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Between- and Within-Patient Associations of Nutritional and Inflammatory Status with Erythropoiesis-Stimulating Agent Responsiveness in Maintenance Hemodialysis: A 36-Month Longitudinal Study

Yukinobu Ikegishi

yikegishi@yahoo.co.jp

Fuefuki Central Hospital

Research Article

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Abstract

Background

The contributions of between-patient differences and within-patient changes in nutritional and inflammatory status to erythropoiesis-stimulating agent (ESA) responsiveness remain unclear. We examined longitudinal associations of the geriatric nutritional risk index (GNRI) and C-reactive protein (CRP) with ESA resistance in maintenance hemodialysis.

Methods

This retrospective 36-month study included 69 hemodialysis patients. Monthly GNRI and log-transformed CRP were decomposed into between-patient and within-patient components. Random-intercept mixed-effects models assessed associations with log-transformed ESA resistance index (ERI). Sensitivity analyses used weekly ESA dose as an alternative outcome, adjusting for hemoglobin and dry weight. Generalized estimating equations assessed next-month ERI after adjustment for current ERI.

Results

Among 2,048 observations, between-patient (β = −0.0273, P = 0.0014) and within-patient (β = −0.0159, P < 0.001) GNRI were inversely associated with concurrent ERI. Between-patient CRP showed a borderline association (β = 0.4361, P = 0.051), whereas within-patient CRP was not associated with ERI. Neither GNRI component was significantly associated with weekly ESA dose. Among 1,921 consecutive-month pairs, between-patient GNRI (β = −0.00240, P = 0.003) and CRP (β = 0.05085, P = 0.013) were associated with next-month ERI, whereas within-patient components were not.

Conclusions

GNRI was associated with concurrent ERI, but not with ESA dose in the alternative-outcome analysis. Between-patient nutritional and inflammatory differences, rather than short-term within-patient changes, were associated with subsequent ERI. Shared mathematical components of GNRI and ERI warrant consideration.

Introduction

Anemia is a common complication of maintenance hemodialysis, and erythropoiesis-stimulating agents (ESAs) remain central to its management. However, responsiveness to ESA therapy varies substantially both between patients and over time within individual patients. ESA hyporesponsiveness has been associated with adverse clinical outcomes and may reflect multiple potentially modifiable factors, including impaired iron availability, inflammation, malnutrition, and intercurrent clinical stressors [1–3].

The erythropoiesis resistance index (ERI), which relates ESA dose to hemoglobin concentration and body weight, is commonly used as a clinical measure of ESA responsiveness [4].

Nutritional and inflammatory status may be particularly relevant to ESA responsiveness in patients undergoing hemodialysis. Protein-energy wasting and chronic inflammation frequently coexist and may impair erythropoiesis through overlapping pathways [2, 5]. Previous studies have demonstrated associations of lower serum albumin, greater inflammatory burden, and poorer nutritional status with reduced ESA responsiveness [2, 5, 6]. The Geriatric Nutritional Risk Index (GNRI), a simple nutritional screening measure derived from serum albumin and body weight relative to ideal body weight, has also been associated with ERI and adverse outcomes in maintenance hemodialysis patients [6, 7]. These observations support a close relationship between the nutritional–inflammatory milieu and ESA responsiveness.

However, an important issue in interpreting these associations is their temporal nature. ESA hyporesponsiveness is not necessarily a stable patient characteristic; longitudinal studies have shown that resistance may be transient and may change in association with evolving clinical conditions [8, 9]. In a self-matched longitudinal analysis of hemodialysis patients, Karaboyas et al. demonstrated that acute increases in C-reactive protein (CRP) were followed by lower hemoglobin levels and greater ESA requirements, supporting a clinically relevant within-patient relationship between inflammation and ESA response [10]. Nevertheless, less is known about whether longitudinal associations between nutritional status and ESA responsiveness predominantly reflect persistent differences between patients or short-term changes within the same patient.

This distinction is important because conventional analyses of repeated measurements may combine two biologically different sources of variation. Patients with chronically poorer nutritional status may consistently exhibit greater ESA resistance than patients with better nutritional status, representing a between-patient association. In contrast, a temporary deterioration in nutritional status within an individual patient may or may not be accompanied by a corresponding change in ESA responsiveness, representing a within-patient association. Separating these components may therefore provide a more clinically meaningful interpretation of longitudinal relationships between nutritional and inflammatory status and ESA responsiveness.

In previous studies conducted at the same dialysis center using overlapping patient data, we examined iron administration and iron indices in relation to ERI over 12 months [11], biological variability—particularly albumin variability—over 24 months [12], and temporal associations of inflammation and iron availability with ERI over 12 months [13]. Two additional accepted studies investigated the combined burden of hypoalbuminemia and inflammation [14] and the contemporaneous association between the number of selected clinical abnormalities and ERI [15]. Although these studies characterized complementary aspects of ESA hyporesponsiveness, none explicitly separated patient-level mean GNRI and CRP from signed within-patient monthly deviations. The present 36-month study addresses this distinct question and compares concurrent ERI, subsequent-month ERI, and weekly ESA dose.

Interpretation of the association between nutritional status and ERI also requires methodological caution. Body weight is incorporated into the denominator of ERI and also contributes to the calculation of GNRI. Consequently, an association between GNRI and ERI could partly reflect shared body-weight-related mathematical structure rather than a direct biological relationship. Evaluating ESA dose as an alternative outcome while accounting for hemoglobin and body weight may help assess the robustness of ERI-based findings. Furthermore, examining whether current changes in nutritional or inflammatory status are associated with subsequent ERI, beyond current ERI, may provide additional insight into the temporal nature of these relationships.

Therefore, in this 36-month longitudinal study of patients receiving maintenance hemodialysis, we aimed to distinguish the between-patient and within-patient associations of nutritional and inflammatory status with ESA responsiveness. Repeated GNRI and CRP measurements were decomposed into patient-level mean values and within-patient deviations, and their associations with concurrent ERI were evaluated using repeated-measures models. We further examined the robustness and temporal characteristics of these associations using ESA dose as an alternative outcome and a lagged analysis of subsequent ERI. We hypothesized that persistent between-patient differences in nutritional and inflammatory status would be associated with ESA responsiveness, whereas short-term within-patient changes would show weaker and less consistent temporal associations.

