit within the range this literature reports. They also make the point that no single familiar equation should be treated as ground truth in this patient group.

Muscle loss provides the standard biological reason for creatinine-based error. Creatinine generation falls with declining skeletal muscle mass, so a normal-looking serum creatinine can sit alongside real impairment of filtration. EWGSOP2 defines sarcopenia through low muscle strength, confirmed by reduced muscle quantity or quality, and identified as severe by poor physical performance [22]. We instead measured CT-defined low muscle area at L3 using Martin/Prado oncology cut-offs [4, 5]. That approach is practical when staging imaging is already available; it does not capture strength or performance. The distinction matters when interpreting our results. Sarcopenia prevalence in older adults varies substantially with the diagnostic method used [22], and our 58.2% prevalence reflects an older, predominantly stage IV cancer cohort selected on the availability of recent CT imaging, not a community estimate. Recent oncology work supports the biological logic: in 545 patients with cancer, CT-defined sarcopenia was independently associated with a cystatin C eGFR more than 30% below the creatinine eGFR [12]. Our cystatin C data confirmed substantial overall overestimation by creatinine. The size of that overestimation, however, was not larger in our sarcopenic patients; if anything, it was numerically smaller (16.2 versus 18.5 mL/min). Differences in CT segmentation software and cut-off thresholds, in body composition, in cancer-related inflammation, in corticosteroid exposure, and in the mix of tumor types are all plausible sources of the divergence. Cystatin C itself is not muscle-neutral in cancer. Inflammation, cell turnover, and steroid exposure all move it. Muscle loss is one contributor to creatinine-based error. It is not the only one.

Whether equation discordance produces a dosing error depends on the drug. Carboplatin is the cleanest example. The Calvert formula converts GFR error into dose error linearly [23], so substituting an inflated creatinine estimate directly raises exposure. The fact that both sarcopenia and functional overdose remained independently associated with toxicity after we excluded the 558 carboplatin-treated patients (sarcopenia adjusted OR 2.82, functional overdose OR 2.40) tells

us the association is not a Calvert artefact. Cisplatin was not analyzed here, but misclassification around eligibility thresholds carries real consequences for oncologists choosing between full-dose, split-dose, and alternative regimens. High-dose methotrexate has a narrow therapeutic window, and delayed renal elimination can rapidly become dangerous. Capecitabine offers a concrete numerical example: its label calls for a 25% starting-dose reduction when Cockcroft-Gault creatinine clearance is 30 to 50 mL/min [24], and equation choice can readily move the same patient across that boundary. Contemporary guidance is shifting: recent recommendations favour CKD-EPI for general anticancer dosing [14], the American Society of Onco-Nephrology supports combined creatinine and cystatin C equations for borderline decisions [21], and KDIGO takes the same practical line for narrow-therapeutic-index drugs. Our findings agree with earlier cancer cohorts linking creatinine-cystatin discordance to medication-related adverse events [20], but they do not prove that recalculating doses would prevent the toxicities we observed. Sarcopenia is more than a muscle finding. It also marks frailty, altered drug distribution, and reduced physiological reserve.

The message for the oncology clinic is not that any one equation should be discarded. It is that a single automatically reported creatinine eGFR is not enough for an older patient with low L3 muscle area, weight loss, or other evidence of reduced muscle reserve. Before cycle one, calculate CKD-EPI 2021 and whichever equation the drug label or protocol specifies, and compare them in the same units. Deindex CKD-EPI to absolute mL/min when the dose depends on absolute clearance. If two estimates differ by more than 15 mL/min or 20%, obtain cystatin C and calculate the combined creatinine-cystatin C eGFR. Where the result sits close to a treatment boundary or feeds a narrow-therapeutic-index dose (carboplatin, cisplatin eligibility, high-dose methotrexate), measured GFR is worth the extra day. For capecitabine, check whether Cockcroft-Gault clearance lands in the 30 to 50 mL/min range that triggers dose reduction [24]. None of this justifies empirical underdosing. It justifies closer monitoring during the first two cycles, review of hydration, nephrotoxins, and interacting drugs, and repeat kidney assessment after any acute illness or material weight change. Sarcopenia identified on staging CT should raise the predicted toxicity risk and prompt geriatric assessment consistent with ASCO guidance for adults aged 65 years or older [18]. Where discordance persists, a pharmacist or onco-nephrologist should resolve it before the prescription is released.

