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Incidence, evolution and risk factors of hypophosphatemia in patients with solid tumors receiving ferric carboxymaltose: a retrospective cohort study

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Abstract

Objectives

Ferric carboxymaltose (FCM) is increasingly used in the management of cancer-related anemia, yet it may cause hypophosphatemia. This retrospective study describes the incidence, evolution and risk factors of hypophosphatemia in a cohort of patients with solid tumors receiving FCM.

Methods

Serum phosphorus concentration was assessed longitudinally using a random intercepts model. The probability of developing hypophosphatemia, as graded by CTCAE version 4.0, was investigated using a multi-state model. Transition hazards were modeled non-parametrically and semi-parametrically by a Cox model. Causal marginal risk differences between baseline interventions on serum phosphorus and/or FCM dose were obtained via G-computation.

Results

In 174 ambulatory patients with solid tumors receiving FCM at two university hospitals between October 2020 and September 2021, the risk of developing moderate-to-severe

hypophosphatemia was 36.0% (95% confidence interval (CI) 28.2%-43.9%) and peaked within 16 days after first FCM administration. The average duration of moderate-to-severe hypophosphatemia was 12.4 days. After adjustment for confounders, lower baseline serum phosphorus (adjusted hazard ratio (aHR) 0.88 per 0.1 mmol/L increase, 95% CI 0.79-0.98) and higher FCM dose (first dose: aHR 1.12 per 1 mg/kg increase, 95% CI 1.01-1.25; second dose: aHR 1.06 per 1 mg/kg increase, 95% CI 1.00-1.13) significantly increased the hazard of moderate-to-severe hypophosphatemia.

Conclusion

Approximately one out of three ambulatory patients with solid tumors may develop moderate-to-severe hypophosphatemia after FCM administration. Baseline serum phosphorus and FCM dose may be modifiable risk factors that should be considered for intervention in order to mitigate the risk of hypophosphatemia.

Keywords

anemia, cancer, ferric carboxymaltose, iron deficiency, intravenous iron, hypophosphatemia

Figure captions

Figure 1. Longitudinal analysis of serum phosphorus concentration (a), the absolute change compared to baseline (b), and the relative change compared to baseline (c) from baseline to 60 days after first administration of ferric carboxymaltose. The values of each patient are represented by a single line. The bold line represents the population mean value per week as estimated by a random intercepts model. Abbreviations: FCM, ferric carboxymaltose.

Figure 2. The state occupation probabilities from baseline to 60 days after first administration of ferric carboxymaltose as predicted non-parametrically by a reversible multi-state model, starting from different entry states: hyperphosphatemia (a), normophosphatemia (b), mild hypophosphatemia (c), moderate hypophosphatemia (d), and the observed state distribution at baseline (e). None of the patients had severe hypophosphatemia at baseline. Abbreviations: FCM, ferric carboxymaltose.

Introduction

Anemia is a common complication in cancer patients that is associated with poor performance status, impaired quality of life and even worse response to cancer treatment [1,2]. It is usually multifactorial and may result from chronic blood loss from gastrointestinal or genitourinary malignancies, myelosuppressive anticancer treatment, bone marrow infiltration, or nutritional deficiencies due to cancer cachexia. Additionally, patients with advanced cancer frequently exhibit a chronic inflammatory state, in which the upregulation of hepcidin by proinflammatory cytokines leads to increased sequestration of iron in macrophages, resulting in functional iron deficiency (i.e., insufficient availability of iron despite adequate iron stores). Chronic inflammation may also suppress erythropoietin production and responsiveness [3,4].

Beyond supportive red blood cell (RBC) transfusions, management of anemia in cancer patients therefore involves identification and treatment of underlying causes other than cancer or the anticancer therapy, correction of iron deficiency, use of erythropoiesis-stimulating agents (ESAs), or a combination of these treatments [4-6]. In particular, the European Society for Medical Oncology (ESMO) recommends intravenous (IV) iron therapy before the initiation of ESA therapy in anemic patients (hemoglobin of ≤11 g/dL or hemoglobin decrease of ≥2 g/dL from a baseline level of ≤12 g/dL) undergoing chemotherapy who present with absolute (serum ferritin of <100 ng/mL) or functional (transferrin saturation of <20% and serum ferritin of ≥100 ng/mL) iron deficiency [6]. Moreover, a Cochrane review and meta-analysis of eight randomized controlled trials (RCTs) has shown that iron supplementation in anemic cancer patients receiving ESA therapy significantly improved the hematological response and reduced the need for RBC transfusion, irrespective of the iron status [7]. This finding has led to the joint recommendation from the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) that the use of iron supplementation should be considered in all ESA-treated cancer patients [5].

The following IV iron compounds are approved by the European Medicines Agency (EMA) [8]: ferric carboxymaltose (FCM), iron dextran, ferric gluconate, ferric derisomaltose (formerly known as iron isomaltoside), and iron sucrose. While hypersensitivity reactions may occur, most often with high-molecular-weight iron dextran, all these iron formulations are usually well tolerated and appear to be equally effective [7,9]. As such, the ESMO and the ASCO/ASH do not support the use of one over another [5,6]. FCM and ferric derisomaltose feature, however, a more convenient dosing schedule, allowing rapid iron supplementation in only one or two infusions [6,10-12]. Unfortunately, both iron formulations may cause hypophosphatemia. In a recent meta-analysis of 42 prospective trials comprising a mixed patient population, yet predominantly without cancer, the pooled incidence of hypophosphatemia was 47% in patients receiving FCM as compared to 4% in patients receiving ferric derisomaltose [13]. Although its clinical course is often asymptomatic and transient, cases of severe or prolonged hypophosphatemia that may ultimately result in asthenia, myopathy, osteomalacia or fractures are increasingly being reported, especially with FCM [13-18].