Materials and Methods

Study design and population

This retrospective longitudinal cohort study was conducted at Fuefuki Central Hospital, Yamanashi, Japan. Patients receiving maintenance hemodialysis (HD) who underwent regular clinical and laboratory assessments between January 2023 and December 2025 were eligible for inclusion. Patients receiving peritoneal dialysis, those treated with a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) instead of an erythropoiesis-stimulating agent (ESA), and those without sufficient longitudinal clinical or laboratory data for the present analysis were excluded.

The source cohort comprised 70 maintenance HD patients, contributing 2,069 patient-month observations. Because the present study aimed to distinguish between-patient differences from within-patient changes using repeated measurements, one patient with fewer than 6 months of available observations was excluded from the primary analysis to ensure sufficient longitudinal information for within-patient assessment. The primary analytic cohort therefore comprised 69 patients contributing 2,064 patient-month observations. Patients with at least 6 months of available observations were retained even when data were not available for the entire 36-month observation period.

The present 36-month dataset extends longitudinal clinical data previously analyzed at the same dialysis center. Patients and observation periods overlap with three published studies examining iron indices and intravenous iron exposure (12 months) [11], biological variability (24 months) [12], and inflammation and

iron availability (12 months) [13], and with two accepted studies examining combined nutritional–inflammatory burden (12 months) [14] and the contemporaneous number of selected clinical abnormalities (12 months) [15]. The current study uses a longer observation window and a distinct between-patient/within-patient decomposition of GNRI and CRP, alongside concurrent, alternative-outcome, and lagged analyses. Overlapping patient-month records do not constitute an independent replication cohort.

Monthly clinical data, laboratory measurements, and ESA doses were retrospectively extracted from the electronic medical records. Because the number of available observations differed among patients, the resulting unbalanced longitudinal dataset was analyzed using statistical methods that accommodated different numbers of repeated measurements per patient.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Fuefuki Central Hospital (Approval No. Fuechu Rin 26 – 2; September 15, 2026). An opt-out approach was used for informed consent because of the retrospective nature of the study.

ESA treatment and assessment of ESA responsiveness

ESA therapy consisted of darbepoetin alfa or epoetin alfa. Because darbepoetin alfa is prescribed in micrograms (μg) and epoetin alfa in international units (IU), ESA doses were harmonized as epoetin alfa-equivalent doses for longitudinal analyses. Darbepoetin alfa was converted using a factor of 200 IU of epoetin alfa per 1 μg of darbepoetin alfa. All ESA doses are therefore expressed as epoetin alfa-equivalent doses throughout the analyses.

ESA responsiveness was assessed using the erythropoiesis resistance index (ERI), calculated as:

ERI = weekly epoetin alfa-equivalent ESA dose (IU/week) / [hemoglobin (g/dL)

× dry weight (kg)].

Higher ERI values indicated lower responsiveness to ESA therapy. Because the distribution of ERI was right-skewed, ERI was transformed as log(ERI + 1) for regression analyses.

Nutritional and inflammatory assessment

Nutritional status was assessed using the geriatric nutritional risk index (GNRI), calculated as:

GNRI = 14.89 × serum albumin (g/dL) + 41.7 × (dry weight / ideal body weight).

Ideal body weight was calculated as 22 × height² (m²). When the ratio of dry weight to ideal body weight exceeded 1.0, the ratio was set to 1.0 according to the conventional GNRI calculation.

C-reactive protein (CRP) was used as the principal marker of systemic inflammation. Because CRP values were right-skewed, CRP was transformed as log(CRP + 1) before longitudinal decomposition and regression analyses. Transferrin saturation (TSAT) and serum ferritin were included as indices of iron availability and iron stores, respectively. Physical stress was defined as infection, surgery, or fracture occurring during the corresponding month and was included as a binary time-varying covariate.

Routine blood samples were obtained before the first HD session of the week.

Between-patient and within-patient decomposition

To distinguish persistent differences between patients from longitudinal changes within individual patients, repeated GNRI and log-transformed CRP measurements were decomposed into between-patient and within-patient components using patient-mean centering.

For GNRI, the between-patient component was defined as each patient's mean GNRI across all available observations during follow-up:

$GNRI_{between,i} = mean(GNRI_i)$

The within-patient component was defined as the deviation of each monthly GNRI measurement from that patient's mean:

$GNRI_{within,it} = GNRI_{it} - mean(GNRI_i)$

The same procedure was applied to log(CRP + 1). Thus, the between-patient components represented differences in average nutritional or inflammatory status across patients, whereas the within-patient components represented deviations from each patient's own average level over time.

Both components were entered simultaneously into the longitudinal models, allowing between-patient and within-patient associations with ESA responsiveness to be estimated separately.

Primary longitudinal analysis

The primary outcome was log(ERI + 1). Associations of nutritional and inflammatory status with concurrent ERI were evaluated using a linear mixed-effects model with a patient-specific random intercept to account for repeated observations within individual patients.

The primary model simultaneously included the between-patient and within-patient components of GNRI and log(CRP + 1). TSAT, ferritin, and physical stress were included as time-varying covariates because iron availability, iron stores, and intercurrent clinical stress may influence ESA responsiveness.

The primary model was specified as:

$\log(ERI_it + 1) = \beta_0 + \beta_1 GNRI_between,i + \beta_2 GNRI_within,it + \beta_3 logCRP_between,i + \beta_4 logCRP_within,it + \beta_5 TSAT_it + \beta_6 Ferritin_it + \beta_7 PhysicalStress_it + u_i + \varepsilon_it$

where u_i represents the patient-specific random intercept and ε_it represents the residual error.

Analyses were performed using complete observations for all variables included in the model. The primary model included 2,048 patient-month observations from 69 patients. The selection of analysis populations is shown in Fig. 1.

Sensitivity analysis using weekly ESA dose

Because body weight contributes to the calculation of both GNRI and ERI, an association between these measures could partly reflect their shared mathematical structure. Therefore, a sensitivity analysis was performed using weekly epoetin alfa-equivalent ESA dose as an alternative outcome.

