

Albumin Variability and Biological Instability Associated With ESA Hyporesponsiveness in Maintenance Hemodialysis Patients

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Research Article

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Abstract

Introduction

Erythropoiesis-stimulating agent (ESA) hyporesponsiveness is common in hemodialysis (HD) patients and is associated with adverse outcomes. Although studies have focused on absolute laboratory values, the clinical significance of biological variability remains unclear. We investigated whether biological instability is associated with ESA hyporesponsiveness and subsequent deterioration in ESA responsiveness.

Methods

This retrospective longitudinal study included 52 HD patients followed for 24 months (2024–2025). Monthly measurements of hemoglobin (Hb), transferrin saturation (TSAT), ferritin, albumin, and C-reactive protein (CRP) were collected. Biological variability was quantified using coefficients of variation (CVs). ESA responsiveness was assessed by the erythropoiesis resistance index (ERI). An exploratory Hematologic Instability Score was generated by assigning one point for each variability measure within the highest tertile.

Results

A total of 1,248 patient-month observations were analyzed. Albumin-CV showed the strongest association with mean ERI ($\rho = 0.521$, $p < 0.001$), followed by Hb-CV ($\rho = 0.378$, $p = 0.0057$). In multivariable analyses including variability measures, Albumin-CV remained independently associated with ERI ($\beta = 2.455$, $p = 0.049$). The Hematologic Instability Score correlated with mean ERI ($\rho = 0.339$, $p = 0.014$), and patients with scores ≥ 3 had significantly higher ERI than those with lower scores (21.32 vs. 13.20, $p = 0.0032$). Early instability scores were also associated with subsequent ERI ($\rho = 0.414$, $p = 0.0023$). Albumin-CV remained independently associated with ERI after adjustment for mean albumin, age, dialysis vintage, and CRP ($\beta = 0.737$, $p = 0.036$).

Conclusion

Albumin variability was the strongest and only independent variability marker associated with ESA hyporesponsiveness. These findings suggest that albumin variability may serve as a clinically useful marker of biological instability associated with ESA hyporesponsiveness in HD patients.

Introduction

Anemia remains a major complication in patients undergoing maintenance hemodialysis (HD), despite substantial advances in erythropoiesis-stimulating agent (ESA) therapy. ESA hyporesponsiveness is

common in HD patients and is associated with increased hospitalization, cardiovascular events, and mortality [1–3]. Because reduced responsiveness to ESA therapy often reflects complex interactions among inflammation, nutritional impairment, iron dysregulation, and comorbid illness, the mechanisms underlying ESA resistance remain incompletely understood [1–3, 11–13].

Traditionally, investigations of ESA hyporesponsiveness have focused on absolute or average values of hemoglobin, transferrin saturation (TSAT), ferritin, C-reactive protein (CRP), and serum albumin [1–3]. Although these measurements provide important information regarding iron availability, inflammatory burden, and nutritional status, they may not adequately capture the dynamic fluctuations that frequently occur in patients receiving long-term HD.

In routine clinical practice, some HD patients maintain relatively stable hematologic and biochemical profiles over time, whereas others exhibit repeated fluctuations in hemoglobin concentration, iron-related parameters, inflammatory markers, and nutritional indices despite similar average laboratory values. Such instability may reflect reduced physiological resilience and increased vulnerability to erythropoietic decompensation. Consequently, biological variability may provide clinically relevant information beyond conventional cross-sectional measurements.

Previous studies have demonstrated associations between hemoglobin variability and adverse clinical outcomes in HD patients [4–6]. Variability in ferritin, TSAT, CRP, and albumin may similarly reflect dynamic changes in iron metabolism, inflammatory activity, nutritional status, intercurrent illness, blood loss, and fluid balance [7–13]. Among these factors, fluctuations in serum albumin may be particularly informative because albumin integrates multiple physiological domains, including nutrition, inflammation, catabolic stress, and overall health status [7–10]. Therefore, albumin variability may serve as a marker of biological instability and impaired physiological resilience.

Recent concepts in chronic disease management have emphasized the importance of vulnerability and resilience rather than isolated abnormalities in individual biomarkers. From this perspective, ESA hyporesponsiveness may represent a broader phenotype of hematologic vulnerability characterized by instability across multiple biological domains. Emerging evidence suggests that inflammation, aging, and impaired hematopoietic reserve may contribute to reduced biological resilience and vulnerability of the hematopoietic system [14–16]. However, the clinical significance of temporal variability in hematologic, nutritional, inflammatory, and iron-related parameters remains poorly understood in maintenance HD patients.