Hypophosphatemia due to FCM is mediated by renal phosphate wasting, but the exact mechanism is incompletely understood. FCM is hypothesized to inhibit the proteolytic cleavage of the phosphate-regulating hormone fibroblast growth factor-23 (FGF23), thereby increasing circulating levels of intact FGF23 and triggering a cascade that is sometimes referred to as the '6H-syndrome' (hypophosphatemia, high FGF23, high urinary phosphate excretion, hypocalcitriolemia, hypocalcemia, and secondary hyperparathyroidism) [13,15]. Risk factors include lower serum phosphorus at baseline, more severe iron deficiency, and preserved kidney function [13,19]. Cancer patients could be even more prone to develop hypophosphatemia after receiving FCM since they already have pre-existing risk factors for hypophosphatemia, such as use of bone-modifying agents (including bisphosphonates and denosumab), administration of chemotherapy affecting the proximal renal tubular function, or malnutrition [20].

The goal of this retrospective study was to describe the incidence and evolution of hypophosphatemia in ambulatory patients with solid tumors receiving FCM and to identify modifiable risk factors at baseline.

Patients and methods

The study population consisted of adult (≥ 18 years) ambulatory patients with solid tumors who consecutively received FCM at the medical oncology day clinics of Ghent University Hospital (n=124) or University Hospital Brussels (n=69) between October 1, 2020, and September 30, 2021. FCM was administered intravenously in one or two fixed doses of 500 or 1,000 mg separated by at least 7 days per treatment course. In case of repeated treatment courses during the study period (n = 19), only the first was considered. The final study cohort comprised 174 patients.

The following patient characteristics were extracted from the electronic health record: age, sex, height, weight, amount of weight loss in 6 months prior to first FCM administration, tumor type, ethnicity, vitamin D supplementation, use of bone-modifying agents (bisphosphonates or denosumab), use of hydrochlorothiazide, use of proton pump inhibitors, chronic glucocorticoid therapy, ongoing chemotherapy with cisplatin, oxaliplatin or ifosfamide, ongoing therapy with anti-epidermal growth factor receptor agents, anti-vascular endothelial growth factor monoclonal antibodies or tyrosine kinase inhibitors, dose and timing of FCM administration, and initiation of phosphate supplementation. The following serum levels were obtained from the laboratory database, starting from 90 days prior to 60 days after the first FCM administration: phosphorus, calcium, magnesium, parathormone, 25-hydroxyvitamin D, hemoglobin, iron, ferritin, transferrin saturation, creatinine, C-reactive protein, and albumin. The last value carried forward was used as baseline level of these laboratory parameters in case of missing value at time of first FCM administration.

The following variables were derived: cancer cachexia, glomerular filtration rate and weight-adjusted FCM doses. Cancer cachexia was defined by the presence of weight loss of >5% in 6 months or body mass index below 20 kg/m^2 along with the presence of systemic inflammation [21]. The modified Glasgow Prognostic Score, which is based upon C-reactive protein and albumin, was used as proxy variable for systemic inflammation [22]. Glomerular filtration rate was estimated using the 2009 equation from the Chronic Kidney Disease Epidemiology Collaboration, which includes serum creatinine, age, sex and ethnicity [23].

Hypophosphatemia was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 as mild (0.60-0.79 mmol/L), moderate (0.30-0.59 mmol/L), or severe (<0.30 mmol/L) [24]. Hyperphosphatemia was defined as a serum phosphorus concentration of >1.45 mmol/L, which is the upper limit of normal used in our laboratories, as CTCAE version 4.0 does not cover hyperphosphatemia [24].

Serum phosphorus concentration was assessed longitudinally until 60 days after first FCM administration using a random intercepts model, a type of linear mixed-effects model, with (categorical) fixed effect per week and random intercept per patient to account for the additional source of variance due to repeated measurements of serum phosphorus within the same patient [25]. The probability of developing hypophosphatemia was investigated using a reversible Markov model with following five states [26]: hyperphosphatemia (>1.45 mmol/L), normophosphatemia (0.80-1.45 mmol/L), mild hypophosphatemia (0.60-0.79 mmol/L), moderate hypophosphatemia (0.30-0.59 mmol/L), and severe hypophosphatemia (<0.30 mmol/L). Transition probabilities were first estimated non-parametrically using the Aalen-Johansen estimator. Subsequently, predictors for moderate to severe hypophosphatemia were univariately explored by jointly modeling the transition hazards from hyperphosphatemia, normophosphatemia or mild hypophosphatemia into moderate or severe hypophosphatemia (so the equivalent of a two-state model) using an Anderson-Gill model, an extension of the semi-

parametric Cox model that (at least partially) accounts for individual patient heterogeneity in the presence of recurrent events [27]. Finally, causal marginal risk differences for developing moderate to severe hypophosphatemia at any time during follow-up between various baseline interventions on serum phosphorus and/or weight-adjusted FCM dose were obtained via G-computation using a two-state model in which the transition hazards from hyperphosphatemia, normophosphatemia or mild hypophosphatemia into moderate or severe hypophosphatemia, and vice versa, were modeled by a multivariate Anderson-Gill model with both exposures and both sets of confounders of the relationship between each exposure and incident hypophosphatemia as covariates. Standard errors and confidence intervals (CIs) were estimated using the non-parametric bootstrap [28,29].

Data analysis was performed in R version 3.3.2 using the *lme4* version 1.1-12, *survival* version 2.44-1.1 and *mstate* version 0.2.11 packages [30].