ESA dose was transformed as log(weekly ESA dose + 1). The model included the same between-patient and within-patient components of GNRI and log(CRP + 1) used in the primary analysis. Hemoglobin and dry weight were entered separately as covariates, together with TSAT, ferritin, and physical stress.

The model was specified as:

$\log(ESA\ dose_it + 1) = \beta_0 + \beta_1 GNRI_between,i + \beta_2 GNRI_within,it + \beta_3 logCRP_between,i + \beta_4 logCRP_within,it + \beta_5 Hb_it + \beta_6 DW_it + \beta_7 TSAT_it + \beta_8 Ferritin_it + \beta_9 PhysicalStress_it + u_i + \varepsilon_it$

This analysis was performed to assess whether associations observed using ERI were reproduced when ESA exposure was modeled without incorporating body weight into the outcome itself.

Lagged analysis

To further explore the temporal relationship between nutritional and inflammatory status and subsequent ESA responsiveness, a lagged analysis was performed. Observations were ordered chronologically within each patient, and log(ERI + 1) at the subsequent monthly observation was used as the outcome. Only observation pairs for which a subsequent monthly measurement was available were included.

The model included current log(ERI + 1), the between-patient and within-patient components of GNRI and log(CRP + 1), TSAT, ferritin, and physical stress. Current ERI was included to assess whether nutritional or inflammatory status was associated with subsequent ERI beyond the patient's current level of ESA responsiveness.

An initial mixed-effects model showed that the patient-level random-effect variance approached the boundary. Therefore, the final lagged analysis was estimated using generalized estimating equations

(GEE) with a Gaussian distribution, an exchangeable working correlation structure, and robust standard errors to account for within-patient correlation.

The lagged analysis included 1,921 paired observations from 69 patients. Eligible pairs comprised consecutive records separated by 20–40 days.

Because of the observational study design and the short interval between repeated assessments, this analysis was interpreted as an assessment of temporal association rather than evidence of a causal effect.

Sensitivity analysis including the full source cohort

To evaluate whether exclusion of the patient with fewer than 6 months of available observations materially influenced the findings, the analyses were repeated using the full source cohort of 70 patients contributing 2,069 patient-month observations.

The same variable definitions, transformations, between- and within-patient decomposition, covariates, and model specifications used in the primary analysis were applied to the full cohort. Results were compared with those obtained in the primary 69-patient cohort to assess the robustness of the findings to the minimum follow-up criterion.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation or median with interquartile range, as appropriate according to their distributions. Categorical variables were summarized as numbers and percentages.

Concurrent longitudinal associations were evaluated using linear mixed-effects models with patient-specific random intercepts. GNRI and log(CRP + 1) were decomposed into between-patient and within-patient components using patient-mean centering. The lagged analysis was performed using GEE with an exchangeable working correlation structure and robust standard errors.

Regression coefficients (β) are presented with 95% confidence intervals (CIs). For clinical interpretation, GNRI associations were additionally expressed per 5-point difference where appropriate.

Missing data were not imputed, and analyses were performed using available complete observations for variables included in each model. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Sensitivity analyses included the alternative weekly ESA-dose outcome, the lagged analysis of subsequent ERI, repetition of the analyses in the full 70-patient source cohort, and additional adjustment of the primary mixed-effects model for calendar year (2023, 2024, and 2025) to examine potential secular changes.

Analyses were performed using R version 4.5.2, with lme4 version 2.0–6, lmerTest version 3.2-1, and geepack version 1.3–13. Data handling used readxl 1.5.0, dplyr 1.2.1, and tidyr 1.3.2. For the mixed-effects models, 95% confidence intervals were calculated using t-distribution critical values and Satterthwaite degrees of freedom from lmerTest, consistent with the reported P values. For the lagged GEE model, 95% Wald confidence intervals were calculated using robust sandwich standard errors.

Results

Study population and longitudinal observations

The source cohort comprised 70 patients receiving maintenance hemodialysis, contributing 2,069 patient-month observations during the 36-month study period. One patient with fewer than 6 months of available observations was excluded from the primary analysis. The primary analytic cohort therefore consisted of 69 patients contributing 2,064 patient-month observations. The number of available observations per patient ranged from 10 to 36 months.

At baseline, the median age was 73.0 years (IQR, 62.0–80.0), and the median dialysis vintage was 42 months (IQR, 5–91). There were 43 men (62.3%) and 26 women (37.7%). At baseline, the median hemoglobin concentration was 10.8 g/dL (interquartile range [IQR], 10.2–11.5), weekly ESA dose was 9,000 IU/week (IQR, 4,500–12,000), and ERI was 15.62 (IQR, 7.95–20.97). Median TSAT and ferritin were 14% (IQR, 11–20) and 58 ng/mL (IQR, 38–101), respectively. Median serum albumin was 3.4 g/dL (IQR, 3.1–3.6), CRP was 0.11 mg/dL (IQR, 0.04–0.60), dry weight was 54.2 kg (IQR, 45.0–63.5), BMI was 21.52 kg/m² (IQR, 19.64–24.05), and GNRI was 90.14 (IQR, 84.46–94.17).

Between-patient and within-patient associations with ERI

The primary mixed-effects model included 2,048 patient-month observations from 69 patients. After adjustment for TSAT, ferritin, and physical stress, both the between-patient and within-patient components of GNRI were inversely associated with concurrent log(ERI + 1). The four exposure-component estimates across the three models are displayed in Fig. 2.

The between-patient GNRI coefficient was − 0.027 per 1-point higher GNRI (95% CI, − 0.044 to − 0.011; P = 0.001), indicating that patients with higher average GNRI during follow-up had lower concurrent ERI. The within-patient GNRI coefficient was − 0.016 (95% CI, − 0.020 to − 0.011; P < 0.001), indicating that observations with GNRI above a patient's own mean were associated with lower concurrent ERI.

For inflammatory status, the between-patient component of log(CRP + 1) showed a borderline positive association with concurrent ERI (β = 0.436; 95% CI, − 0.002 to 0.874; P = 0.051). In contrast, the within-patient component of log(CRP + 1) was not significantly associated with concurrent ERI (β = −0.026; 95% CI, − 0.080 to 0.028; P = 0.340).

