Research Square

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Longitudinal Association Between Hemoglobin A1c and Erythropoietin Responsiveness in Patients With Diabetes Receiving Maintenance Hemodialysis

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Research Article

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Abstract

Introduction

HbA1c may underestimate glycemic exposure in patients receiving maintenance hemodialysis because erythrocyte turnover is affected by renal anemia and erythropoiesis-stimulating agent (ESA) therapy. We examined whether longitudinal changes in ESA responsiveness were associated with HbA1c independently of measured blood glucose.

Methods

This retrospective longitudinal study included 38 patients with diabetes receiving maintenance hemodialysis, contributing 1,149 repeated observations. Three-observation rolling means of blood glucose and the erythropoietin resistance index (ERI) were decomposed into within-patient and between-patient components. Linear mixed-effects models with patient-specific random intercepts evaluated associations with HbA1c.

Results

Within-patient increases in three-observation rolling mean blood glucose were positively associated with HbA1c (β = 0.0102, 95% CI 0.0093 to 0.0111, P < 0.001). In contrast, within-patient increases in ERI were associated with lower HbA1c after adjustment for measured blood glucose and other covariates (β = −0.0284, 95% CI − 0.0348 to − 0.0220, P < 0.001), whereas the between-patient ERI component was not significant (β = 0.0047, 95% CI − 0.0276 to 0.0370, P = 0.776). The within-patient association remained consistent across multiple sensitivity analyses.

Conclusion

In patients with diabetes receiving maintenance hemodialysis, within-patient increases in ERI were associated with lower HbA1c after adjustment for routinely measured blood glucose, whereas between-patient differences in ERI were not. Temporal variation in ESA responsiveness may provide additional context when interpreting serial HbA1c values. Because continuous glucose monitoring was not performed, independence from actual glycemic exposure could not be established.

Introduction

Glycated hemoglobin (HbA1c) is widely used as a marker of long-term glycemic control in patients with diabetes; however, its interpretation is challenging in patients undergoing maintenance hemodialysis (HD). Renal anemia, erythropoiesis-stimulating agent (ESA) therapy, iron administration, blood

transfusion, and shortened erythrocyte lifespan may alter HbA1c independently of glucose concentrations [1–4].

Recent studies using continuous glucose monitoring (CGM) have further demonstrated discrepancies between HbA1c and directly measured glycemia in patients receiving dialysis [5, 6]. Accordingly, HbA1c in patients with advanced chronic kidney disease and kidney failure should be interpreted in the context of complementary glycemic information, including direct glucose measurements and CGM-derived metrics [7–10].

ESA treatment can influence HbA1c through changes in erythropoiesis and erythrocyte turnover [2, 4]. However, it remains unclear whether temporal changes in ESA responsiveness within the same patient are associated with corresponding changes in HbA1c after accounting for measured blood glucose. The erythropoietin resistance index (ERI), which incorporates ESA dose, body weight, and hemoglobin concentration, is commonly used as an index of ESA responsiveness in patients receiving HD [11]. Because ERI varies over time, distinguishing within-patient changes in ERI from persistent differences in ERI between patients may provide insight into whether changes in erythropoietic responsiveness contribute to longitudinal variation in HbA1c.

Therefore, we used longitudinal repeated-measures data with within-between decomposition to investigate the association between ERI and HbA1c in patients with diabetes receiving maintenance HD. Specifically, we examined whether temporal changes in ERI within individual patients were associated with serial HbA1c values independently of measured blood glucose, while distinguishing these within-patient associations from between-patient differences in long-term mean ERI.

Methods

Study design and participants

This retrospective longitudinal observational study was conducted at Fuefuki Central Hospital, Yamanashi, Japan. Patients with diabetes mellitus receiving maintenance hemodialysis between January 2023 and December 2025 were screened for eligibility. Patients with at least eight HbA1c measurements during the observation period and sufficient longitudinal clinical and laboratory data for the analysis were included. Patients receiving a hypoxia-inducible factor prolyl hydroxylase inhibitor were excluded. Follow-up duration varied among patients because of death or other reasons for termination of follow-up. The final study population comprised 38 patients contributing 1,149 repeated observations, with each observation corresponding to an HbA1c measurement occasion (Fig. 1). All 38 patients with diabetes met the requirement of at least eight HbA1c measurements; none were excluded for insufficient measurement frequency.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee of Fuefuki Central Hospital on September 15, 2026 (approval number:

Fuefuki Rin 26 – 3). The requirement for individual informed consent was waived by the ethics committee because of the retrospective observational nature of the study.

Hemodialysis treatment and anemia management

Maintenance hemodialysis was generally performed three times weekly using standard bicarbonate-based dialysis. Renal anemia was managed with erythropoiesis-stimulating agents (ESAs) and intravenous iron according to routine clinical practice. Darbepoetin alfa doses were converted to epoetin-equivalent doses using a conversion ratio of 1 μg darbepoetin alfa to 200 IU epoetin [12]. The erythropoietin resistance index (ERI) was calculated as the weekly epoetin-equivalent ESA dose divided by post-dialysis target weight and hemoglobin concentration and was expressed as IU/kg/week/g/dL [12].