Results

The final study cohort comprised 174 patients. Baseline characteristics are summarized in Table 1. The median age was 63.5 (first and third quartile (Q1-Q3) 54.0-70.0) years with a female-to-male ratio of approximately 2:1. Breast cancer was the most prevalent tumor type (29.3%). The majority of patients (71.8%) received ongoing chemotherapy. Anemia (hemoglobin of ≤11 g/dL [6]) was present in 89.1% of patients. Iron deficiency was documented in 92.5% of patients, which was absolute (serum ferritin of <100 ng/mL [6]), functional (transferrin saturation of <20% and serum ferritin of ≥100 ng/mL [6]), and not otherwise specified (transferrin saturation of <20% and missing value for serum ferritin) in 38.5%, 55.3%, and 6.2% of cases, respectively. One patient (0.6%) had neither anemia nor iron deficiency. The median cumulative FCM dose was 1000 (Q1-Q3 1000-1500) mg and 17.0 (Q1-Q3 12.4-22.7) mg/kg adjusted for weight. 45.4% of patients received a second FCM dose, which was administered at a median of 9.0 (Q1-Q3 7.0-14.0) days after the first dose.

[Table 1 near here]

The baseline prevalence of moderate and severe hypophosphatemia was 4.0% and 0.0%, respectively. After FCM administration, the observed incidence of moderate and severe hypophosphatemia was 27.0% and 2.9%, respectively. No cases of hypophosphatemia-related death were observed. Phosphate replacement was initiated in 20.1% of patients, by means of dietary advise (2.9%), oral phosphate supplements (82.9%) or IV phosphate administration (14.3%). The reason for hospital admission in those patients who received IV phosphate supplementation was, however, not directly related to hypophosphatemia.

Longitudinal analysis of serum phosphorus concentration, as presented in Figure 1, showed that there was a significant change over time ($P<0.001$). The mean serum phosphorus concentration was 1.07 (95% CI 1.03 to 1.10) mmol/L at baseline. A sharp decline in mean serum phosphorus concentration was already observed throughout the first week after first FCM administration until reaching a nadir of 0.81 (95% CI 0.76 to 0.86) mmol/L during the second week, corresponding to a mean absolute change of -0.26 (95% CI -0.31 to -0.21) mmol/L and a mean relative change of -24.2% (95% CI -28.8% to -19.7%) compared to baseline. On average, serum phosphorus concentration then gradually returned toward baseline within six weeks after first FCM administration.

[Figure 1 near here]

The probability of developing hypophosphatemia was assessed using a multi-state model, in which the transition of one state to another was modeled. The state occupation probabilities are depicted in Figure 2, starting from different entry states (2a: hyperphosphatemia, 2b: normophosphatemia, 2c: mild hypophosphatemia and 2d: moderate hypophosphatemia; none of the patients had severe hypophosphatemia at baseline) and starting from the observed state distribution at baseline (2e). The risk of developing moderate to severe hypophosphatemia at

any time during follow-up was 36.0% (95% CI 28.2% to 43.9%) in the overall population and it varied with the entry state, increasing in states with lower serum phosphorus concentration. The probability of having moderate hypophosphatemia changed over time, peaking at 22.6% (95% CI 14.8% to 30.5%) within 16 days after first FCM administration and steadily decreasing thereafter, whereas the probability of having severe hypophosphatemia remained low throughout the study period with a maximum of 2.1% (95% CI 0.0% to 5.3%) at day 18 after first FCM administration. Patients who eventually developed moderate to severe hypophosphatemia experienced, on average, moderate to severe hypophosphatemia during 12.4 days (20.6% of follow-up time).

[Figure 2 near here]

Predictors of the transition from hyperphosphatemia, normophosphatemia or mild hypophosphatemia into moderate or severe hypophosphatemia were identified using an Anderson-Gill model. Fifty-nine transitions were observed in 52 unique patients. Results of the univariate analyses are presented in Supplementary File 1. The results of the multivariate Anderson-Gill model are presented in Table 2. This model indicated that the hazard for moderate to severe hypophosphatemia, adjusted for confounders, was 12% lower per 0.1 mmol/L increase in baseline serum phosphorus concentration (adjusted hazard ratio (aHR) of 0.88 per 0.1 mmol/L, 95% CI 0.79 to 0.98, P=0.021), 12% higher per 1 mg/kg increase in first FCM dose (aHR of 1.12 per 1 mg/kg, 95% CI 1.01 to 1.25, P=0.038), and 6% higher per 1 mg/kg increase in second FCM dose (aHR of 1.06 per 1 mg/kg, 95% CI 1.00 to 1.13, P=0.071). Using G-computation, this could be translated into marginal causal risk differences between various baseline interventions on both exposures. In particular, the absolute risk of developing moderate to severe hypophosphatemia decreased by 5.7% (95% CI 5.2% to 6.1%) when increasing baseline serum phosphorus concentration by 0.2 mmol/L only in non-hyperphosphatemic patients, by 1.7% (95% CI 1.3% to 2.1%) when limiting the weight-

adjusted FCM dose at first administration to 15 mg/kg while adding the excess to the second dose, and by 7.3% (95% CI 6.6% to 8.0%) when doing these two interventions jointly.

[Table 2 near here]

Discussion

Correction of iron deficiency represents a cornerstone of management of cancer-related anemia [4-6]. FCM is an IV iron formulation increasingly used in this setting [31,32]. Although its side effects were initially thought to be trivial, it is becoming notorious for causing hypophosphatemia [13-16]. This is, to our knowledge, the first study that used multi-state modeling to assess the occurrence and evolution of hypophosphatemia in ambulatory patients with solid tumors receiving FCM along with causal inference to identify relevant interventions on baseline risk factors.