We therefore evaluated the relationships between temporal variability in hematologic, iron-related, inflammatory, and nutritional parameters and ESA responsiveness in maintenance HD patients. We also examined whether cumulative biological instability was associated with subsequent deterioration in ESA responsiveness. We hypothesized that greater biological instability, particularly instability in nutritional status, would be associated with higher erythropoiesis resistance index (ERI), reflecting increased hematologic vulnerability in maintenance HD patients.

Methods

Study Design and Participants

This retrospective longitudinal observational study was conducted in maintenance hemodialysis (HD) patients at a single dialysis center.

During the study period, 57 maintenance hemodialysis patients were treated at our dialysis center. Seven patients initiated hemodialysis during the observation period. Four newly initiated patients were excluded because sufficient longitudinal data for variability analyses were not available. Three newly initiated patients with at least 21 months of follow-up data were included in the analyses. In addition, one patient receiving a hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor was excluded because ESA doses could not be converted to epoetin-equivalent units. The final study cohort consisted of 52 patients.

The study protocol was approved by the institutional ethics committee and conducted in accordance with the Declaration of Helsinki.

Data Collection

Monthly clinical and laboratory data were extracted from electronic medical records and dialysis charts during the 24-month observation period from January 2024 to December 2025.

Collected variables included:

- Hemoglobin (Hb, g/dL)
- ESA dose (epoetin-equivalent units/week)
- Transferrin saturation (TSAT, %)
- Ferritin (ng/mL)
- Serum albumin (g/dL)
- C-reactive protein (CRP, mg/dL)
- Body weight
- Intravenous iron administration

ESA dose (IU/week), including epoetin alfa or darbepoetin alfa; doses were converted to epoetin equivalents ($1 \mu\text{g}$ darbepoetin alfa $\approx$ 200 IU epoetin), based on previously published conversion methods [19].

Definition of ESA Hyporesponsiveness

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

ERI = weekly ESA dose / body weight (kg) / hemoglobin (g/dL)

Higher ERI values indicate reduced responsiveness to ESA therapy.

For each patient, mean ERI during the observation period was calculated and used as the primary measure of ESA hyporesponsiveness.

Assessment of Biological Variability

To quantify temporal instability, intra-individual variability was assessed using the coefficient of variation (CV):

$CV (\%) = \text{standard deviation} / \text{mean} \times 100$

Variability measures were calculated using monthly measurements obtained throughout the observation period for:

- Hemoglobin (Hb-CV)

- **TSAT (TSAT-CV)**

- • Ferritin (Ferritin-CV)
- • Albumin (Albumin-CV)

- **CRP (CRP-CV)**

Because temporal variability may reflect reduced physiological resilience and impaired biological stability, these variability measures were evaluated as indicators of biological instability across hematologic, nutritional, inflammatory, and iron-related domains. Particular attention was paid to albumin variability because serum albumin integrates multiple physiological processes, including nutritional status, inflammation, catabolic stress, and overall health condition.

Hematologic Instability Score

To evaluate cumulative instability across multiple biological domains, an exploratory Hematologic Instability Score was constructed.

For each variability measure (Hb-CV, TSAT-CV, Ferritin-CV, Albumin-CV, and CRP-CV), patients in the highest tertile of variability received one point. The total score ranged from 0 to 5, with higher scores indicating greater overall instability.

Because this score has not been previously validated, analyses involving the score were considered exploratory and hypothesis-generating.

Primary Analysis

The primary analysis evaluated associations between biological variability measures and mean ERI during the 24-month observation period from January 2024 to December 2025.

Spearman correlation coefficients were calculated to assess associations between:

- Hb-CV

- **TSAT-CV**

- • Ferritin-CV
- • Albumin-CV

- **CRP-CV**

- Hematologic Instability Score

and mean ERI.

To identify the variability measure most strongly associated with ESA hyporesponsiveness, a multivariable linear regression model was constructed including Hb-CV, TSAT-CV, Ferritin-CV, Albumin-CV, and CRP-CV simultaneously. Mean ERI was used as the dependent variable.

Temporal Analyses

To explore whether biological instability preceded ESA hyporesponsiveness, temporal analyses were performed at two different time scales.

For short-term analyses, the 2025 observation period was divided into two consecutive six-month intervals:

- • Early period: January–June 2025
- • Late period: July–December 2025

Variability measures and Hematologic Instability Scores were calculated during the early period and compared with mean ERI during the subsequent late period.

For longer-term analyses, variability measures calculated during 2024 were compared with mean ERI during 2025. This analysis was performed to evaluate whether biological instability was associated with future ESA responsiveness over a longer time horizon.

Statistical Analysis

Continuous variables are presented as mean $\pm$ standard deviation or median (interquartile range), as appropriate.

Correlations were evaluated using Spearman rank correlation coefficients.