Clinical and laboratory measurements

Clinical and laboratory data were obtained from electronic medical records. Variables included hemoglobin, HbA1c, blood glucose, ESA dose, ERI, serum albumin, C-reactive protein (CRP), transferrin saturation, ferritin, intravenous iron use, body weight, body mass index, glucose-lowering treatment, and physical stress. Blood glucose values represented routine pre-dialysis plasma glucose measurements and were not necessarily obtained under fasting conditions.

Physical stress was defined as the occurrence of an acute clinical event, such as infection or surgery, during the month of each HbA1c measurement and was treated as a time-varying binary variable (present or absent).

To approximate the glycemic exposure represented by HbA1c, rolling mean blood glucose was calculated from the current and two preceding available monthly records for each patient. Rolling mean ERI was calculated using the same approach. These rolling means were calculated before restricting the dataset to observations with available HbA1c. When monthly records were missing, a three-observation window could extend beyond three calendar months. As a sensitivity analysis, rolling means were calculated from available measurements in the current and two preceding calendar months.

Within-patient and between-patient decomposition

To distinguish longitudinal changes within individual patients from differences between patients, selected time-varying variables were decomposed into within-patient and between-patient components. For each variable, the between-patient component was defined as the patient-specific mean across all available observations during follow-up. The within-patient component was calculated as the value at each observation minus the corresponding patient-specific mean.

Accordingly, the within-patient coefficient represents the expected difference in HbA1c associated with a deviation from an individual's usual level of the exposure, whereas the between-patient coefficient represents the difference in HbA1c associated with differences in long-term mean exposure levels between patients.

Statistical analysis

Longitudinal associations with HbA1c were evaluated using linear mixed-effects models with a patient-specific random intercept to account for repeated measurements within individuals. The primary within-between model simultaneously included the within- and between-patient components of three-observation rolling mean blood glucose, three-observation rolling mean ERI, serum albumin, and log-transformed CRP [log(CRP + 1)], together with physical stress and follow-up month. The prespecified primary coefficient of interest was the within-patient component of three-observation rolling mean ERI.

Because hemoglobin concentration and body weight are mathematical components of ERI, sensitivity analyses additionally adjusted for these variables. Hemoglobin was decomposed into within-patient and between-patient components in the hemoglobin-adjusted model. In the sensitivity model including both hemoglobin and dry weight, these variables were entered as time-varying covariates without within-between decomposition. Additional sensitivity analyses excluded patients with a history of blood transfusion, excluded observations above the 99th percentile of rolling mean ERI, assessed the influence of individual patients using leave-one-patient-out analyses, accounted for serial correlation using generalized estimating equations with an AR(1) working correlation indexed by observation order, and examined rolling mean ERI lagged by one and two preceding monthly records.

All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Study population

The final dataset comprised 38 patients and 1,149 repeated observations. Each observation corresponded to an HbA1c measurement occasion. At the first available study observation, mean HbA1c was 6.02 ± 1.27%, mean hemoglobin was 11.07 ± 1.26 g/dL, median ERI was 15.26 (IQR 7.55–19.77), and median weekly ESA dose was 9,000 (IQR 4,500–12,000) IU/week (Table 1).

Table 1
Baseline characteristics of the study population.

Characteristic	Value (n = 38)
Age, years	70.2 ± 13.4
Male sex, n (%)	27 (71.1)
Dialysis vintage, months	48.5 (16.5–108.8)
HbA1c, %	6.02 ± 1.27
Blood glucose, mg/dL	166.2 ± 60.6
Hemoglobin, g/dL	11.07 ± 1.26
ESA dose, IU/week	9000 (4500–12000)
ERI, IU/week/kg/(g/dL)	15.26 (7.55–19.77)
Dry weight, kg	59.15 ± 16.30
BMI, kg/m²	23.17 ± 5.20
Serum albumin, g/dL	3.32 ± 0.47
CRP, mg/dL	0.09 (0.03–0.32)
TSAT, %	13.5 (11.0–16.5)
Ferritin, ng/mL	51.5 (37.3–92.0)
Glucose-lowering treatment	
Insulin, n (%)	8 (21.1)
GLP-1 receptor agonist, n (%)	6 (15.8)
DPP-4 inhibitor, n (%)	11 (28.9)
α-Glucosidase inhibitor, n (%)	3 (7.9)

Table 1. Baseline characteristics of the study population.

Values are presented as mean ± standard deviation, median (interquartile range), or number (percentage), as appropriate. Laboratory and clinical variables were obtained from the first available study observation for each patient. Glucose-lowering treatments were not mutually exclusive. BMI, body mass index; CRP, C-reactive protein; DPP-4, dipeptidyl peptidase-4; ERI, erythropoietin resistance index; ESA, erythropoiesis-stimulating agent; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; TSAT, transferrin saturation.