The observed incidence of moderate and severe hypophosphatemia in this study was 27.0% and 2.9%, respectively. Using a multi-state model, which accounted for censoring of patients whose serum phosphorus was only measured for a short period of time, the overall risk of developing moderate to severe hypophosphatemia at any time during follow-up was 36.0% (95% CI 28.2% to 43.9%) and peaked within 16 days after first FCM administration. These findings are in line with a recent meta-analysis that reported a pooled incidence of hypophosphatemia of 47% following FCM administration, albeit with less strict cutoffs used for hypophosphatemia (ranging from below 0.60 to below 0.84 mmol/L) and with only few cancer patients included [13].

Data from studies in cancer patients are, in fact, limited and somewhat conflicting. In the FCM arm of the IRON-CLAD trial, a RCT assessing its efficacy and safety for the treatment of chemotherapy-induced anemia in patients with non-myeloid malignancies, 60.0% and 4.3% of 70 patients with normal serum phosphorus concentration at baseline developed grade 3 and

grade 4 hypophosphatemia (according to CTCAE version 4.0), respectively, and 15.7% of all 121 patients required phosphate replacement during the 18-week study period [33]. In a prospective cohort of 84 anemic patients also receiving chemotherapy for a non-myeloid malignancy, the rate of hypophosphatemia (defined as a serum phosphorus concentration below 0.65 mmol/L) was 46.4% at week 3 after FCM administration. All cases were considered to be asymptomatic yet were treated with oral phosphate supplements [34]. By contrast, hypophosphatemia was observed in only 6.1% of patients in another prospective cohort of 367 patients with solid tumors or hematological malignancies who were followed over a three-month period after FCM administration, although the cutoff to define hypophosphatemia and the frequency of laboratory testing were not specified [32]. Other studies comprising anemic patients with solid tumors receiving FCM, either in the perioperative setting [35-39] or during systemic treatment [31,40-44], did not report on the rate of hypophosphatemia. Thus, the occurrence of FCM-induced hypophosphatemia may be underreported in the oncology literature and may thereby remain underrecognized by prescribing oncologists.

In this study, mean serum phosphorus concentration fell by 0.26 (95% CI 0.21 to 0.31) mmol/L or 24.2% (95% CI 19.7% to 28.8%) below baseline, with a nadir reached approximately two weeks after first FCM administration followed by a gradual recovery over four weeks. A similar pattern was found in the IRON-CLAD trial [33] as well as in a meta-analysis of individual patient data from 6,879 (mainly non-cancer) patients [17]. The average duration of moderate to severe hypophosphatemia was 12.4 days. None of the prospective studies among patients with [31-33] or without [13,17] cancer analyzed the duration of hypophosphatemia. Nevertheless, persistence of hypophosphatemia beyond six weeks has previously been described, especially in patients with pre-existing risk factors for hypophosphatemia and in patients receiving repeated treatment courses with FCM [14,15,17,19]. As such, the product labeling for FCM includes the recommendation for monitoring serum phosphorus in those patients [10,12].

The following have been consistently identified by previous studies as risk factors for hypophosphatemia after FCM administration: lower serum phosphorus at baseline [19,45], more severe iron deficiency (including lower serum ferritin and lower transferrin saturation) [13,17,19,34], preserved kidney function [13,45], lower body weight or body mass index [17,19,45], and higher FCM dose(s) [17]. Of these, baseline serum phosphorus and FCM dose may be modifiable and should therefore be considered for intervention in order to mitigate the risk of hypophosphatemia. This study showed that the absolute risk of developing moderate to severe hypophosphatemia decreased by 5.7% (95% CI 5.2% to 6.1%) when increasing baseline serum phosphorus concentration by 0.2 mmol/L in non-hyperphosphatemic patients and by 7.3% (95% CI 6.6% to 8.0%) when additionally limiting the weight-adjusted FCM dose at first administration to 15 mg/kg while adding the excess to the second dose (the US Food and Drug Administration-approved and European product labeling for FCM allows a single dose of 15 mg/kg [12] and 20 mg/kg [10], respectively, up to a maximum of 1,000 mg). Alternatively, ferric derisomaltose (EMA-approved but not available in every member state of the European Union [8]) or ferumoxytol (not EMA-approved [8]), two iron formulations with also a convenient dosing schedule yet low-to-no hypophosphatemia risk [13,16], can be used.

Finally, this study suggests that cancer patients may indeed be at higher baseline risk of hypophosphatemia (although prior FCM administration could not be excluded and may have contributed) [20], as the minimal proportion of patients with moderate to severe hypophosphatemia remained around 4% throughout the study period. In particular, the significant association between the use of bone-modifying agents, such as bisphosphonates or denosumab, and moderate to severe hypophosphatemia in FCM-treated cancer patients warrants further studies evaluating a possible interaction.

Some authors have disputed the clinical relevance of transient hypophosphatemia based exclusively on laboratory measurement of serum phosphorus [14,17]. An individual patient data

meta-analysis retrospectively identified potential signs and symptoms of hypophosphatemia in 8.8% of patients receiving FCM, but did not find a correlation with the reported serum phosphorus concentration [17]. However, symptoms of hypophosphatemia that may be subtle, such as fatigue and weakness, are rarely reported as treatment-related adverse events in studies [15] and are not easily distinguishable from other causes, especially not in anemic patients undergoing anticancer therapy. Moreover, resolution of hypophosphatemia does not always reflect normalization of bone and mineral metabolism [18,19]. Ongoing or worsening fatigue, weakness or bone pain in patients receiving FCM should therefore prompt the clinician to measure serum phosphorus. A comprehensive review of clinical findings and recommendations for management are described elsewhere [15].