Among the covariates, higher TSAT was associated with lower ERI (β=−0.017; 95% CI, − 0.020 to − 0.015; P < 0.001), whereas physical stress was associated with higher ERI (β = 0.233; 95% CI, 0.116–0.351; P <

0.001). Ferritin was also inversely associated with ERI (P < 0.001).

Expressed on a clinically interpretable scale, a 5-point higher between-patient GNRI corresponded to an approximately 12.6% lower ERI + 1, whereas a 5-point higher within-patient GNRI corresponded to an approximately 7.7% lower concurrent ERI + 1.

Sensitivity analysis using weekly ESA dose

Because body weight is incorporated into both GNRI and ERI, weekly ESA dose was examined as an alternative outcome, with hemoglobin and dry weight entered separately as covariates. The analysis included 2,048 patient-month observations from 69 patients.

In contrast to the primary ERI analysis, neither the between-patient nor the within-patient GNRI component was significantly associated with weekly ESA dose. The between-patient GNRI coefficient was 0.027 (95% CI, − 0.015 to 0.069; P = 0.209), and the within-patient coefficient was − 0.005 (95% CI, − 0.016 to 0.007; P = 0.438).

Similarly, neither between-patient nor within-patient log(CRP + 1) reached statistical significance in the ESA-dose model. The between-patient coefficient was 1.000 (95% CI, − 0.038 to 2.038; P = 0.059), whereas the within-patient coefficient was 0.036 (95% CI, − 0.093 to 0.166; P = 0.581).

Hemoglobin was inversely associated with ESA dose (β=−0.089; *P* < 0.001), and physical stress was positively associated with ESA dose (β = 0.411; 95% CI, 0.130–0.691; *P* = 0.004).

Thus, the significant associations of both between-patient and within-patient GNRI components with concurrent ERI were not reproduced when weekly ESA dose was used as the alternative outcome.

Associations with subsequent ERI

The lagged analysis included 1,921 paired observations from 69 patients. Current ERI was strongly associated with ERI at the subsequent monthly observation (β = 0.926; 95% CI, 0.890–0.961; P < 0.001). Eligible pairs comprised consecutive records separated by 20–40 days.

After adjustment for current ERI and other covariates, the between-patient GNRI component remained inversely associated with subsequent ERI (β=−0.0024; 95% CI, − 0.0040 to − 0.0008; *P* = 0.003). However, the within-patient GNRI component was not associated with subsequent ERI (β = 0.0010; 95% CI, − 0.0016 to 0.0036; *P* = 0.461).

Similarly, higher between-patient log(CRP + 1) was associated with higher subsequent ERI (β = 0.0508; 95% CI, 0.0106 to 0.0911; P = 0.013), whereas the within-patient CRP component was not significantly associated with subsequent ERI (β = 0.0182; 95% CI, − 0.0128 to 0.0492; P = 0.249). TSAT, ferritin, and physical stress were not significantly associated with subsequent ERI after adjustment for current ERI.

These findings indicated that between-patient differences in nutritional and inflammatory status were associated with subsequent-month ERI after adjustment for current ERI, whereas within-patient

deviations in GNRI or CRP were not significantly associated with subsequent-month ERI.

Sensitivity analysis including all 70 patients

The primary analyses were repeated in the full source cohort of **70 patients**, including the patient with fewer than 6 months of available observations. Inclusion of this patient did not materially alter the direction, magnitude, or statistical interpretation of the principal associations.

The between- and within-patient GNRI associations with concurrent ERI remained significant, whereas the within-patient CRP association remained nonsignificant. Similarly, the weekly ESA-dose sensitivity analysis did not demonstrate a significant GNRI association, and the lagged analysis continued to show between-patient, but not within-patient, associations of GNRI and CRP with subsequent ERI.

These findings indicated that the results were robust to inclusion of the patient with short follow-up.

Sensitivity analysis adjusted for calendar year

After additional adjustment of the primary mixed-effects model for calendar year, the between-patient GNRI component (β = −0.0278; 95% CI, − 0.0442 to − 0.0115; P = 0.0011) and the within-patient GNRI component (β = −0.0121; 95% CI, − 0.0167 to − 0.0074; P < 0.001) remained inversely associated with concurrent log(ERI + 1). The between-patient log(CRP + 1) component showed a positive association (β = 0.4691; 95% CI, 0.0326 to 0.9057; P = 0.036), whereas the within-patient component remained nonsignificant (β = −0.0110; 95% CI, − 0.0647 to 0.0427; P = 0.689). The full model is reported in Supplementary Table S1. The within-patient GNRI coefficient was attenuated compared with the primary model.

Discussion

In this 36-month longitudinal study of patients receiving maintenance hemodialysis, we examined the associations of nutritional and inflammatory status with ESA responsiveness by separating persistent between-patient differences from short-term within-patient changes. Three principal findings emerged. First, lower GNRI was associated with higher concurrent ERI at both the between-patient and within-patient levels, whereas higher CRP showed a borderline positive association with concurrent ERI at the between-patient level. Second, neither the between-patient nor the within-patient GNRI association observed for concurrent ERI was reproduced when weekly ESA dose was analyzed as an alternative outcome with hemoglobin and dry weight entered separately into the model. Third, after adjustment for current ERI, within-patient changes in GNRI and CRP were not associated with ERI at the subsequent monthly assessment, whereas between-patient differences in GNRI and CRP remained associated with subsequent ERI. Taken together, these findings suggest that persistent between-patient differences in nutritional and inflammatory status may be more consistently associated with ESA hyporesponsiveness than short-term within-patient fluctuations. However, given the multifactorial nature of ESA hyporesponsiveness, the potential mathematical coupling between GNRI and ERI, and the limited

number of patients in this single-center cohort, these associations should be interpreted cautiously and should not be considered evidence of causality or predictive performance.

ESA hyporesponsiveness is a complex and multifactorial clinical phenotype. Reviews by Wu and Chinnadurai [1] and Santos et al. [3] have emphasized that inadequate iron availability, inflammation, nutritional impairment, and other comorbid conditions may contribute to reduced ESA responsiveness in patients with CKD. Among patients receiving maintenance hemodialysis, malnutrition and inflammation frequently coexist and may jointly contribute to impaired erythropoiesis. Rattanasompattikul et al. [2] demonstrated an association between the malnutrition–inflammation complex and reduced ESA responsiveness in long-term hemodialysis patients. Feret et al. [5] similarly reported relationships among nutritional status, malnutrition–inflammation burden, body composition, and erythropoietin resistance. Our finding that patients with persistently lower GNRI and higher CRP tended to have higher ERI is broadly consistent with this body of evidence and supports the concept that ESA hyporesponsiveness occurs within a broader clinical context of nutritional and inflammatory burden.