Primary within-between analysis

Both between-patient and within-patient components of three-observation rolling mean blood glucose were positively associated with HbA1c (between: $\beta = 0.0130$, 95% CI 0.0078 to 0.0181, $P < 0.001$; within: $\beta = 0.0102$, 95% CI 0.0093 to 0.0111, $P < 0.001$). The relationship between rolling mean blood glucose and HbA1c is illustrated in Fig. 2; model estimates are presented in Table 2.

Table 2
Associations with HbA1c in linear mixed-effects models.

Variable	Basic model	Within-between model	Hb-adjusted model
Three-observation rolling mean blood glucose	0.01025 (0.00937 to 0.01114); P < 0.001	—	—
Three-observation rolling mean ERI	-0.02740 (-0.03368 to -0.02113); P < 0.001	—	—
Blood glucose, within	—	0.01018 (0.00928 to 0.01108); P < 0.001	0.01022 (0.00933 to 0.01111); P < 0.001
Blood glucose, between	—	0.01295 (0.00783 to 0.01808); P < 0.001	0.01284 (0.00802 to 0.01767); P < 0.001
ERI, within	—	-0.02835 (-0.03475 to -0.02195); P < 0.001	-0.02497 (-0.03145 to -0.01850); P < 0.001
ERI, between	—	0.00469 (-0.02761 to 0.03700); P = 0.776	-0.01051 (-0.04370 to 0.02269); P = 0.535
Hemoglobin, within	—	—	0.06937 (0.04178 to 0.09695); P < 0.001
Hemoglobin, between	—	—	-0.43629 (-0.81960 to -0.05298); P = 0.026
Serum albumin	0.22615 (0.10371 to 0.34860); P < 0.001	—	—
Albumin, within	—	0.21481 (0.08955 to 0.34008); P < 0.001	0.13928 (0.01174 to 0.26683); P = 0.032
Albumin, between	—	0.68791 (0.06286 to 1.31296); P = 0.031	0.79987 (0.20378 to 1.39595); P = 0.009
log(CRP + 1)	0.10009 (0.00495 to 0.19522); P = 0.039	—	—
log(CRP + 1), within	—	0.10047 (0.00484 to 0.19610); P = 0.039	0.07691 (-0.01813 to 0.17195); P = 0.113
log(CRP + 1), between	—	-0.18932 (-1.07447 to 0.69584); P = 0.675	-0.26462 (-1.09957 to 0.57033); P = 0.534
Physical stress	-0.06931 (-0.26880 to 0.13017); P = 0.496	-0.07304 (-0.27277 to 0.12670); P = 0.474	-0.00970 (-0.20876 to 0.18935); P = 0.924
Follow-up time	0.00379 (0.00087 to 0.00672); P = 0.011	0.00374 (0.00081 to 0.00668); P = 0.012	0.00306 (0.00015 to 0.00598); P = 0.040

Table 2. Associations with HbA1c in linear mixed-effects models.

Values are regression coefficients (95% confidence intervals); P values are two-sided. All models included a patient-specific random intercept and were fitted to 1,149 observations from 38 patients. The basic model included three-observation rolling mean blood glucose, three-observation rolling mean ERI, serum albumin, log(CRP + 1), physical stress, and follow-up time. The within-between model decomposed three-observation rolling mean blood glucose, three-observation rolling mean ERI, serum albumin, and log(CRP + 1) into within-patient and between-patient components. The hemoglobin-adjusted model additionally included within-patient and between-patient hemoglobin components and was considered a sensitivity analysis because hemoglobin is included in the denominator of ERI. CI, confidence interval; CRP, C-reactive protein; ERI, erythropoietin resistance index; HbA1c, hemoglobin A1c.

In contrast, the within-patient component of three-observation rolling mean ERI was inversely associated with HbA1c (β = −0.0284, 95% CI − 0.0348 to − 0.0220, P < 0.001), whereas the between-patient component was not significantly associated with HbA1c (β = 0.0047, 95% CI − 0.0276 to 0.0370, P = 0.776). These findings indicate that HbA1c tended to be lower during periods when an individual's rolling mean ERI was higher than that individual's usual level, after adjustment for measured blood glucose and the other included covariates. The within-patient relationship is illustrated in Fig. 3.

Sensitivity analyses

After additional adjustment for hemoglobin, the within-patient ERI association remained statistically significant (β = −0.0250, 95% CI − 0.0315 to − 0.0186, P < 0.001). Excluding three patients with a history of blood transfusion left 35 patients and 1,058 observations; the association was essentially unchanged (β = −0.0276, 95% CI − 0.0348 to − 0.0203, P < 0.001). Further adjustment for hemoglobin and dry weight attenuated but did not eliminate the association (β = −0.0218, 95% CI − 0.0283 to − 0.0152, P < 0.001). Selected adjusted estimates are shown in Fig. 5.