Group comparisons were performed using Student's t-test or the Mann–Whitney U test, as appropriate.

Multivariable linear regression analyses were used to identify independent associations with mean ERI.

All statistical tests were two-sided, and a p value < 0.05 was considered statistically significant.

Because analyses involving the Hematologic Instability Score and temporal prediction models were exploratory, results were interpreted as hypothesis-generating.

Statistical analyses were performed using R version 4.5.2

In the present study, hematologic instability was defined a priori as increased temporal variability across hematologic, nutritional, inflammatory, and iron-related parameters. This construct was intended to reflect reduced biological stability and increased vulnerability of the erythropoietic system in maintenance HD patients.

Results

Study Population

A total of 52 maintenance hemodialysis patients were included in the final analysis. During the study period, 57 patients received maintenance hemodialysis at our center. Among seven patients who initiated hemodialysis during the observation period, four were excluded because of insufficient follow-up data for variability analyses, whereas three patients with at least 21 months of follow-up were included. One patient receiving a HIF-PH inhibitor was excluded. The final dataset comprised 1,248 patient-month observations collected during the 24-month observation period.

Baseline patient characteristics are summarized in Table 1.

Table 1
Baseline characteristics of the study population (n = 52)

Variable	Value
Age, years	71.6 ± 12.6
Male sex, n (%)	28 (53.8)
Dialysis vintage, months	91.9 ± 60.3
Hemoglobin, g/dL	10.8 ± 1.3
ESA dose, U/week	8,481 ± 4,674
ERI	15.6 ± 11.8
Intravenous iron administration, mg/month	44.6 ± 66.1
TSAT, %	18.1 ± 8.1
Ferritin, ng/mL	58 (31–122)
Albumin, g/dL	3.33 ± 0.51
CRP, mg/dL	0.08 (0.02–0.39)
Dry weight, kg	55.8 ± 17.9

Associations Between Biological Variability and ESA Hyporesponsiveness

To evaluate whether ESA hyporesponsiveness was associated with temporal biological instability, variability measures were calculated using monthly measurements obtained during the 24-month observation period.

Among all variability measures examined, Albumin-CV demonstrated the strongest association with mean ERI (Spearman $\rho = 0.521$, $p < 0.001$) (Fig. 1). Hb-CV was also significantly associated with ERI ($\rho = 0.378$, $p = 0.0057$), whereas Ferritin-CV and TSAT-CV showed weaker associations.

These findings indicate that ESA hyporesponsiveness was more strongly associated with instability in nutritional status than with variability in iron-related parameters alone (Table 2).

Table 2
Associations between biological variability measures and mean erythropoiesis resistance index (ERI)

Variable	Spearman ρ	p value
Hb-CV	0.378	0.0057
TSAT-CV	0.241	0.085
Ferritin-CV	0.196	0.164
Albumin-CV	0.521	< 0.001
CRP-CV	0.177	0.209
Hematologic Instability Score	0.339	0.014

Multivariable Analyses (Table 3)

Table 3
Multivariable linear regression analysis of biological variability measures associated with mean erythropoiesis resistance index (ERI)

Variable	β coefficient	95% Confidence Interval	p value
Hb-CV	1.324	-0.842 to 3.490	0.225
TSAT-CV	0.083	-0.092 to 0.258	0.343
Ferritin-CV	0.021	-0.034 to 0.076	0.447
Albumin-CV	2.455	0.007 to 4.903	0.049
CRP-CV	0.004	-0.008 to 0.016	0.521
Model statistics:			
$R^2 = 0.37$ Adjusted $R^2 = 0.30$ Overall model p = 0.002			
Dependent variable: Mean erythropoiesis resistance index (ERI).			

Multivariable linear regression analyses were performed to identify independent associations between variability measures and mean ERI.

When Hb-CV, TSAT-CV, Ferritin-CV, Albumin-CV, and CRP-CV were simultaneously entered into the model, Albumin-CV remained independently associated with mean ERI ($\beta = 2.455$, 95% CI 0.007–4.903, $p = 0.049$).

Although Hb-CV demonstrated a positive association with ERI in univariate analyses, its statistical significance was attenuated after adjustment. No independent associations were observed for TSAT-CV, Ferritin-CV, or CRP-CV.

Among all variability measures examined, Albumin-CV was the only variable independently associated with ESA hyporesponsiveness.

Exploratory Long-Term Analysis

To assess whether biological instability preceded subsequent ESA hyporesponsiveness, variability measures calculated during 2024 were compared with mean ERI during 2025.

Albumin-CV demonstrated a significant association with subsequent ERI in univariate analyses ($\rho = 0.393$, $p = 0.0044$). In contrast, the Hematologic Instability Score did not demonstrate a significant long-term association with ERI.