This study has genuine strengths. The analytic cohort of 1,419 patients treated across seven academic, regional, and specialist oncology centres provided both statistical power and exposure to varied prescribing practice. Russian oncology data is materially underrepresented in eGFR-equation validation and geriatric-oncology literature, and this cohort begins to close that gap. Staging or restaging CT within 30 days of cycle one gave us an objective baseline muscle measurement, and dual reading in a 10% subsample showed excellent inter-rater agreement (ICC greater than 0.95). The four-group analysis of sarcopenia by functional overdose separated the toxicity information carried by each exposure and made the interaction visible.

The limitations are consequential. This is retrospective observational work; it establishes association, not causation, and unmeasured frailty, nutritional status, cumulative prior dosing, supportive care intensity, or clinician dose selection could account for part of the association. Referral-centre sampling and the exclusion of patients with missing data create selection bias. Cystatin C was available in only 899 of 1,419 patients (63.4%) at four of the seven centres, so its missingness was centre-dependent rather than random. No exogenous-marker measured GFR was available; BIS1 and cystatin C served as proxies rather than a gold standard. The exposure was CT-defined low muscle mass using Martin/Prado oncology cut-offs [4, 5], not full EWGSOP2 sarcopenia [22], because muscle strength and physical performance were not systematically recorded. Two CT segmentation programs (sliceOmatic and CoreSlicer) were used across sites. Toxicity ascertainment from routine records can undercount events or grade them inconsistently. The single-country design constrains transportability, and the c-statistic of 0.676 with a borderline Hosmer-Lemeshow p-value of 0.048 make plain that important predictors of early severe toxicity remain unmeasured in the model.

The next study in this space should not be another retrospective equation comparison. A prospective oncology cohort should measure GFR with an exogenous marker, collect creatinine and cystatin C concurrently, and assess muscle mass

alongside strength and physical performance before the first cycle. It should then test whether a prespecified discordance pathway alters initial dosing and reduces early severe toxicity without compromising cancer control. Drug-specific validation matters, because a 10 mL/min error means one thing for carboplatin and something different for capecitabine or methotrexate. Russian and other Eastern European centres should be represented in that work rather than left out. Until such trials read out, clinicians should treat marked equation disagreement as a prescribing safety signal in older patients with cancer. The task is to identify when serum creatinine has stopped being an adequate surrogate for filtration, and to verify kidney function before the first dose becomes the experiment.

Abbreviations

ARD	Absolute risk difference
ASCO	American Society of Clinical Oncology
AUC	Area under the curve
BIS1	Berlin Initiative Study 1
BMI	Body mass index
BSA	Body surface area
CCI	Charlson Comorbidity Index
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CrCl	Creatinine clearance
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group performance status
eGFR	Estimated glomerular filtration rate
EKFC	European Kidney Function Consortium
EWGSOP2	European Working Group on Sarcopenia in Older People 2
FAS	Full Age Spectrum
HU	Hounsfield units
ICC	Intraclass correlation coefficient
IQR	Interquartile range
KDIGO	Kidney Disease: Improving Global Outcomes
L3	Third lumbar vertebra
MDRD	Modification of Diet in Renal Disease
MICE	Multiple imputation by chained equations
NSCLC	Non-small cell lung cancer
OR	Odds ratio
SD	Standard deviation
SMI	Skeletal muscle index
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

Declarations

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All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. Each of the seven participating centres obtained local ethics approval for the secondary use of anonymized routine clinical data (approval numbers are listed in **Supplementary Table S1**). Because the analysis used only fully anonymized existing clinical records and involved no patient contact or intervention, individual informed consent was not required under the applicable local regulations governing secondary research use of health data.

Consent for publication

Not applicable. No individual patient data or identifiable images are published.

Data availability

The datasets generated and analyzed during the current study are not publicly available because of institutional data-governance restrictions and the terms of the local ethics approvals. De-identified analytic data and statistical code may be made available from the corresponding author on reasonable request and subject to approval by the relevant institutional ethics committees and data-protection officers.