Exclusion of observations above the 99th percentile of rolling mean ERI yielded a similar estimate (β = −0.0269, 95% CI − 0.0339 to − 0.0199, P < 0.001). In leave-one-patient-out analyses, the within-patient ERI coefficient remained negative in all 38 analyses (range, − 0.0301 to − 0.0237; all P < 0.001). An AR(1) generalized estimating equation (GEE) model also supported the association (β = −0.0330, 95% CI − 0.0497 to − 0.0164, P < 0.001). Model fit statistics are presented in Table 3.

Table 3
Performance of the linear mixed-effects models.

Model	Observations	Patients	AIC	BIC	Log-likelihood	Random-intercept variance	Residual variance
Basic model	1149	38	1744.5	1790.0	-863.3	0.444	0.230
Within-between model	1149	38	1746.4	1812.0	-860.2	0.377	0.230
Hb-adjusted model	1149	38	1721.7	1797.4	-845.8	0.333	0.225

Table 3. Performance of the linear mixed-effects models.

All three linear mixed-effects models were fitted to the same 1,149 observations from 38 patients using maximum-likelihood estimation for model comparison. AIC, Akaike information criterion; BIC, Bayesian information criterion. Lower AIC and BIC values indicate better relative fit among models fitted to the same dataset. Random-intercept variance represents between-patient heterogeneity in baseline HbA1c, and residual variance represents within-patient unexplained variability.

One-record and two-record lagged rolling mean ERI remained associated with HbA1c, although the magnitude of the association progressively attenuated (one-record lag: β = −0.0196, 95% CI − 0.0262 to − 0.0131, P < 0.001; two-record lag: β = −0.0094, 95% CI − 0.0162 to − 0.0027, P = 0.006). These findings indicate that the association was strongest contemporaneously and weakened with increasing record-based lag.

Discussion

The principal finding of this study was that within-patient increases in ERI were associated with lower HbA1c after adjustment for measured blood glucose, whereas between-patient differences in ERI were not associated with HbA1c. Thus, the observed association did not simply reflect lower HbA1c among patients with chronically high ERI; rather, HbA1c tended to be lower during periods when ERI was elevated relative to an individual's usual level. The consistency of this association across multiple sensitivity analyses suggests that temporal changes in erythropoietic status may be relevant to the interpretation of serial HbA1c values in patients receiving maintenance hemodialysis.

HbA1c reflects glucose exposure over the circulating lifespan of erythrocytes and is therefore influenced by erythrocyte turnover. In patients receiving maintenance HD, renal anemia, ESA therapy, iron treatment, blood loss, inflammation, and transfusion may alter erythrocyte survival and age distribution, potentially affecting HbA1c independently of glycemic exposure [1–4]. Previous studies have shown that ESA treatment can reduce HbA1c without a corresponding reduction in measured glucose [2, 4]. Our findings

extend these observations by suggesting that the relevant association may occur dynamically within individual patients: when ESA responsiveness changes relative to a patient's usual state, the relationship between HbA1c and measured glucose may also change.

Recent CGM studies have demonstrated clinically relevant discordance between HbA1c and directly measured glycemia in patients receiving dialysis [5, 6]. The present study adds a longitudinal perspective to this literature. By decomposing ERI into within-patient and between-patient components, we found that its association with HbA1c was primarily attributable to temporal variation within individuals rather than stable differences between patients. This distinction is clinically relevant because a patient's current HbA1c may be influenced not only by glycemic exposure but also by changes in erythropoietic state relative to that patient's usual condition.

Several sensitivity analyses supported the robustness of the primary finding. Exclusion of patients with a history of blood transfusion produced little change in the within-patient ERI coefficient, suggesting that transfusion-related distortion of HbA1c was unlikely to account for the overall association. Additional adjustment for hemoglobin and body weight attenuated but did not eliminate the association. This analysis is particularly relevant because both variables are mathematical components of ERI. The findings were also robust to exclusion of extreme ERI values, leave-one-patient-out analyses, and an alternative model accounting for serial correlation.

The temporal analyses require cautious interpretation. The ERI–HbA1c association was strongest contemporaneously and attenuated at one- and two-record lags, although both lagged associations remained statistically significant. Because adjacent three-observation rolling averages may share overlapping measurement periods, the lagged analyses cannot establish the timing or duration of a biological effect. Furthermore, ERI is a composite clinical index rather than a direct measure of erythrocyte production, turnover, or lifespan. The biological mechanism underlying the observed temporal pattern therefore cannot be determined from these data. A representative patient course is shown in Fig. 4 to illustrate the longitudinal patterns.

Importantly, these findings should not be interpreted as indicating that an increase in ERI itself causes HbA1c to decrease. ERI is a composite index influenced by ESA dose, hemoglobin concentration, body weight, inflammation, nutritional status, and iron availability. Changes in ESA dose are also clinical responses to changing anemia status rather than externally assigned exposures. ERI should therefore be considered a marker of ESA responsiveness and erythropoietic state rather than a causal exposure. Our results suggest that temporal changes in this state may be relevant when interpreting longitudinal HbA1c measurements.