This study has some methodological limitations. First, we assumed that state transitions were observed at the times of laboratory measurement of serum phosphorus or right-censored. In addition, the Markov property implies that the probability of transition to a future state only depends on the current state and not on the history. As the exact transition times were actually unknown (and state misclassification may have occurred) and the probability of transition may also have been dependent on the time spent in the current state, a hidden (semi-)Markov model with interval-censored transition times would have been more appropriate. Secondly, death was not recorded and thereby not treated as a competing risk, possibly resulting in overestimation of the transition probabilities. The risk of death throughout the study period of 60 days was, however, presumably low, since the majority of patients received ongoing anticancer therapy and all patients were deemed eligible for FCM, from which the clinical benefit is mainly derived in the longer term. A third limitation, due to the small sample size, is that the baseline transition hazards from hyperphosphatemia, normophosphatemia or mild hypophosphatemia into moderate or severe hypophosphatemia, and vice versa, were considered to be the same and that recurrent events within a patient were assumed to be independent and to share a common

baseline hazard. Fourthly, data on the dose and exact timing of phosphate supplementation were not available, such that causal estimation of the effect of phosphate supplementation on hypophosphatemia was not possible. Finally, the validity of the causal estimates relies on several strong (untestable) assumptions [28,29,46]. For instance, data on the patient's dietary pattern and parathyroid hormone/vitamin D levels were lacking and may have residually confounded the relationship between baseline and incident hypophosphatemia. Moreover, hypothetical interventions on baseline serum phosphorus (for instance, through phosphate supplementation) or weight-adjusted FCM dose are likely to violate the consistency assumption. These estimates should therefore be considered exploratory in nature, yet they may yield some preliminary insights and guidance for clinicians pending further interventional and cost-effectiveness studies.

Conclusion

Approximately one out of three ambulatory patients with solid tumors may develop moderate to severe hypophosphatemia after FCM administration. Baseline serum phosphorus and FCM dose may be modifiable risk factors that should be considered for intervention in order to mitigate the risk of hypophosphatemia and its associated impairment in quality of life.

Statements and declarations

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Authors' contribution

AD, KK, SD, SR, HD and LL contributed to the study conception. AD and KK applied for the ethics approval and collected the data. AD performed the statistical analysis and drafted the manuscript. KK, SD, SR, HD and LL were involved in the data interpretation and critically revised the draft versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

This study was approved by the local ethics committees of Ghent University Hospital (project number BC-11548) and University Hospital Brussels (project number EC-2022-129).

Consent to participate

The need for informed consent was waived by the local ethics committees due to the retrospective nature of this study.

Consent to publish

Not applicable.

Data availability

The dataset generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Code availability

The code used during the current study are available from the corresponding author on reasonable request.

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Table 1. Baseline characteristics (n=174).

Variable	Summary statistics[a]
Age (years)	63.5 (54.0-70.0)
Body mass index (kg/m^2)	24.4 (21.7-26.9)
Sex	
male	57 (32.8%)
female	117 (67.2%)
Ethnicity	
Asian	3 (1.7%)
Black	1 (0.6%)
Caucasian	170 (97.7%)
Tumor type	
breast	51 (29.3%)
gastrointestinal	20 (11.5%)
genitourinary	16 (9.2%)
gynaecological	24 (13.8%)
head and neck	11 (6.3%)
lung	11 (6.3%)
melanoma	18 (10.3%)
sarcoma	19 (10.9%)
other	4 (2.3%)
Anemia[b]	155 (89.1%)
Iron deficiency	
absolute[c]	62 (35.6%)
functional[d]	89 (51.1%)
not otherwise specified[e]	10 (5.7%)
no	6 (3.4%)
missing	7 (4.0%)
Chemotherapy	
cisplatin/oxaliplatin/ifosfamide	23 (13.2%)
other	102 (58.6%)
no	49 (28.2%)
Anti-EGFR/anti-VEGF/TKI therapy	18 (10.3%)
Bone-modifying agent use	20 (11.5%)
Vitamin D supplementation	57 (32.8%)
Hydrochlorothiazide use	15 (8.6%)
Proton pump inhibitor use	100 (57.5%)
Chronic glucocorticoid therapy	19 (10.9%)
eGFR (mL/min/1.73m^2)[f]	89.4 (75.4-98.2)
Cancer cachexia[g]	18 (10.3%)
Baseline serum phosphorus	
hyperP (>1.45 mmol/L)	8 (4.6%)
normoP (0.80-1.45 mmol/L)	142 (81.6%)
mild hypoP (0.60-0.79 mmol/L)	16 (9.2%)
moderate hypoP (0.30-0.59 mmol/L)	7 (4.0%)
severe hypoP (<0.30 mmol/L)	0 (0.0%)
missing	1 (0.6%)
Cumulative FCM dose (mg)	
500	27 (15.5%)
1000	70 (40.2%)
1500	64 (36.8%)

2000	13 (7.5%)
Weight-adjusted FCM dose (mg/kg)	
first dose	13.9 (11.1-16.7)
second dose	8.3 (7.0-10.0)
cumulative dose	17.0 (12.4-22.7)
Second FCM dose	79 (45.4%)
Time between FCM doses (days)	9.0 (7.0-14.0)
Baseline laboratory parameters	
phosphorus (mmol/L)	1.06 (0.92-1.21); 1 missing values
calcium (mmol/L)	2.24 (2.19-2.30); 0 missing values
magnesium (mmol/L)	0.77 (0.71-0.82); 1 missing values
hemoglobin (g/dL)	9.6 (8.8-10.3); 0 missing values
iron (µg/dL)	32.0 (22.0-44.0); 7 missing values
ferritin (µg/L)	240.0 (36.0-516.0); 17 missing values
transferrin saturation (%)	12.0 (7.4-16.6); 7 missing values

[a]Categorical variables are presented as count (proportion). Continuous variables are presented as median (first-third quartile). Summary statistics for baseline parathormone and 25-hydroxyvitamin D are not shown due to a high number of missing values (165 and 133, respectively).