GNRI has previously been linked to ESA responsiveness in maintenance hemodialysis populations. Okazaki et al. [6] reported an association between GNRI and ERI, while Yajima et al. [7] demonstrated that GNRI and ERI were also associated with cardiovascular mortality. Our results extend these observations by distinguishing two conceptually different sources of longitudinal association. The between-patient component represents whether patients with persistently poorer nutritional status have greater ESA hyporesponsiveness than patients with better nutritional status, whereas the within-patient component represents whether deviations from a patient's own usual nutritional status correspond to changes in ESA responsiveness. In the primary analysis, both components of GNRI were inversely associated with concurrent ERI. Thus, patients with lower average GNRI had higher ERI, and within the same patient, months with lower-than-usual GNRI were also associated with higher concurrent ERI.

Additional adjustment for calendar year did not materially alter the inverse associations of either GNRI component with concurrent ERI, although the within-patient coefficient was attenuated. The between-patient CRP association crossed the conventional significance threshold in the calendar-year-adjusted sensitivity analysis, whereas it was borderline in the primary model. This sensitivity to time adjustment warrants caution in interpreting the inflammatory association and highlights the potential influence of secular changes during follow-up.

The latter finding, however, requires cautious interpretation. ERI is a ratio-based measure that incorporates both hemoglobin and body weight, and Chait et al. [4] have raised important methodological concerns regarding the interpretation of ERI as a measure of ESA responsiveness. This issue is particularly relevant to the present study because GNRI also incorporates body weight. Consequently, changes in body weight can affect both GNRI and ERI and may strengthen an inverse association between the two indices even without a corresponding biological change in ESA requirement. We therefore performed a sensitivity analysis using weekly ESA dose as an alternative outcome, with hemoglobin and dry weight entered separately into the model. In contrast to the primary

ERI analysis, neither the between-patient nor the within-patient GNRI component was significantly associated with weekly ESA dose. Most importantly, the significant within-patient association between GNRI and ERI was not reproduced using this alternative outcome. These findings raise the possibility that the observed GNRI–ERI association, particularly its within-patient component, may be influenced by shared body-weight-related mathematical structure. However, the absence of a statistically significant association in the alternative-outcome analysis does not establish that the original association was entirely attributable to mathematical coupling.

The findings for inflammation showed a somewhat different pattern. Higher average CRP showed a borderline positive association with concurrent ERI at the between-patient level, whereas deviations in CRP from a patient's own average were not significantly associated with concurrent ERI. Chronic inflammation is a recognized contributor to ESA hyporesponsiveness through multiple pathways, including impaired iron availability and utilization and suppression of erythropoiesis [1–3]. Thus, the observed between-patient association is biologically plausible and consistent with previous studies of inflammation and ESA responsiveness. However, the absence of a significant within-patient association suggests that routine month-to-month changes in CRP do not necessarily correspond directly to concurrent changes in ESA responsiveness.

The temporal nature of ESA hyporesponsiveness is particularly relevant to interpretation of these findings. ESA hyporesponsiveness is not necessarily a fixed patient characteristic. Using international DOPPS data, Goodkin et al. [8] demonstrated that ESA hyporesponsiveness among patients receiving hemodialysis was frequently transient. Similarly, Gillespie et al. [9] used a case-crossover design to examine factors associated with transitions in ESA responsiveness, highlighting the dynamic nature of this clinical phenotype. These observations support the importance of moving beyond conventional between-patient comparisons and examining changes occurring within individual patients over time.

These findings should be interpreted alongside five earlier studies from overlapping clinical records. The iron-focused study examined iron indices and prior-month intravenous iron exposure [11], whereas the 24-month variability study associated albumin variability, summarized using a coefficient of variation, with mean ERI [12]. A coefficient of variation measures the magnitude of fluctuations and differs from the signed monthly within-patient deviations estimated here. In the inflammation/iron-availability study, prior-month CRP, but not same-month CRP, was associated with ERI [13]; differences from the present within-patient CRP findings may reflect distinct exposure definitions, temporal estimands, and adjustment sets. Two subsequently accepted studies evaluated the cumulative burden of low albumin and elevated CRP [14] and the concurrent count of low BMI, hypoalbuminemia, elevated CRP, and acute clinical events [15]. The latter also reported an association with weekly ESA dose, whereas the GNRI components in our alternative-outcome model were not statistically significant. These results are not directly interchangeable: the earlier studies used categorical cumulative measures of coexisting abnormalities, whereas the present study evaluates continuous between-patient means and signed within-patient deviations of GNRI and CRP. The current findings therefore provide a complementary analytical perspective, not independent validation of the earlier reports.

Karaboyas et al. [10] addressed this issue directly using a self-matched longitudinal design in DOPPS and showed that episodes of increased inflammation were accompanied by changes in anemia management and ESA response. Their findings provide important evidence that acute inflammatory changes can influence ESA responsiveness within individual patients. Our results do not contradict this possibility but suggest that the relationship may depend on how inflammatory exposure is defined and on the timing of measurements. Karaboyas et al. focused on discrete increases in CRP representing inflammatory events, whereas our within-patient component captured deviations in routinely measured monthly CRP across the observation period. Differences in the magnitude and duration of inflammatory exposure, measurement intervals, and study populations may therefore contribute to the differing findings.

Our lagged analysis provides additional information regarding temporal ordering. Current ERI was strongly associated with ERI at the subsequent monthly assessment, indicating substantial short-term persistence of ESA responsiveness. After accounting for current ERI, however, neither within-patient GNRI nor within-patient CRP was associated with subsequent ERI. In contrast, the between-patient components of both GNRI and CRP remained associated with subsequent ERI. Thus, although patients with persistently poorer nutritional status or greater inflammatory burden tended to exhibit higher ESA resistance over time, a short-term deterioration in GNRI or increase in CRP were not significantly associated with ERI at the next monthly assessment after adjustment for current ERI.