This study has several limitations. First, it was a retrospective, single-center study involving a modest number of independent patients despite the large number of repeated observations. Second, glycemic exposure was estimated from routine pre-dialysis blood glucose measurements, which were not necessarily obtained under fasting conditions and cannot characterize glycemic exposure as comprehensively as CGM. Glycated albumin was also unavailable. Consequently, residual differences

between the measured blood glucose values used in our models and true glycemic exposure cannot be excluded. Third, follow-up duration varied among patients, including because of death, raising the possibility of informative dropout. Fourth, residual confounding by changes in glucose-lowering treatment, iron therapy, inflammation, nutritional status, and intercurrent illness cannot be excluded. Finally, because of the observational design, causal inference is not possible.

From a clinical perspective, temporal changes in ESA responsiveness may provide useful context when interpreting serial HbA1c measurements in patients receiving maintenance HD. A decrease in HbA1c during a period of increasing ERI may not necessarily indicate a proportional improvement in glycemic exposure. However, because glycemic exposure was estimated from routinely measured pre-dialysis blood glucose rather than CGM, the observed association cannot be considered independent of actual glycemic exposure. When HbA1c appears discordant with measured glucose or the clinical course, complementary assessment using direct glucose measurements, CGM, or glycated albumin may help clarify glycemic status [5–10].

Conclusion

In patients with diabetes receiving maintenance hemodialysis, within-patient increases in ERI were associated with lower HbA1c after adjustment for routinely measured blood glucose, whereas between-patient differences in ERI were not. These findings suggest that temporal variation in ESA responsiveness may be relevant when interpreting serial HbA1c values. Prospective multicenter studies incorporating CGM, alternative glycemic biomarkers, and measures of erythrocyte kinetics are needed to clarify whether this association is independent of actual glycemic exposure.

Declarations

Data Sharing Statement

The individual-level data supporting the findings of this study are not publicly available due to patient confidentiality, ethical considerations, and institutional restrictions.

Reporting Checklist Statement (STROBE)

This study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Conflict of Interest

Yukinobu Ikegishi declares that he has no conflict of interest.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee of Fuefuki Central Hospital on September 15, 2026 (approval number: Fuefuki Rin 26 – 3). The requirement for individual informed consent was waived by the ethics committee because of the retrospective observational nature of the study.

Consent to Publish

Consent to Publish declaration: not applicable.

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Author Contribution

Y.I. wrote the main manuscript text and Y.I. prepared figures 1-3. Y.I. reviewed the manuscript.