[b]Hemoglobin of ≤11 g/dL.

[c]Serum ferritin of <100 ng/mL.

[d]Transferrin saturation of <20% and serum ferritin of ≥100 ng/mL.

[d]Transferrin saturation of <20% and missing value for serum ferritin.

[f]Estimated using the 2009 equation from the Chronic Kidney Disease Epidemiology Collaboration [22].

[g]Weight loss of >5% in 6 months or body mass index of <20 kg/m^2 along with the presence of systemic inflammation based on the modified Glasgow Prognostic Score [20, 21].

Abbreviations: eGFR, estimated glomerular filtration rate; EGFR, epidermal growth factor receptor; FCM, ferric carboxymaltose; (hyper/normo/hypo)P, phosphatemia; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Table 2. Multivariate Anderson-Gill model for moderate to severe hypophosphatemia.

Variable	β (SE)	HR (95% CI)	P
Weight-adjusted FCM dose (per 1 mg/kg)			
first dose	0.11 (0.055)	1.12 (1.01-1.25)	0.038
second dose	0.06 (0.032)	1.06 (1.00-1.13)	0.071
Baseline phosphorus (per 0.1 mmol/L)	-0.13 (0.055)	0.88 (0.79-0.98)	0.021
Bone-modifying agent use	0.81 (0.363)	2.25 (1.10-4.58)	0.026
Vitamin D supplementation	0.23 (0.345)	1.25 (0.64-2.46)	0.514
Hydrochlorothiazide use	0.19 (0.381)	1.21 (0.57-2.55)	0.622
Proton pump inhibitor use	-0.08 (0.270)	0.93 (0.55-1.57)	0.775
Chronic glucocorticoid therapy	0.30 (0.371)	1.35 (0.65-2.80)	0.416
Cisplatin/oxaliplatin/ifosfamide therapy	-0.38 (0.433)	0.69 (0.29-1.60)	0.383
Anti-EGFR/anti-VEGF/TKI therapy	0.34 (0.486)	1.40 (0.54-3.64)	0.486
Baseline eGFR[a] (per 10 mL/min/1.73m^2)	-0.03 (0.064)	0.97 (0.86-1.10)	0.644
Cancer cachexia[b]	0.44 (0.430)	1.55 (0.67-3.59)	0.310
Weight (per 1 kg)	-0.01 (0.014)	0.99 (0.96-1.02)	0.399

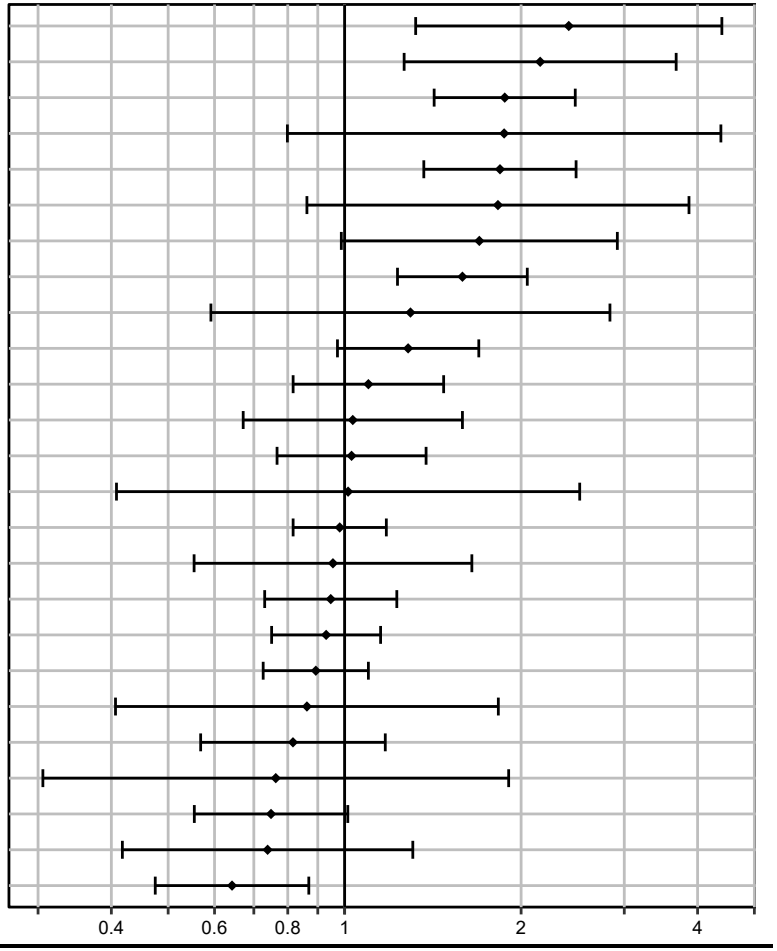
[a]Estimated using the 2009 equation from the Chronic Kidney Disease Epidemiology Collaboration [22].

[b]Weight loss of >5% in 6 months or body mass index of <20 kg/m^2 along with the presence of systemic inflammation based on the modified Glasgow Prognostic Score [20, 21].