Independent Association Between Albumin Variability and ESA Hyporesponsiveness

To further evaluate the independent association between albumin variability and ESA hyporesponsiveness, an exploratory multivariable regression model was constructed including Albumin-CV, mean albumin, mean CRP, age, and dialysis vintage. In this model, Albumin-CV remained independently associated with mean ERI ($\beta = 0.737$, 95% CI 0.049–1.425, $p = 0.036$), whereas mean albumin, age, dialysis vintage, and CRP were not independently associated with ERI (Supplementary Table 1).

These findings suggest that temporal instability in albumin provides clinically relevant information beyond absolute albumin levels and may reflect a distinct dimension of biological instability associated with ESA hyporesponsiveness.

Hematologic Instability Score

To evaluate cumulative instability across multiple biological domains, an exploratory Hematologic Instability Score was constructed using Hb-CV, TSAT-CV, Ferritin-CV, Albumin-CV, and CRP-CV.

The Hematologic Instability Score was positively correlated with mean ERI during the 24-month observation period ($\rho = 0.339$, $p = 0.014$).

Patients with an instability score ≥ 3 exhibited substantially higher mean ERI than those with lower scores (21.32 vs. 13.20, $p = 0.0032$) (Fig. 2).

These findings suggest that cumulative instability across hematologic, nutritional, inflammatory, and iron-related domains is associated with reduced ESA responsiveness.

Short-Term Temporal Analysis

To further explore temporal relationships, variability measures calculated during January–June 2025 were compared with mean ERI during July–December 2025.

Hb-CV during the first six months was significantly associated with subsequent ERI ($\rho = 0.445$, $p = 0.001$). Similarly, the Hematologic Instability Score demonstrated a significant positive association with subsequent ERI ($\rho = 0.414$, $p = 0.0023$).

Patients with an instability score ≥ 3 during the first six months exhibited higher ERI during the subsequent six months compared with patients with lower scores (21.39 vs. 13.15, $p = 0.0030$) (Fig. 3).

These findings suggest that short-term biological instability may precede worsening ESA responsiveness.

Summary of Findings

Among all biological variability measures examined, Albumin-CV demonstrated the strongest association with ESA hyporesponsiveness and was the only variability measure independently associated with concurrent ERI after multivariable adjustment. Furthermore, albumin variability remained independently associated with ERI after adjustment for mean albumin, age, dialysis vintage, and inflammatory status. In addition, cumulative instability across multiple biological domains, as reflected by the Hematologic Instability Score, was associated with higher ERI and short-term deterioration in ESA responsiveness. These findings suggest that ESA hyporesponsiveness may reflect a broader phenotype of biological instability and hematologic vulnerability in maintenance HD patients.

Discussion

The present study evaluated whether temporal variability in hematologic, iron-related, inflammatory, and nutritional parameters was associated with ESA hyporesponsiveness in maintenance hemodialysis (HD) patients. The principal finding was that albumin variability demonstrated the strongest association with ESA hyporesponsiveness among all biological variability measures examined and remained independently associated with concurrent ERI after multivariable adjustment. In addition, a cumulative Hematologic Instability Score was associated with higher ERI and short-term deterioration in ESA responsiveness. These findings suggest that ESA hyporesponsiveness may reflect a broader phenotype of biological instability and hematologic vulnerability rather than isolated abnormalities in iron availability alone.

ESA hyporesponsiveness is traditionally attributed to iron deficiency, inflammation, blood loss, inadequate dialysis, malnutrition, and comorbid illness [1–3, 11–13]. Most previous studies have focused on absolute or average values of hemoglobin, TSAT, ferritin, CRP, and albumin [1–3]. Although these measurements provide valuable information regarding iron availability and clinical status, patients receiving maintenance HD are repeatedly exposed to physiological stressors including infection, hospitalization, nutritional deterioration, volume fluctuations, and changes in iron administration. Such factors create a dynamic biological environment that may not be adequately captured by single laboratory measurements. Our findings suggest that temporal variability may provide clinically relevant information beyond conventional cross-sectional biomarkers.

Among the individual variability measures, albumin variability demonstrated the strongest association with ERI. This observation is notable because serum albumin integrates multiple physiological processes, including nutritional status, inflammation, fluid balance, catabolic stress, and intercurrent illness [7–10]. Consequently, fluctuations in albumin may represent a marker of reduced biological resilience rather than nutritional impairment alone.