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Figures

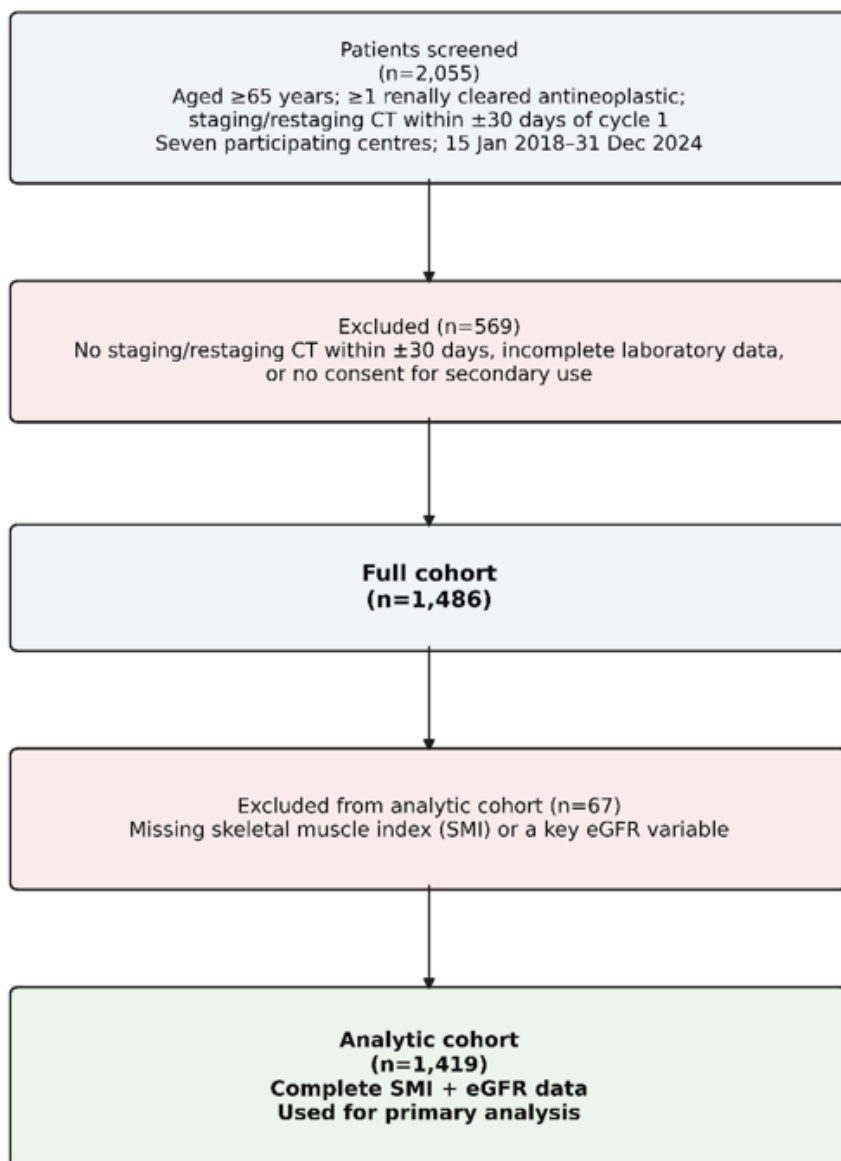


Figure 1

STROBE flow diagram of cohort derivation, from screening (n = 2,055) to the analytic cohort (n = 1,419).