These findings suggest an important distinction between chronic patient-level characteristics and short-term time-varying changes. Persistent low GNRI and elevated CRP may identify a broader clinical phenotype characterized by protein-energy wasting, chronic inflammation, comorbidity, impaired iron utilization, or other factors associated with reduced ESA responsiveness. In contrast, short-term variation in a single nutritional or inflammatory marker may not be sufficient to explain changes in ESA requirement. This interpretation is consistent with the multifactorial framework of ESA hyporesponsiveness described in previous reviews [1, 3] and with evidence that ESA responsiveness itself can transition over time [8, 9].

The present findings also have implications for the clinical use of GNRI and ERI. GNRI remains a practical nutritional risk indicator in patients receiving maintenance hemodialysis, and its between-patient association with ERI supports its value in identifying patients with a greater overall clinical burden associated with ESA hyporesponsiveness [6, 7]. However, our results do not support interpreting short-term changes in GNRI as a direct surrogate for changes in ESA requirement. Similarly, ERI should not necessarily be regarded as a specific marker of a single underlying abnormality. Rather, persistent or changing ESA hyporesponsiveness should prompt reassessment of multiple potentially reversible factors, including nutritional status, inflammation, iron availability, and intercurrent clinical stress [1, 3]. In longitudinal studies in particular, investigators should consider whether exposure and outcome measures share mathematical components and, where possible, confirm findings using alternative outcome definitions.

Our findings suggest that associations between nutritional and inflammatory markers and ESA responsiveness should not be interpreted as uniform across patients, time scales, or outcome definitions. Although the observed GNRI–ERI associations may partly reflect mathematical coupling, distinguishing between-patient and within-patient components offers a complementary approach to understanding the heterogeneity of ESA hyporesponsiveness in longitudinal hemodialysis data.

Several limitations should be acknowledged. First, this was a retrospective, single-center study with a relatively small number of patients, which may limit generalizability and statistical power, particularly for within-patient inflammatory associations. Although the repeated-measures design provided a large number of patient-month observations, these observations were clustered within a limited number of individuals and therefore do not provide the same information as an equivalent number of independent participants. Second, residual confounding cannot be excluded. ESA responsiveness is influenced by multiple factors, and detailed information on all potential determinants, including comorbid disease burden, dialysis adequacy, occult or overt blood loss, severity of infectious or inflammatory events, and micronutrient abnormalities, was not incorporated into the present models. Third, GNRI is a composite index based on serum albumin and body weight. Both components may be influenced not only by nutritional status but also by inflammation, hydration status, and underlying illness; therefore, GNRI should be interpreted as a nutritional risk indicator rather than a direct measure of nutritional intake or body composition.

Fourth, ERI itself has important methodological limitations because it is a ratio incorporating ESA dose, hemoglobin, and body weight [4]. The shared body-weight component of GNRI and ERI creates the possibility of mathematical coupling. Although we addressed this issue by analyzing weekly ESA dose with hemoglobin and dry weight entered separately, this alternative outcome is also influenced by clinical treatment decisions and therefore does not provide a pure biological measure of ESA responsiveness. Fifth, the monthly measurement interval may not capture biological effects occurring over shorter time scales and may also be too short to detect some delayed effects of nutritional or inflammatory changes on erythropoiesis. The absence of a significant lagged within-patient association should therefore not be interpreted as evidence that changes in nutritional or inflammatory status have no biological effect on erythropoiesis. Finally, because of the observational design, neither the concurrent nor lagged associations can establish causality.

Declarations

Ethics approval and consent to participate

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Fuefuki Central Hospital (Approval No. Fuechu Rin 26 − 2; September 15, 2026). An opt-out approach was used for informed consent because of the retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

The author declares that there are no competing interests.

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Author Contribution

YI conceived and designed the study, collected and analyzed the data, interpreted the results, and drafted and revised the manuscript. The author read and approved the final manuscript.

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Availability of data and materials

The datasets supporting the findings of this study are available from the corresponding author upon reasonable request, subject to ethical and institutional restrictions. Individual-level patient data are not publicly available to protect patient confidentiality. De-identified aggregate results, analytic code, and methodological information may be made available to qualified researchers subject to institutional approval.

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Tables

Table 1

Baseline characteristics of the study population

Characteristic	Available n	Value
Age (years)	69	73.0 (62.0–80.0)
Male, n (%)	69	43 (62.3%)
Female, n (%)	69	26 (37.7%)
Dialysis vintage (months)	69	42 (5–91)
Hemoglobin (g/dL)	69	10.8 (10.2–11.5)
Weekly ESA dose (epoetin-equivalent IU/week)	69	9000 (4500–12000)
ESA resistance index	69	15.62 (7.95–20.97)
Transferrin saturation (%)	69	14 (11–20)
Ferritin (ng/mL)	69	58 (38–101)
Serum albumin (g/dL)	69	3.4 (3.1–3.6)
C-reactive protein (mg/dL)	69	0.11 (0.04–0.60)
Body mass index (kg/m²)	69	21.52 (19.64–24.05)
Dry weight (kg)	69	54.2 (45.0–63.5)
Geriatric nutritional risk index	69	90.14 (84.46–94.17)

Values are presented as median (interquartile range [IQR]) unless otherwise indicated. The analytic cohort included 69 patients after exclusion of one patient. ESA, erythropoiesis-stimulating agent; ERI, erythropoiesis-stimulating agent resistance index; GNRI, geriatric nutritional risk index.

Table 2

Between- and within-patient associations with concurrent ERI

Variable	β	95% CI	P value
GNRI, between-patient	-0.0273	-0.0437 to -0.0109	0.0014
GNRI, within-patient	-0.0159	-0.0205 to -0.0114	< 0.001
log(CRP + 1), between-patient	0.4361	-0.0019 to 0.8742	0.051
log(CRP + 1), within-patient	-0.0263	-0.0805 to 0.0278	0.340
TSAT	-0.0171	-0.0196 to -0.0147	< 0.001
Ferritin	-0.000518	-0.000780 to -0.000256	< 0.001
Physical stress	0.2331	0.1155 to 0.3506	< 0.001

Outcome: log(ERI + 1). Patient-specific random-intercept mixed-effects model including 69 patients and 2048 observations, adjusted for TSAT, ferritin, and physical stress. Between-patient and within-patient terms represent differences in patient means and deviations from patient means, respectively. Confidence intervals (CIs) were calculated using Satterthwaite degrees of freedom, consistent with lmerTest P values. β, regression coefficient; ERI, erythropoiesis-stimulating agent resistance index; GNRI, geriatric nutritional risk index; CRP, C-reactive protein; TSAT, transferrin saturation.