Importantly, the association between albumin variability and ESA hyporesponsiveness remained significant after adjustment for mean albumin, age, dialysis vintage, and inflammatory status. This finding suggests that temporal instability in albumin provides information beyond absolute albumin levels and may reflect a distinct dimension of biological vulnerability. In maintenance HD patients, repeated fluctuations in albumin may indicate reduced physiological resilience and increased susceptibility to erythropoietic dysfunction, even when average nutritional status appears relatively preserved.

Hemoglobin variability was also significantly associated with ERI and with subsequent ESA hyporesponsiveness in the six-month temporal analyses. Previous studies have reported associations between hemoglobin variability and adverse clinical outcomes in HD patients [4–6]. The present findings extend these observations by suggesting that increased hemoglobin variability may identify patients with reduced biological stability of erythropoiesis. Importantly, early hemoglobin instability was associated with later ERI, raising the possibility that instability may emerge before clinically overt deterioration of ESA responsiveness becomes apparent.

In contrast, TSAT variability was not independently associated with ERI after adjustment. Several explanations are possible. TSAT is influenced by recent iron administration, timing of blood sampling, nutritional status, and short-term biological fluctuations [1, 11–13]. Consequently, TSAT variability may contain substantial random variation that limits its ability to reflect clinically meaningful instability. Alternatively, iron availability alone may be insufficient to explain ESA hyporesponsiveness in many HD patients. The stronger associations observed for albumin variability, hemoglobin variability, and the cumulative instability score support a broader multidimensional model of ESA hyporesponsiveness.

An important finding was that instability measures calculated during the first six months were associated with ERI during the subsequent six months. Although causality cannot be established in this observational study, these findings suggest that biological instability may precede deterioration in ESA responsiveness. From a clinical perspective, repeated fluctuations in hemoglobin, albumin, ferritin, and inflammatory markers may represent early warning signals of emerging erythropoietic dysfunction rather than simply reflecting established anemia.

The present findings may also have practical clinical implications. In routine dialysis care, anemia management is generally guided by absolute laboratory values such as hemoglobin, TSAT, ferritin, CRP, and albumin. However, our results suggest that temporal variability, particularly albumin variability, may provide complementary information regarding biological resilience and vulnerability that is not captured by single measurements. Patients demonstrating increased albumin variability or elevated Hematologic

Instability Scores may warrant closer evaluation for occult inflammation, nutritional deterioration, recurrent illness, or other factors contributing to impaired erythropoiesis. Variability-based assessment may therefore help identify biologically vulnerable patients before overt ESA hyporesponsiveness becomes clinically apparent.

The concept of hematologic vulnerability may provide a useful framework for understanding ESA hyporesponsiveness in maintenance HD patients. Rather than representing a static disorder attributable to a single abnormal laboratory value, ESA hyporesponsiveness may reflect a state of reduced biological resilience characterized by instability across multiple interacting physiological domains. In this model, nutritional instability, inflammation, iron dysregulation, and physiological stress collectively contribute to an unstable erythropoietic state, which subsequently manifests as increased ESA requirements and impaired hemoglobin maintenance. Recent studies highlighting interactions among inflammation, aging, clonal hematopoiesis, and impaired hematopoietic reserve provide biological support for this framework [14–16] (Fig. 4).

These observations may also help explain the heterogeneous clinical presentations observed in vulnerable dialysis patients. Previous reports have described ESA-resistant anemia associated with copper deficiency, severe infection, nutritional deterioration, and marrow abnormalities mimicking myelodysplastic syndrome [17, 18]. Although the underlying mechanisms differ, these conditions may share a common feature of impaired biological resilience and instability of erythropoietic regulation. Longitudinal variability measures may therefore identify vulnerable patients before overt clinical decompensation becomes apparent.

Incorporation of longitudinal variability measures into routine dialysis care may help identify patients at risk for future ESA hyporesponsiveness.

Several limitations should be acknowledged. First, this was a single-center retrospective study with a relatively small sample size. Second, residual confounding cannot be excluded because detailed information regarding hospitalization, infection episodes, occult blood loss, and other clinical stressors was not available for all patients. Third, ESA dose adjustment and iron administration may themselves influence variability measures. Fourth, hepcidin and other regulators of iron metabolism were not evaluated. Finally, the Hematologic Instability Score was exploratory and has not been externally validated. Therefore, the present findings should be considered hypothesis-generating.

In conclusion, albumin variability demonstrated the strongest association with ESA hyporesponsiveness among the biological variability measures examined and remained independently associated with ERI after adjustment for clinical covariates. Biological instability across nutritional, inflammatory, hematologic, and iron-related domains was associated with impaired ESA responsiveness and short-term deterioration in erythropoietic function. These findings suggest that albumin variability may serve as a clinically useful marker of biological instability associated with ESA hyporesponsiveness in HD patients. Future multicenter studies are warranted to validate variability-based measures and determine

whether early identification of biologically vulnerable patients can facilitate targeted interventions before overt ESA hyporesponsiveness develops.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to ethical restrictions and institutional regulations, individual-level patient data cannot be publicly shared. De-identified aggregate data, analytic code for risk score calculation, and detailed methodological information are available to qualified researchers for the purpose of reproducing the results reported in this article.