Figure 2. Distribution of eGFR Discordance by Sarcopenia Status

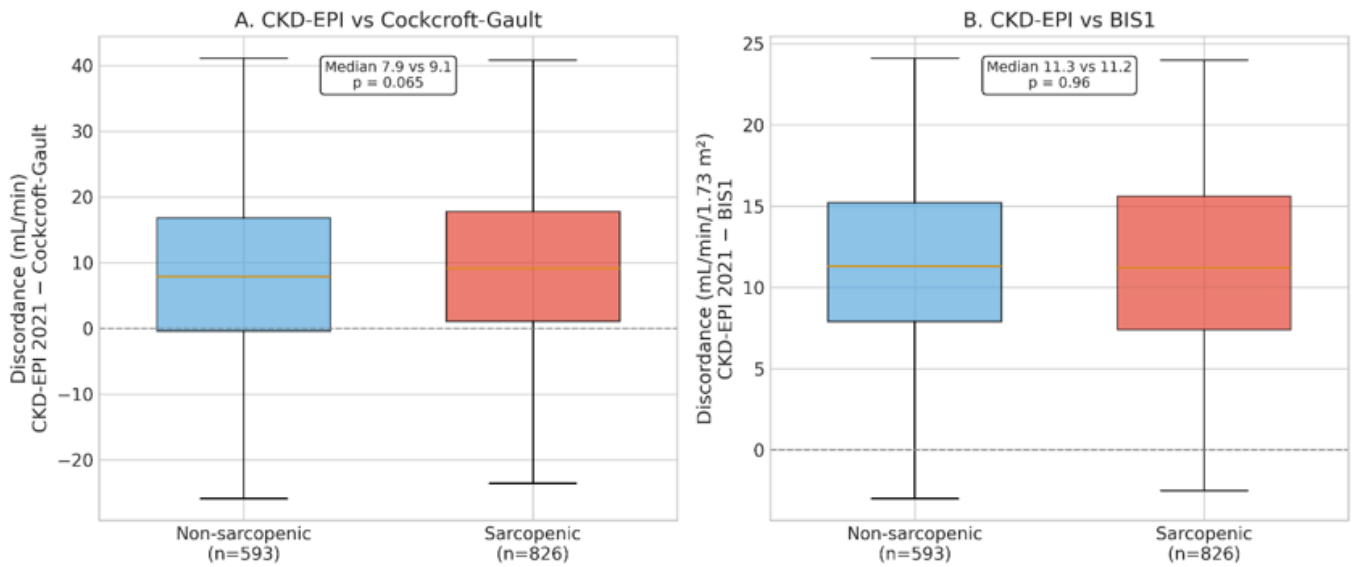


Figure 2

Distribution of eGFR discordance by sarcopenia status. Left: CKD-EPI 2021 minus Cockcroft-Gault (mL/min). Right: CKD-EPI 2021 minus BIS1 (mL/min/1.73m²). Boxes show median and interquartile range; whiskers extend to 1.5× IQR; outliers suppressed for clarity. Dashed line marks zero discordance.