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Figures

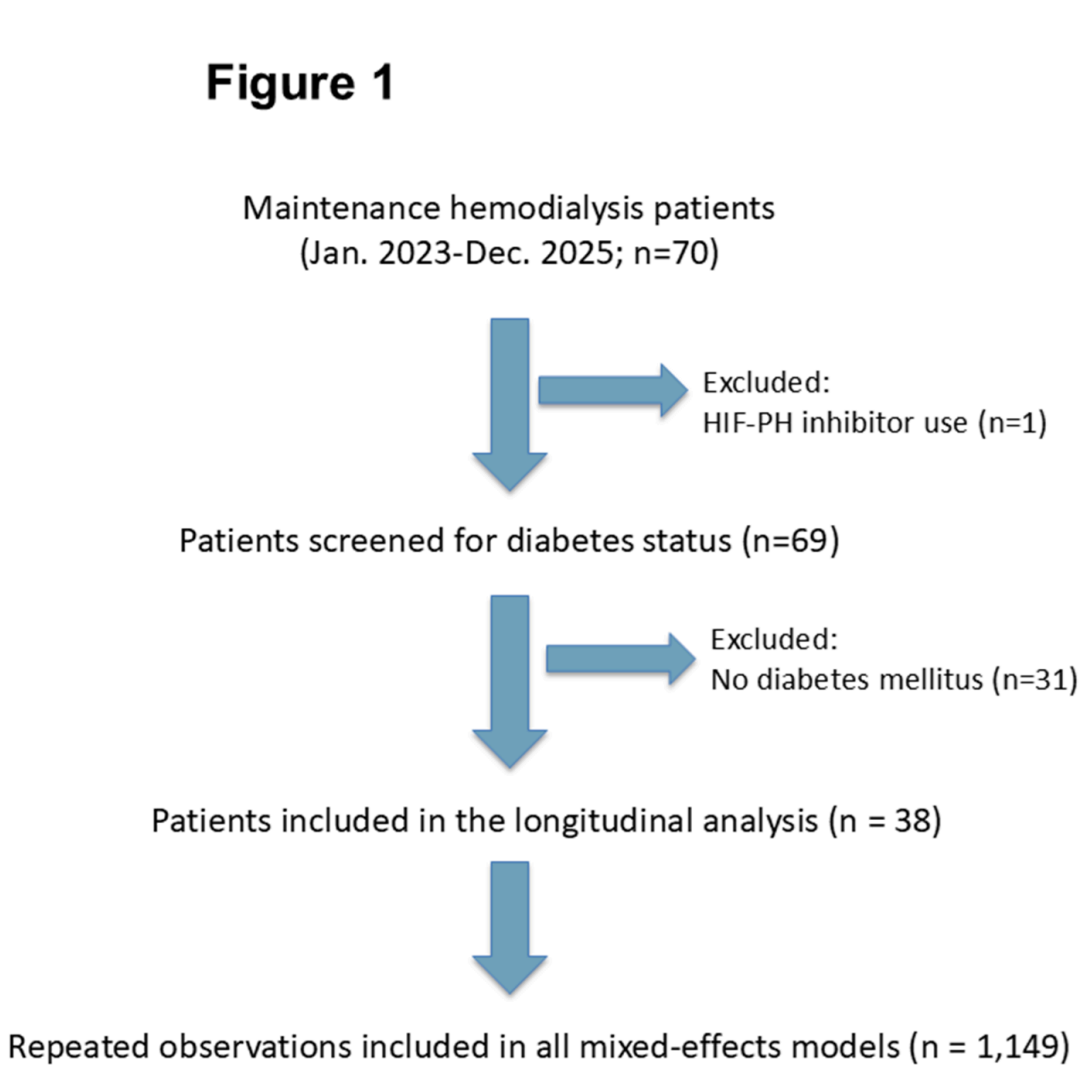


Figure 1

Flow diagram of patient selection

A total of 38 patients with diabetes receiving maintenance hemodialysis contributed 1,149 repeated observations to the longitudinal analysis. HIF-PH, hypoxia-inducible factor prolyl hydroxylase.