Reporting Checklist Statement (STROBE)

This study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The completed STROBE checklist is provided as Supplementary Material.

Declarations

Conflicts of Interest

The authors declare that they have no conflicts of interest related to this work.

Ethics Approval

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. Fuefuki Rin 25 – 10; January 10, 2026). Written informed consent was obtained from all participants prior to inclusion in the study. Patient data were anonymized before analysis.

A multivariable linear regression analysis was performed using mean ERI as the dependent variable. Independent variables included Albumin-CV, mean serum albumin, age, dialysis vintage, and mean C-reactive protein (CRP). Albumin variability remained independently associated with mean ERI after adjustment for nutritional status, inflammatory status, age, and dialysis vintage, suggesting that temporal instability in albumin provides information beyond absolute albumin levels.

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Author Contribution

Y.I wrote the main manuscript text and prepared figures and tables.

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Figures

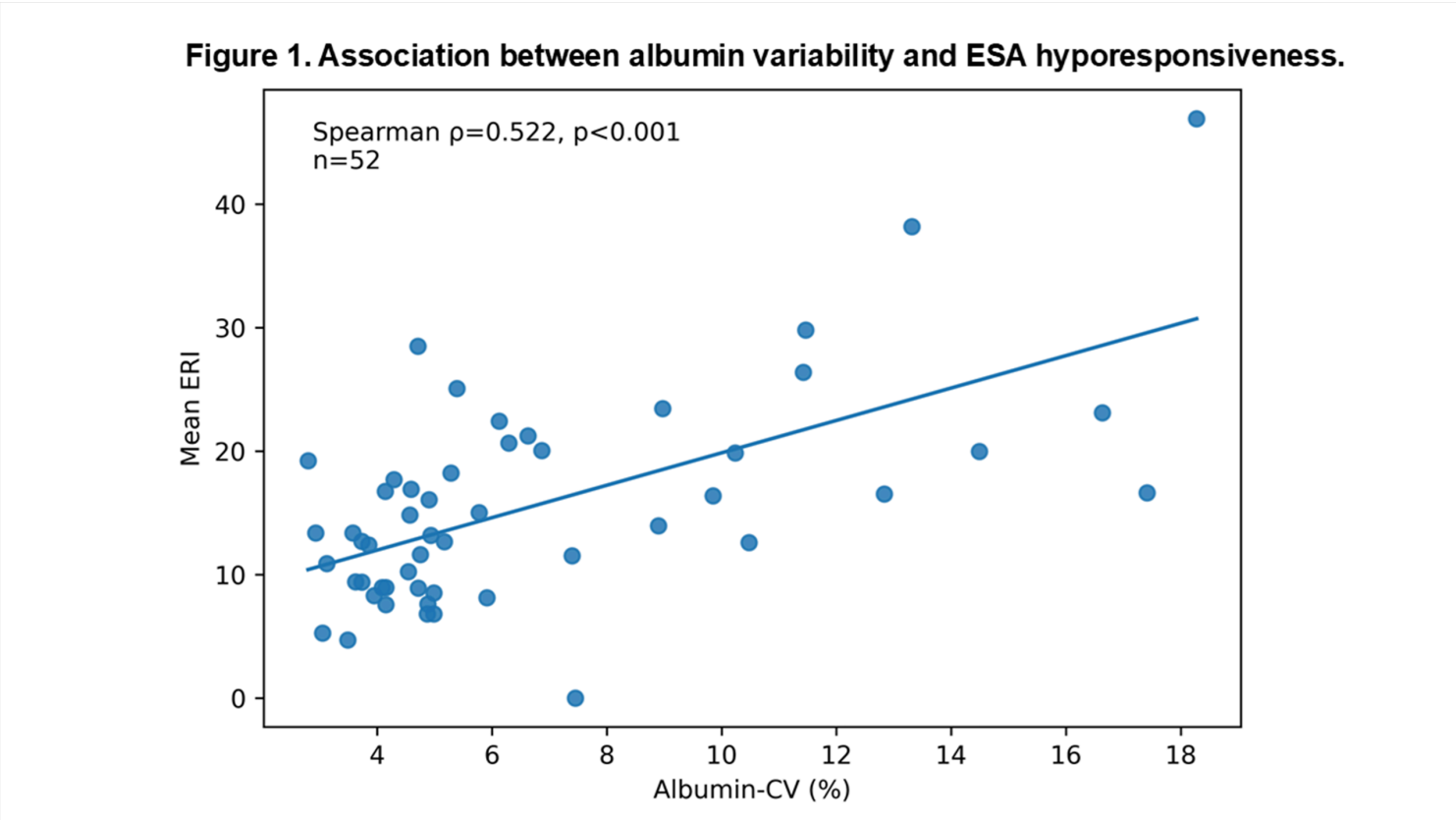


Figure 1

Association between albumin variability and ESA hyporesponsiveness.