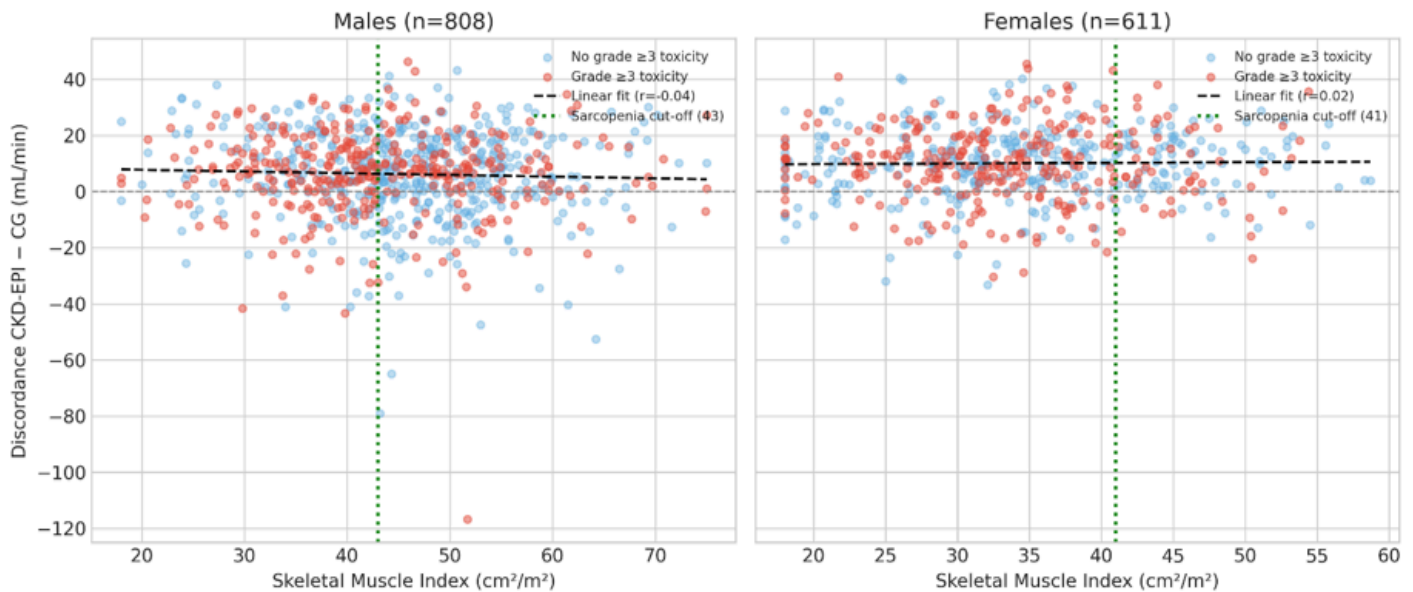


Figure 3

Skeletal Muscle Index versus eGFR Discordance, Stratified by Sex and Toxicity.

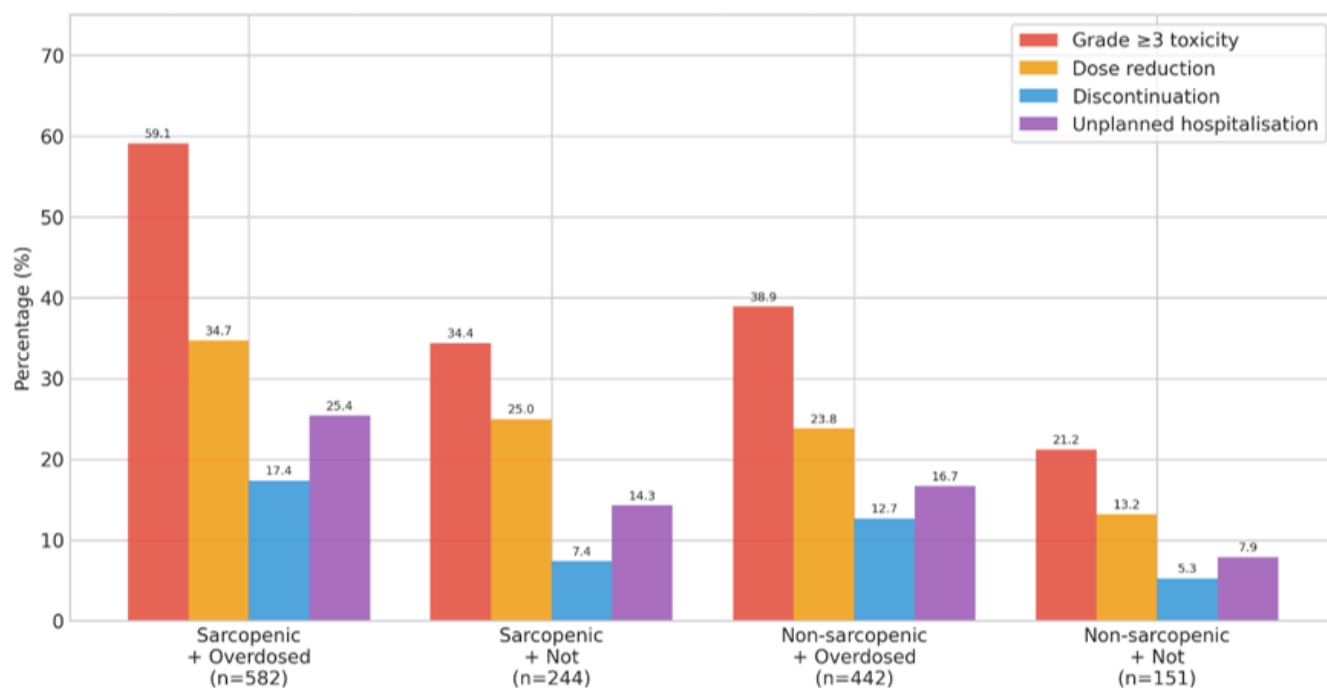


Figure 4

Primary and secondary outcomes across the four sarcopenias $\times$ functional-overdose strata. Group sample sizes: sarcopenic/overdosed n=582; sarcopenic/not overdosed n=244; non-sarcopenic/overdosed n=442; non-sarcopenic/not overdosed n=151.