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; EGFR, epidermal growth factor receptor; FCM, ferric carboxymaltose; HR, hazard ratio; SE, standard error; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

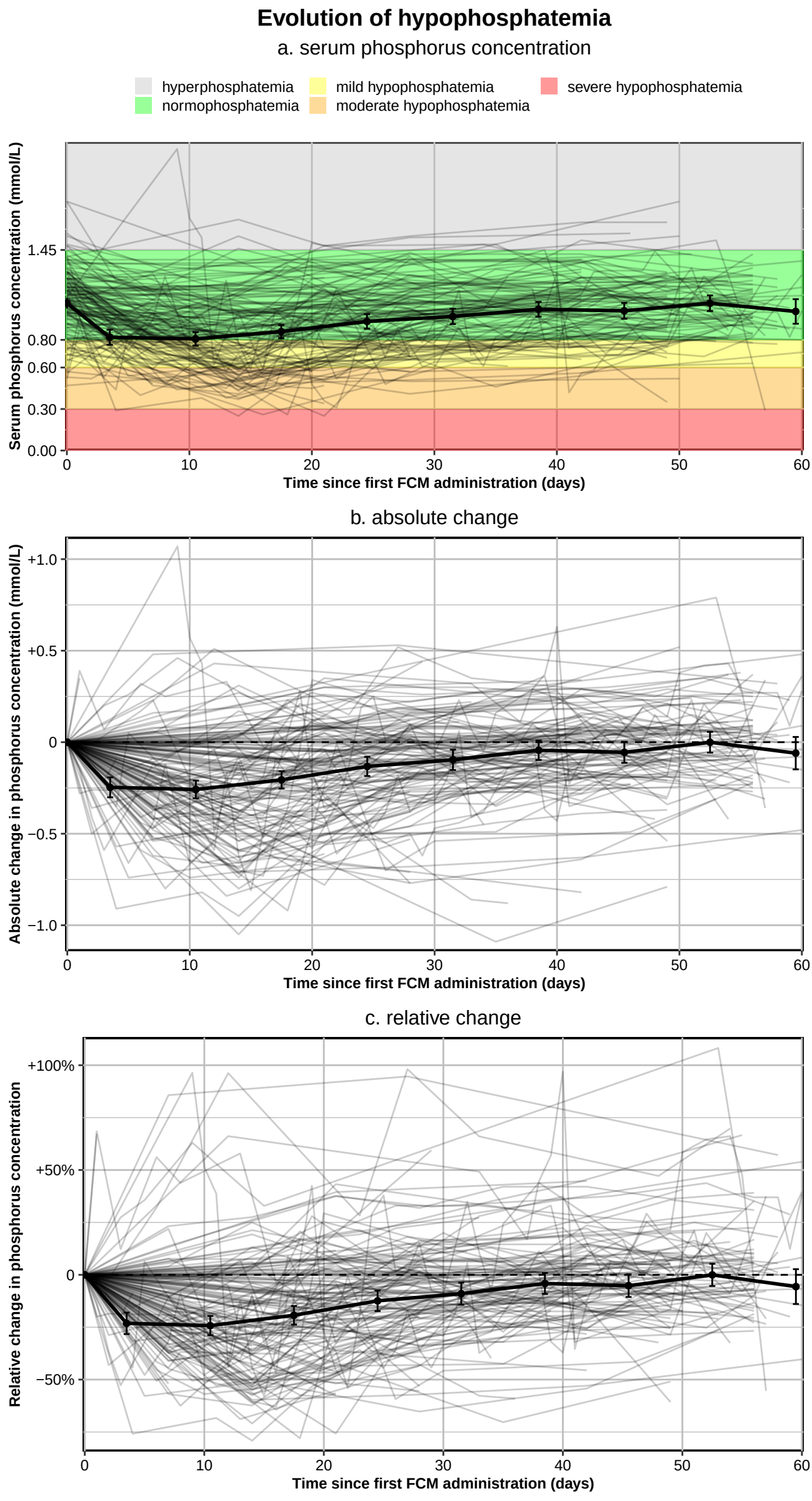
Supplementary File 1. Univariate Anderson-Gill models for moderate to severe hypophosphatemia.