Scatter plot showing the relationship between the coefficient of variation of serum albumin (Albumin-CV) and mean erythropoiesis resistance index (ERI) during the 24-month observation period in 52 maintenance hemodialysis patients. Albumin-CV demonstrated the strongest association with mean ERI among all variability measures examined (Spearman $\rho = 0.521$, $p < 0.001$). Higher albumin variability was associated with greater ESA hyporesponsiveness.

Figure 2. Mean ERI according to Hematologic Instability Score.

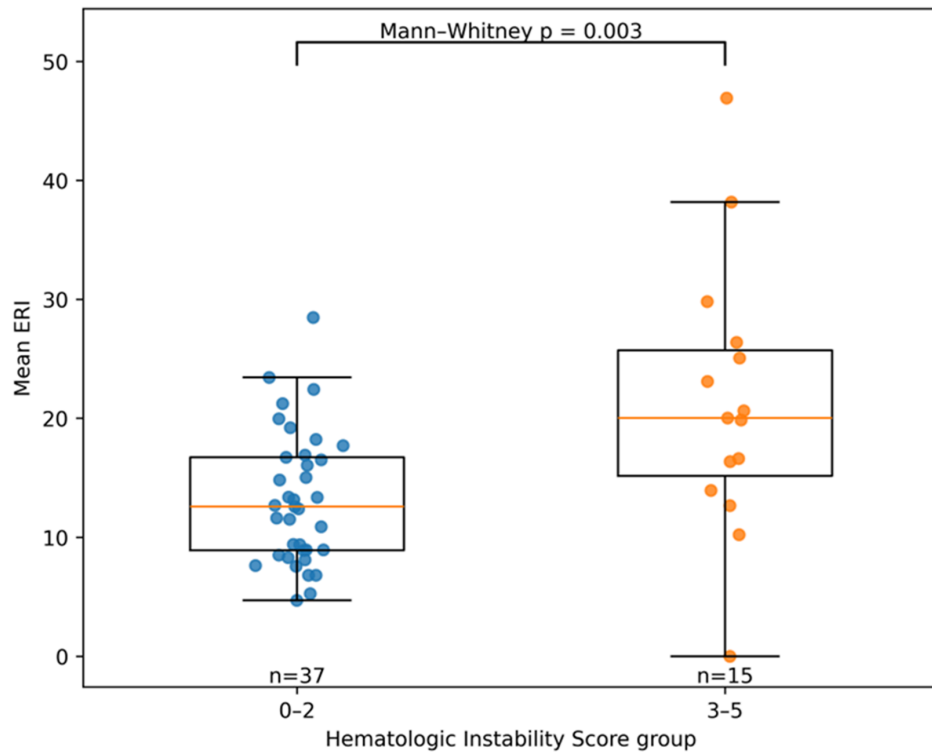


Figure 2

Mean ERI according to Hematologic Instability Score.

Comparison of mean erythropoiesis resistance index (ERI) between patients with low instability scores (0–2) and high instability scores (3–5). The Hematologic Instability Score was calculated using variability measures of hemoglobin, transferrin saturation, ferritin, serum albumin, and C-reactive protein. Patients with higher instability scores exhibited significantly greater ESA hyporesponsiveness (21.32 vs. 13.20, $p = 0.0032$).

Figure 3. Association between early biological instability and subsequent ESA hyporesponsiveness.