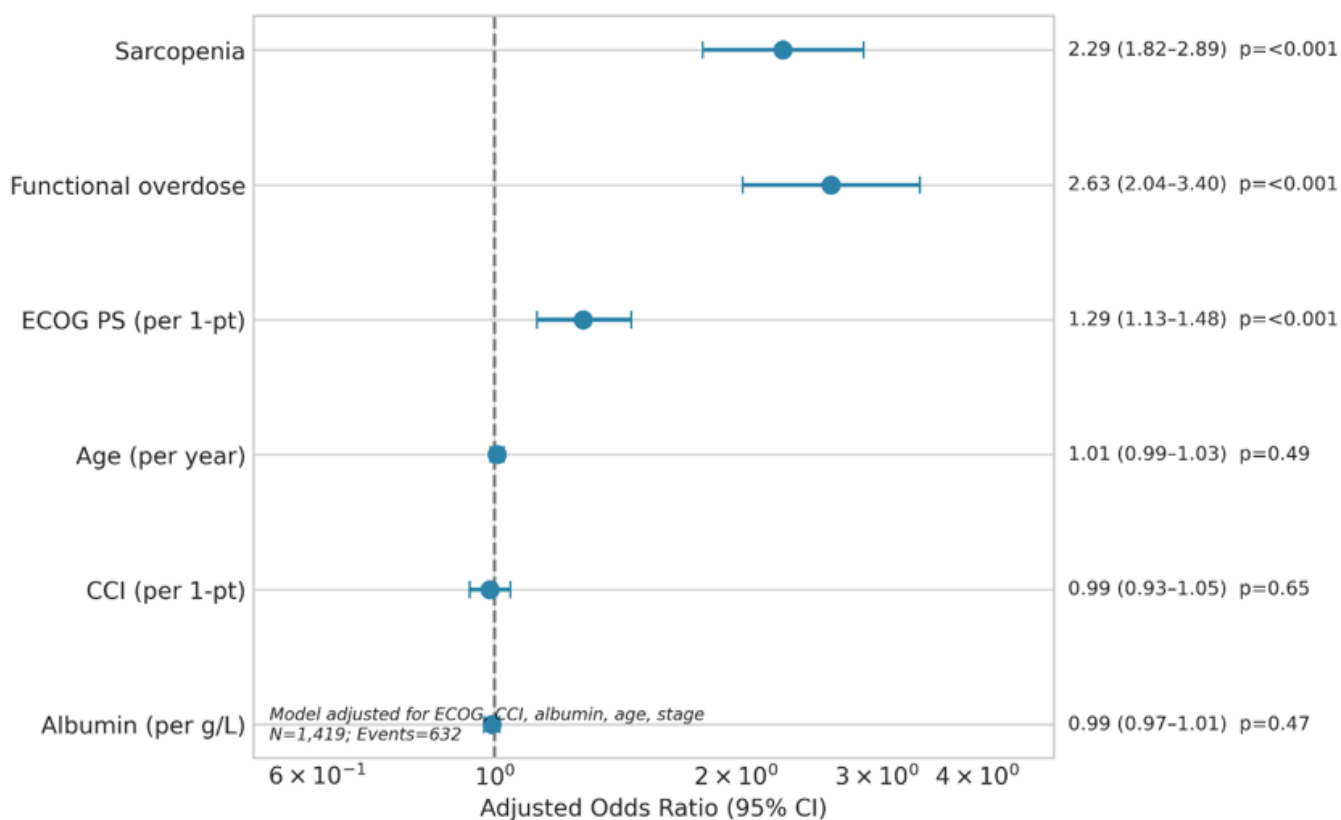


Figure 5

Adjusted odds ratios for grade ≥ 3 toxicity from the primary multivariable logistic regression model (Table 4). Squares represent point estimates; horizontal lines represent 95% confidence intervals; dashed vertical line marks the null (OR=1.0).