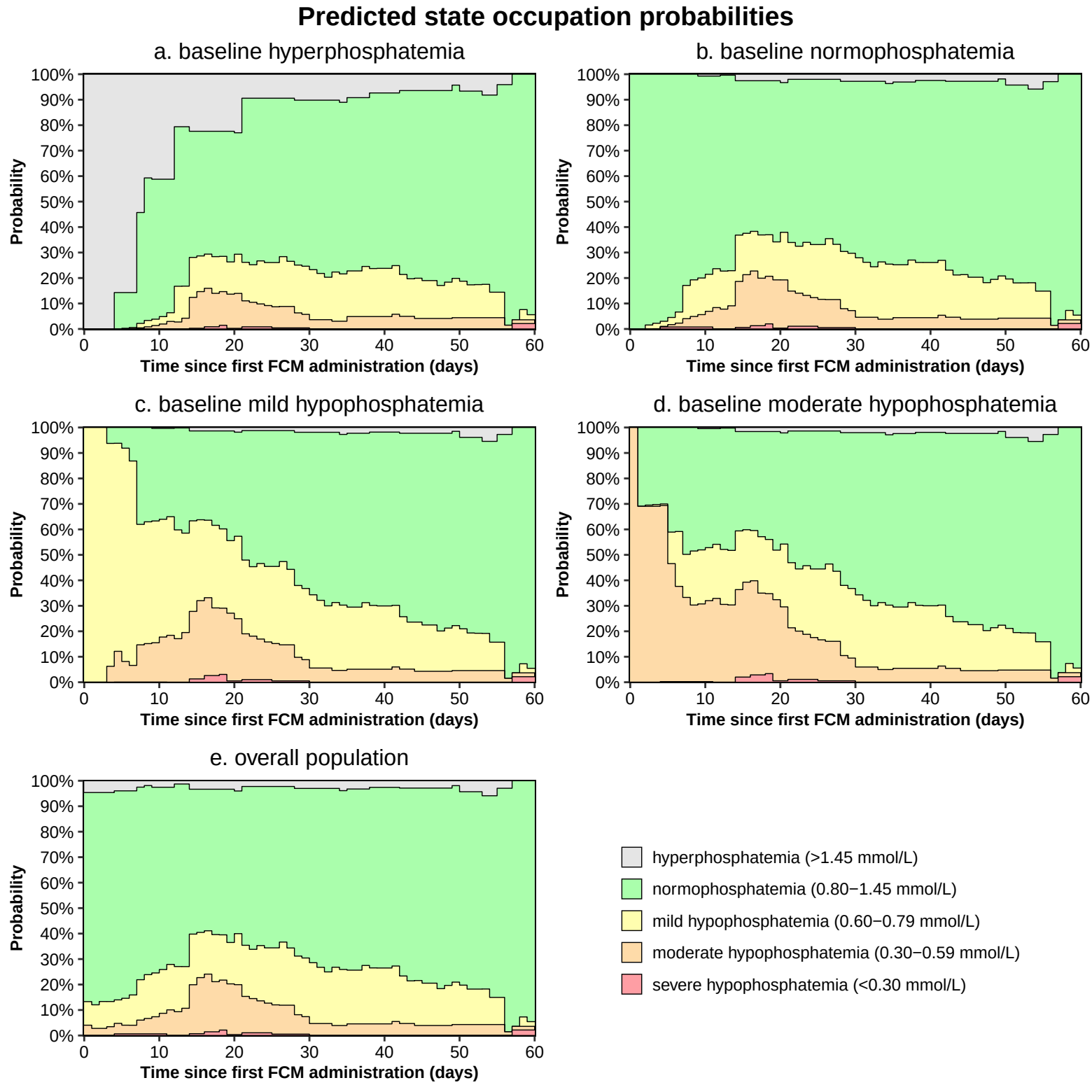
Variable	β (SE)	HR (95% CI)	P	Forest plot
Bone-modifying agent use	0.88 (0.307)	2.41 (1.32-4.40)	0.004	
Administration of second FCM dose	0.77 (0.273)	2.16 (1.26-3.68)	0.005	
Weight-adjusted cumulative FCM dose*	0.63 (0.141)	1.88 (1.42-2.47)	<0.001	
Chronic glucocorticoid therapy	0.63 (0.434)	1.87 (0.80-4.38)	0.149	
Weight-adjusted first FCM dose*	0.61 (0.153)	1.84 (1.37-2.48)	<0.001	
Cancer cachexia	0.60 (0.383)	1.83 (0.86-3.87)	0.116	
Vitamin D supplementation	0.53 (0.277)	1.70 (0.99-2.92)	0.056	
Weight-adjusted second FCM dose*	0.46 (0.130)	1.59 (1.23-2.05)	<0.001	
Hydrochlorothiazide use	0.26 (0.400)	1.30 (0.59-2.84)	0.518	
Baseline magnesium*	0.25 (0.142)	1.28 (0.97-1.69)	0.078	
Age*	0.09 (0.151)	1.10 (0.82-1.48)	0.536	
Baseline 25-hydroxyvitamin D*	0.03 (0.220)	1.03 (0.67-1.59)	0.883	
Baseline eGFR*	0.03 (0.149)	1.03 (0.77-1.38)	0.854	
Baseline parathormone*	0.01 (0.464)	1.01 (0.41-2.52)	0.977	
Baseline transferrin saturation*	-0.02 (0.093)	0.98 (0.82-1.18)	0.837	
Proton pump inhibitor use	-0.05 (0.278)	0.96 (0.55-1.65)	0.869	
Baseline ferritine*	-0.05 (0.132)	0.95 (0.73-1.23)	0.681	
Baseline iron*	-0.07 (0.109)	0.93 (0.75-1.15)	0.506	
Baseline hemoglobin*	-0.11 (0.105)	0.89 (0.73-1.10)	0.283	
Cisplatin/oxaliplatin/ifosfamide therapy	-0.15 (0.384)	0.86 (0.41-1.83)	0.700	
Baseline calcium*	-0.20 (0.185)	0.82 (0.57-1.17)	0.273	
Anti-EGFR/anti-VEGF/TKI therapy	-0.27 (0.467)	0.76 (0.31-1.91)	0.562	
Baseline phosphorus*	-0.29 (0.154)	0.75 (0.55-1.01)	0.060	
Male sex	-0.30 (0.291)	0.74 (0.42-1.31)	0.299	
Body mass index*	-0.44 (0.154)	0.64 (0.48-0.87)	0.004	



*Continuous variables were scaled.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; EGFR, epidermal growth factor receptor; FCM, ferric carboxymaltose; HR, hazard ratio; SE, standard error; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.


Evolution of hypophosphatemia
a. serum phosphorus concentration
hyperphosphatemia
normophosphatemia
mild hypophosphatemia
moderate hypophosphatemia
severe hypophosphatemia
Serum phosphorus concentration (mmol/L)
1.45
0.80
0.60
0.30
0.00
0
10
20
30
40
50
60
Time since first FCM administration (days)
b. absolute change
Absolute change in phosphorus concentration (mmol/L)
+1.0
+0.5
0
−0.5
−1.0
Time since first FCM administration (days)
c. relative change
Relative change in phosphorus concentration
+100%
+50%
0
−50%
Time since first FCM administration (days)


Predicted state occupation probabilities
a. baseline hyperphosphatemia
b. baseline normophosphatemia
c. baseline mild hypophosphatemia
d. baseline moderate hypophosphatemia
e. overall population
Probability
Time since first FCM administration (days)
hyperphosphatemia (>1.45 mmol/L)
normophosphatemia (0.80−1.45 mmol/L)
mild hypophosphatemia (0.60−0.79 mmol/L)
moderate hypophosphatemia (0.30−0.59 mmol/L)
severe hypophosphatemia (<0.30 mmol/L)