Table 3

Sensitivity analysis using weekly ESA dose as the outcome

Variable	β	95% CI	P value
GNRI, between-patient	0.0267	-0.0153 to 0.0686	0.209
GNRI, within-patient	-0.0045	-0.0159 to 0.0069	0.438
log(CRP + 1), between-patient	0.9997	-0.0383 to 2.0376	0.059
log(CRP + 1), within-patient	0.0364	-0.0929 to 0.1657	0.581
Hemoglobin	-0.0888	-0.1291 to -0.0485	< 0.001
Dry weight	-0.0398	-0.0535 to -0.0262	< 0.001
TSAT	-0.0245	-0.0305 to -0.0185	< 0.001
Ferritin	-0.002042	-0.002671 to -0.001413	< 0.001
Physical stress	0.4106	0.1303 to 0.6909	0.004

Outcome: log(weekly ESA dose + 1). Patient-specific random-intercept mixed-effects model including 69 patients and 2048 observations, adjusted for hemoglobin, dry weight, TSAT, ferritin, and physical stress. Between-patient and within-patient terms represent differences in patient means and deviations from patient means, respectively. Confidence intervals (CIs) were calculated using Satterthwaite degrees of freedom. β, regression coefficient; ESA, erythropoiesis-stimulating agent; GNRI, geriatric nutritional risk index; CRP, C-reactive protein; TSAT, transferrin saturation.

Table 4

Current nutritional and inflammatory status and subsequent ERI

Variable	β	95% CI	P value
Current log(ERI + 1)	0.9258	0.8903 to 0.9613	< 0.001
GNRI, between-patient	-0.0024	-0.0040 to -0.0008	0.003
GNRI, within-patient	0.0010	-0.0016 to 0.0036	0.461
log(CRP + 1), between-patient	0.0508	0.0106 to 0.0911	0.013
log(CRP + 1), within-patient	0.0182	-0.0128 to 0.0492	0.249
TSAT	0.0007	-0.0006 to 0.0019	0.308
Ferritin	0.000070	-0.000136 to 0.000276	0.507
Physical stress	0.0430	-0.0568 to 0.1427	0.398

Outcome: subsequent-month log(ERI + 1). Gaussian generalized estimating equations (GEE) with exchangeable working correlation and robust sandwich standard errors; 69 patients and 1921 eligible consecutive-month pairs (20–40 days apart). Confidence intervals (CIs) are 95% robust Wald intervals. Between-patient and within-patient terms represent differences in patient means and deviations from patient means, respectively. β, regression coefficient; ERI, erythropoiesis-stimulating agent resistance index; GNRI, geriatric nutritional risk index; CRP, C-reactive protein; TSAT, transferrin saturation.

Figures

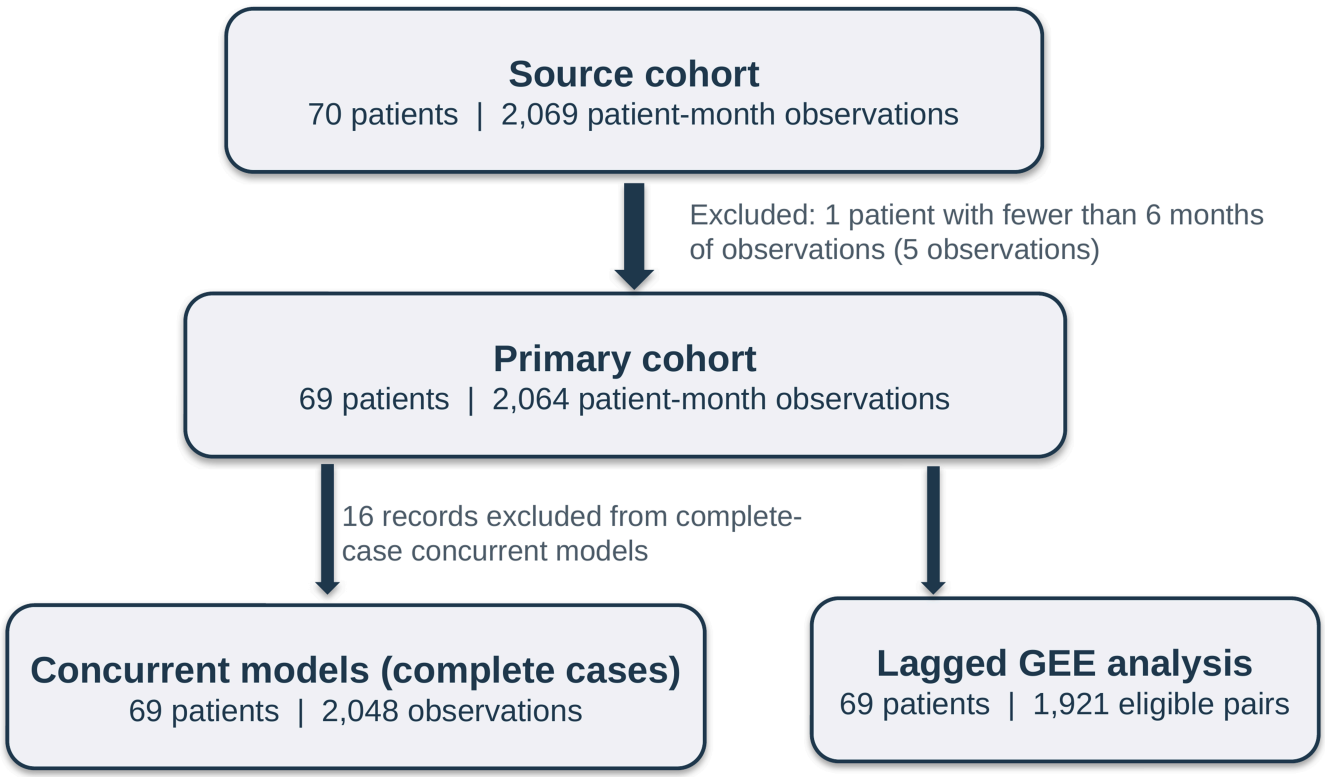


Figure 1

Flowchart of cohort selection and analysis populations.