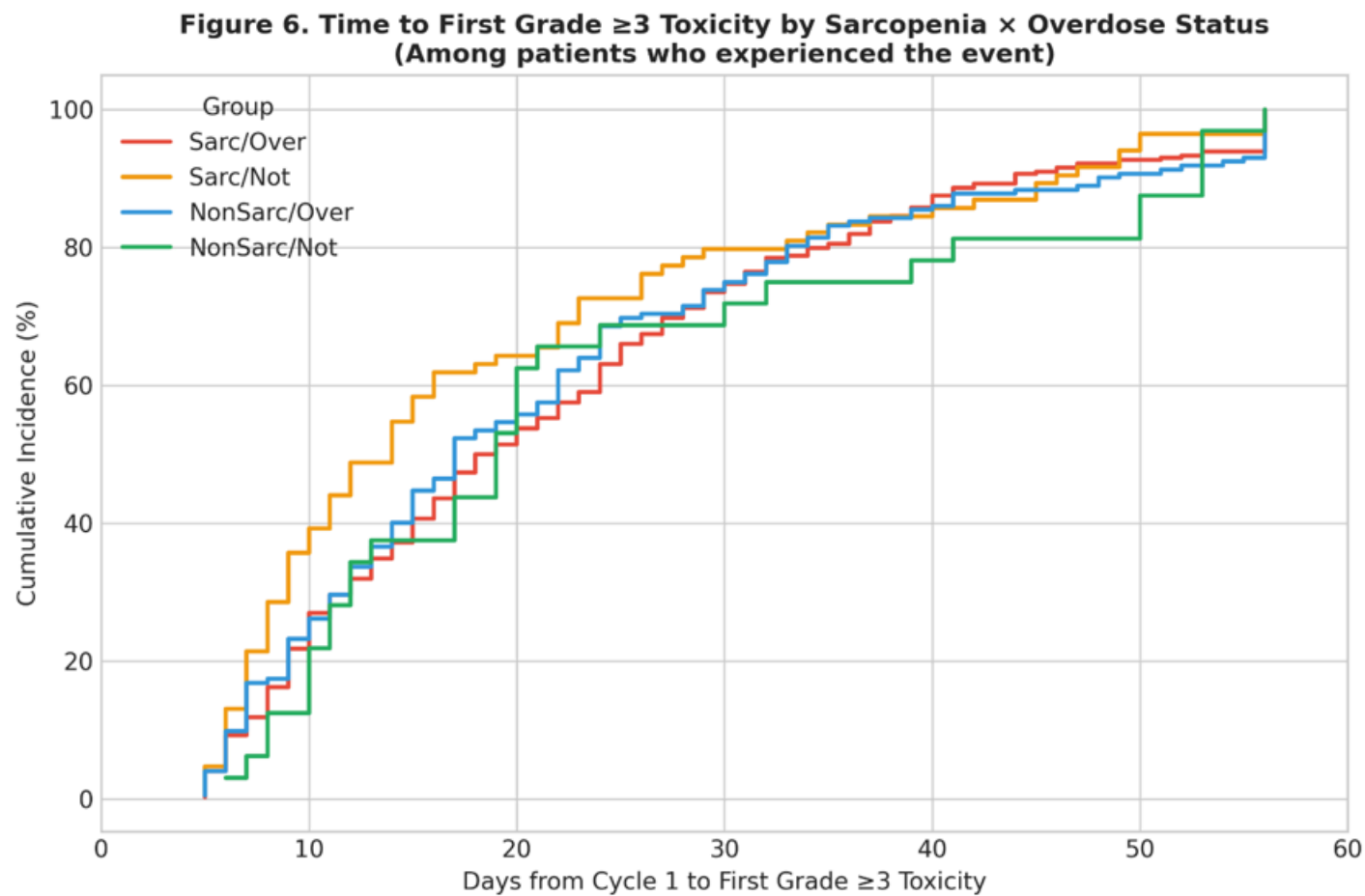


Figure 6

Time to First Grade ≥ 3 Toxicity by Sarcopenia $\times$ Overdose Status (Among patients who experienced the event).

Supplementary Files

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- [SupplementaryMaterialeGFRSarcopeniaAntineoplastic.docx](#)