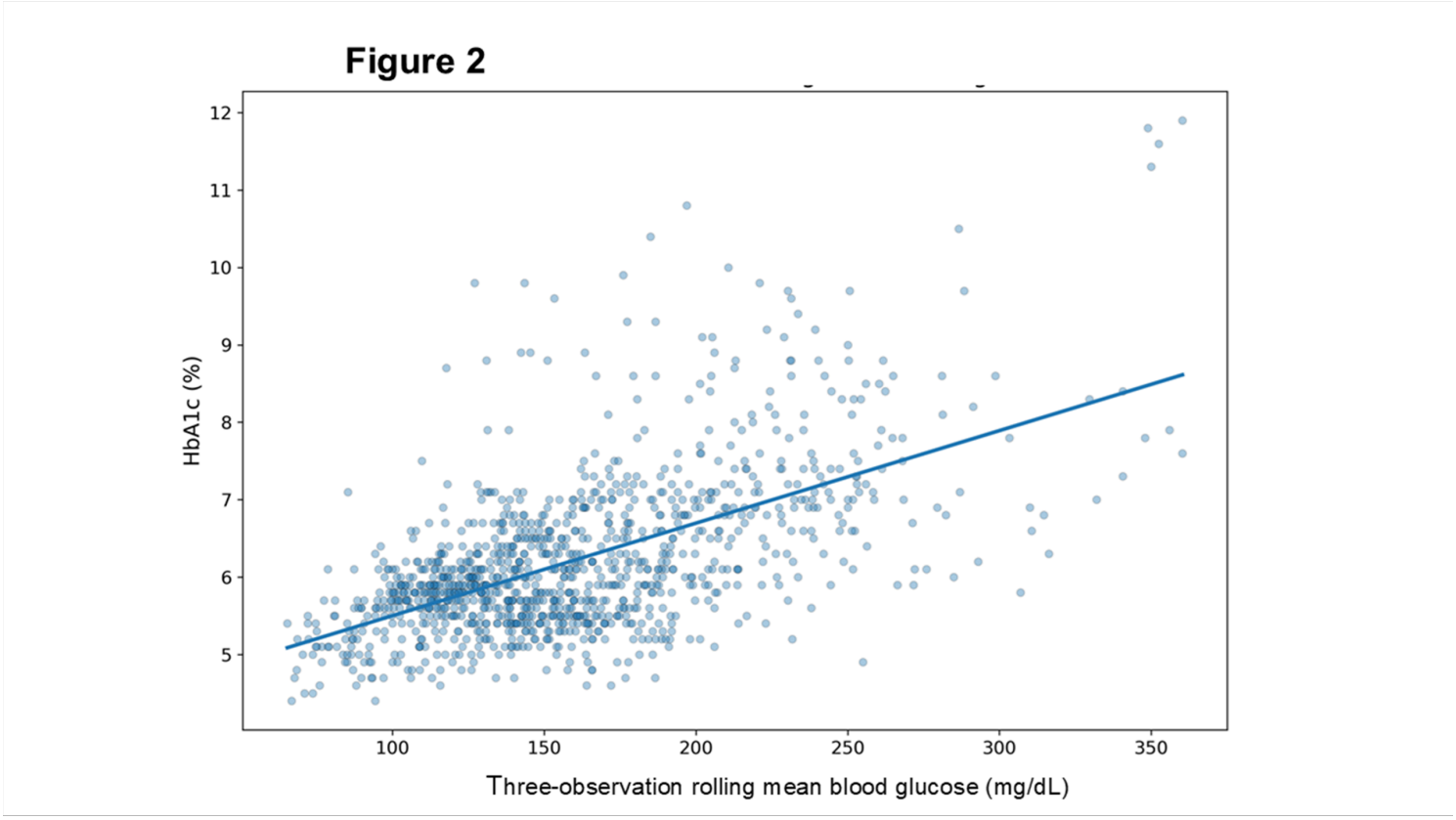


Figure 2

Association between three-observation rolling mean blood glucose and HbA1c

Scatter plot of repeated observations from the 38-patient cohort. Each point represents one HbA1c observation paired with the corresponding three-observation rolling mean blood glucose value. The fitted line illustrates the overall positive association between measured glycemic exposure and HbA1c. The inferential longitudinal analyses accounting for repeated measurements and within-patient versus between-patient effects are presented in Table 2.

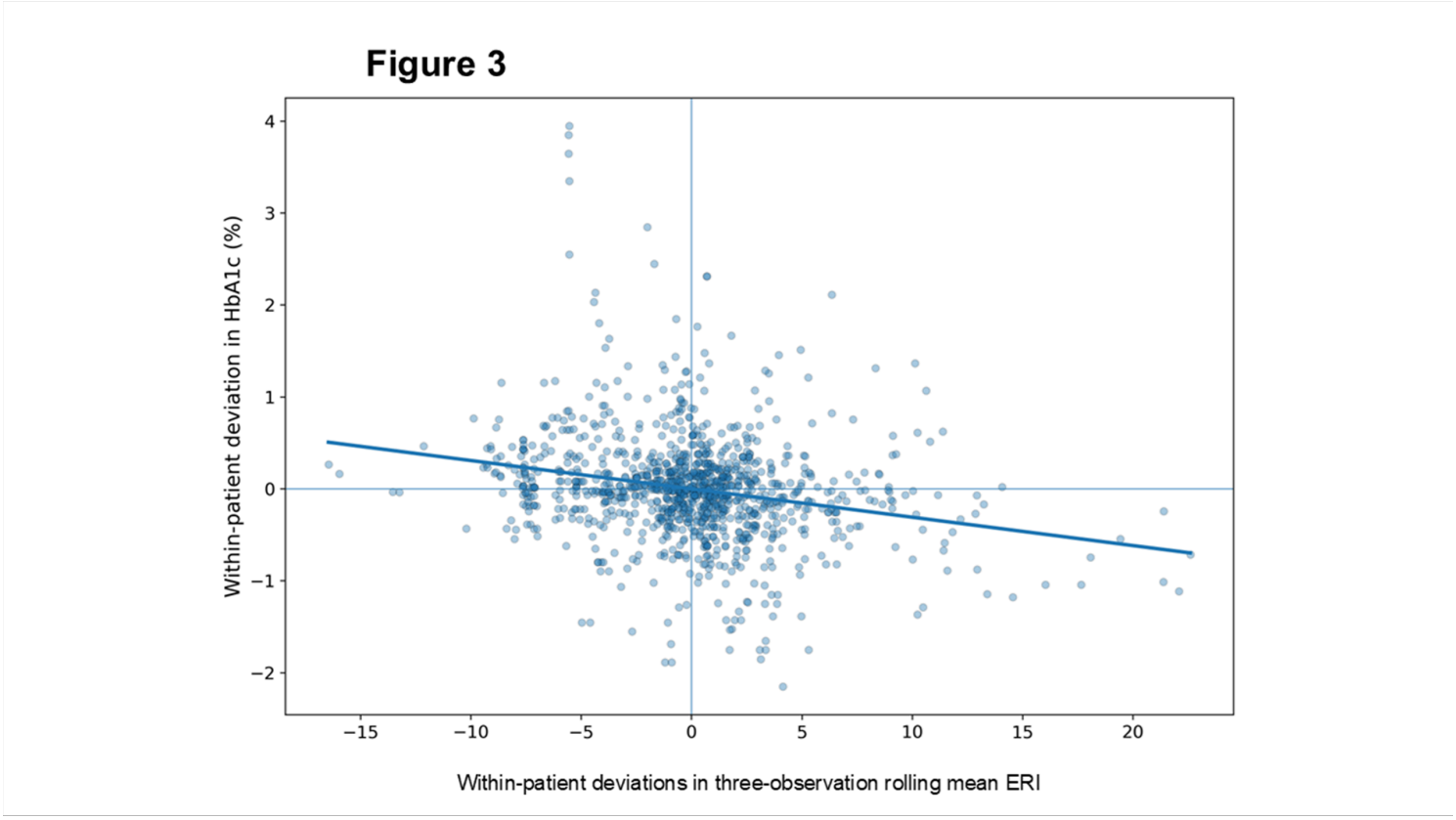


Figure 3

Within-patient association between erythropoietin resistance index and HbA1c

Scatter plot showing within-patient deviations in three-observation rolling mean ERI and HbA1c from each patient's own mean. Each point represents one repeated observation. Negative values indicate measurements below the patient's usual level and positive values indicate measurements above the patient's usual level. The fitted line illustrates the inverse within-patient association; the corresponding adjusted mixed-effects estimate is presented in Table 2. ERI, erythropoietin resistance index; HbA1c, hemoglobin A1c.