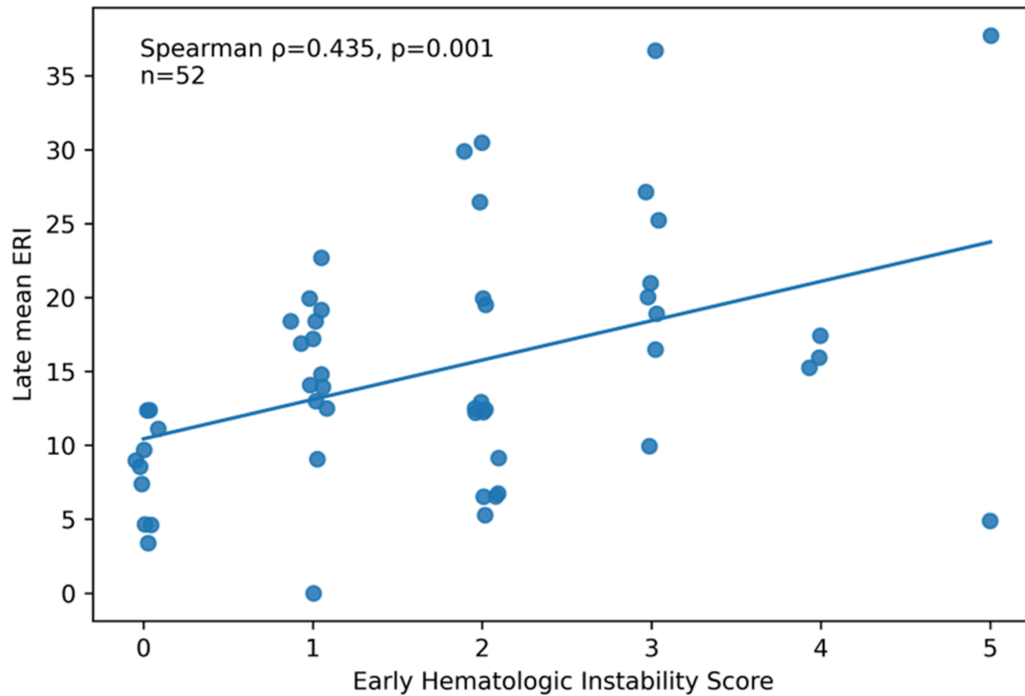


Figure 3

Association between early biological instability and subsequent ESA hyporesponsiveness.

Relationship between Hematologic Instability Score calculated during January–June 2025 and mean erythropoiesis resistance index (ERI) during July–December 2025. Patients with higher instability scores during the first six months exhibited significantly higher ERI during the subsequent six months (21.39 vs. 13.15, $p = 0.0030$). These findings suggest that biological instability may precede deterioration in ESA responsiveness.

Figure 4. Proposed conceptual framework of biological instability and hematologic vulnerability in maintenance hemodialysis patients.

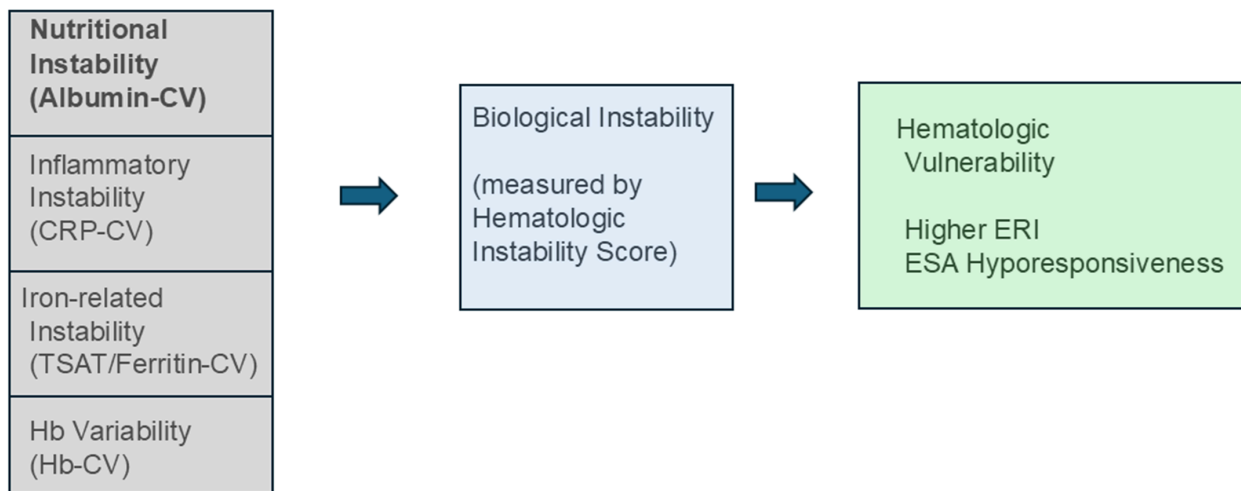


Figure 4

Proposed conceptual framework of biological instability and hematologic vulnerability in maintenance hemodialysis patients.

Variability in nutritional, inflammatory, iron-related, and hematologic parameters may collectively contribute to biological instability. This unstable state may manifest clinically as hematologic vulnerability, characterized by impaired responsiveness to erythropoiesis-stimulating agents (ESAs). Among the variability measures examined, albumin variability demonstrated the strongest association with erythropoiesis resistance index (ERI).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTable1.docx](#)