The source cohort comprised 70 patients receiving maintenance hemodialysis, contributing 2,069 patient-month observations during the 36-month study period (January 2023 to December 2025). One patient with fewer than 6 months of available observations (5 patient-month observations) was excluded, leaving 69 patients and 2,064 patient-month observations in the primary cohort. After exclusion of 16 observations with missing data for variables required in the concurrent models, 2,048 observations from 69 patients were included in the primary ERI and alternative weekly ESA-dose analyses. The subsequent-month analysis included 1,921 eligible consecutive-month pairs from 69 patients, with pairs defined by an interval of 20–40 days between observations.

ERI, erythropoiesis resistance index; ESA, erythropoiesis-stimulating agent.

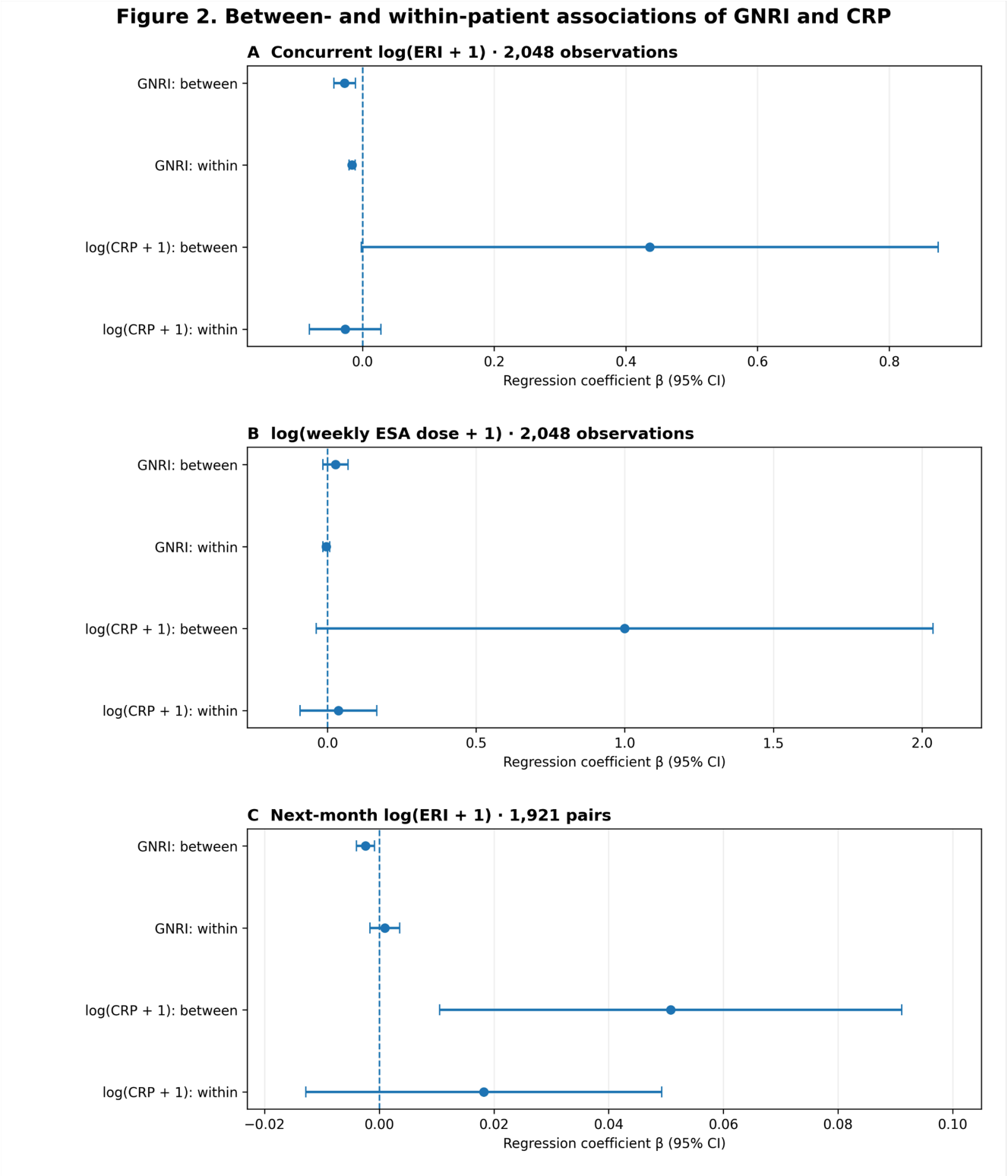


Figure 2

Between- and within-patient associations of GNRI and CRP with ESA responsiveness.

Points indicate regression coefficients (β), and horizontal error bars represent 95% confidence intervals (CIs). Dashed vertical lines indicate zero.

(A) Concurrent log(ERI + 1), estimated using a patient-specific random-intercept linear mixed-effects model (2,048 observations).

(B) Concurrent log(weekly ESA dose + 1), estimated using a patient-specific random-intercept linear mixed-effects model additionally adjusted for hemoglobin and dry weight (2,048 observations).

(C) Next-month log(ERI + 1), estimated using Gaussian generalized estimating equations adjusted for current log(ERI + 1) (1,921 eligible consecutive-month pairs).

All models included transferrin saturation, ferritin, and physical stress as covariates. Between-patient components represent patient-specific means, whereas within-patient components represent deviations from these means. For panels A and B, 95% CIs were calculated using t-distribution critical values with Satterthwaite degrees of freedom. For panel C, robust Wald 95% CIs were used. Horizontal-axis scales differ among panels.

GNRI, geriatric nutritional risk index; CRP, C-reactive protein; ERI, erythropoiesis resistance index; ESA, erythropoiesis-stimulating agent.

Supplementary Files

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- SupplementaryTableS1BMC.docx