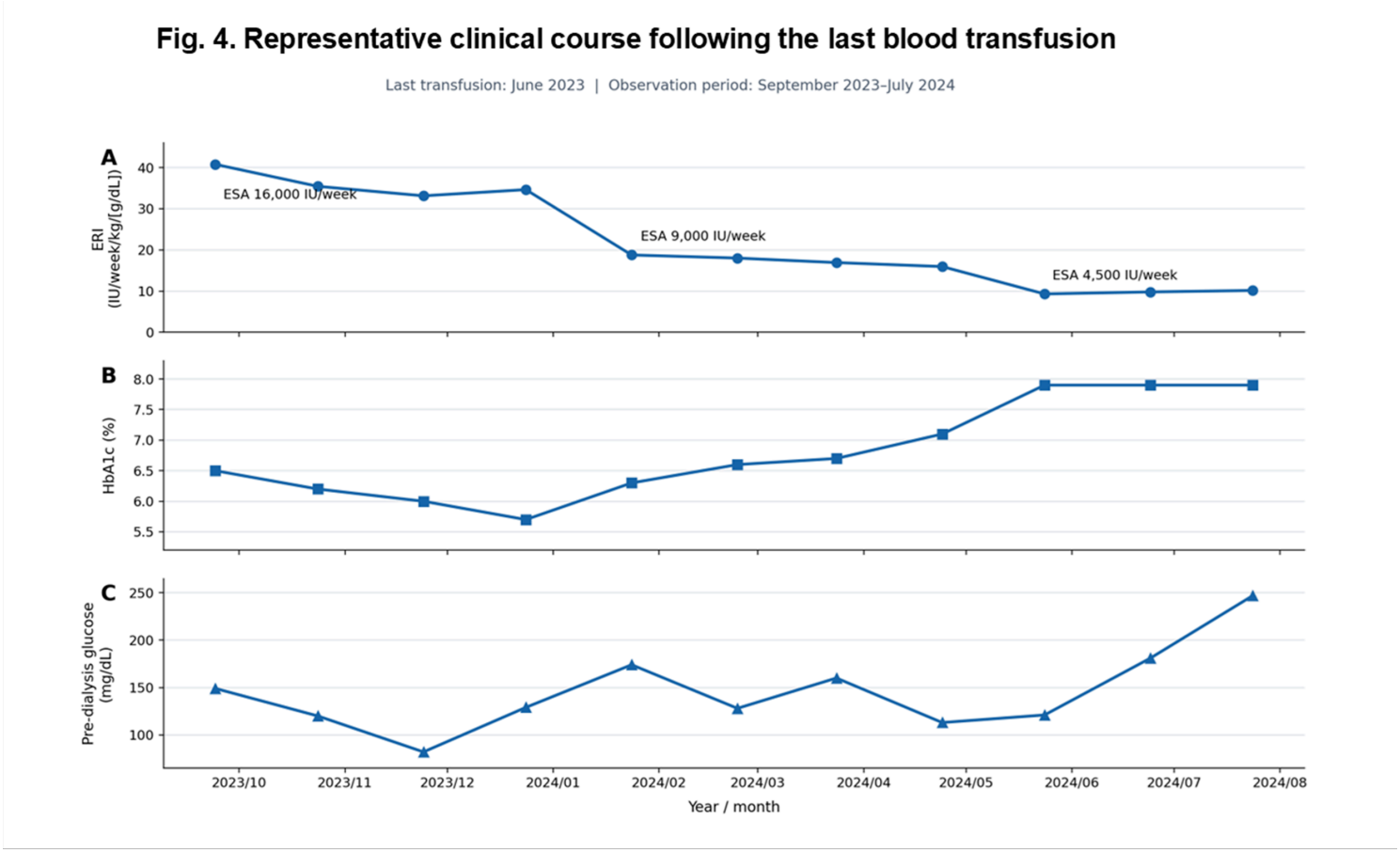


Figure 4

Representative clinical course following the last blood transfusion

Serial changes in (A) erythropoietin resistance index (ERI), (B) HbA1c, and (C) pre-dialysis blood glucose from September 2023 to July 2024 are shown for a representative patient. The patient's last blood transfusion occurred in June 2023. ERI decreased over the observation period, accompanied by reductions in the weekly erythropoiesis-stimulating agent (ESA) dose from 16,000 to 9,000 and subsequently to 4,500 IU/week, whereas HbA1c generally increased. Individual pre-dialysis blood glucose measurements exhibited substantial month-to-month variability. This descriptive figure does not establish a causal relationship between changes in ERI and HbA1c.

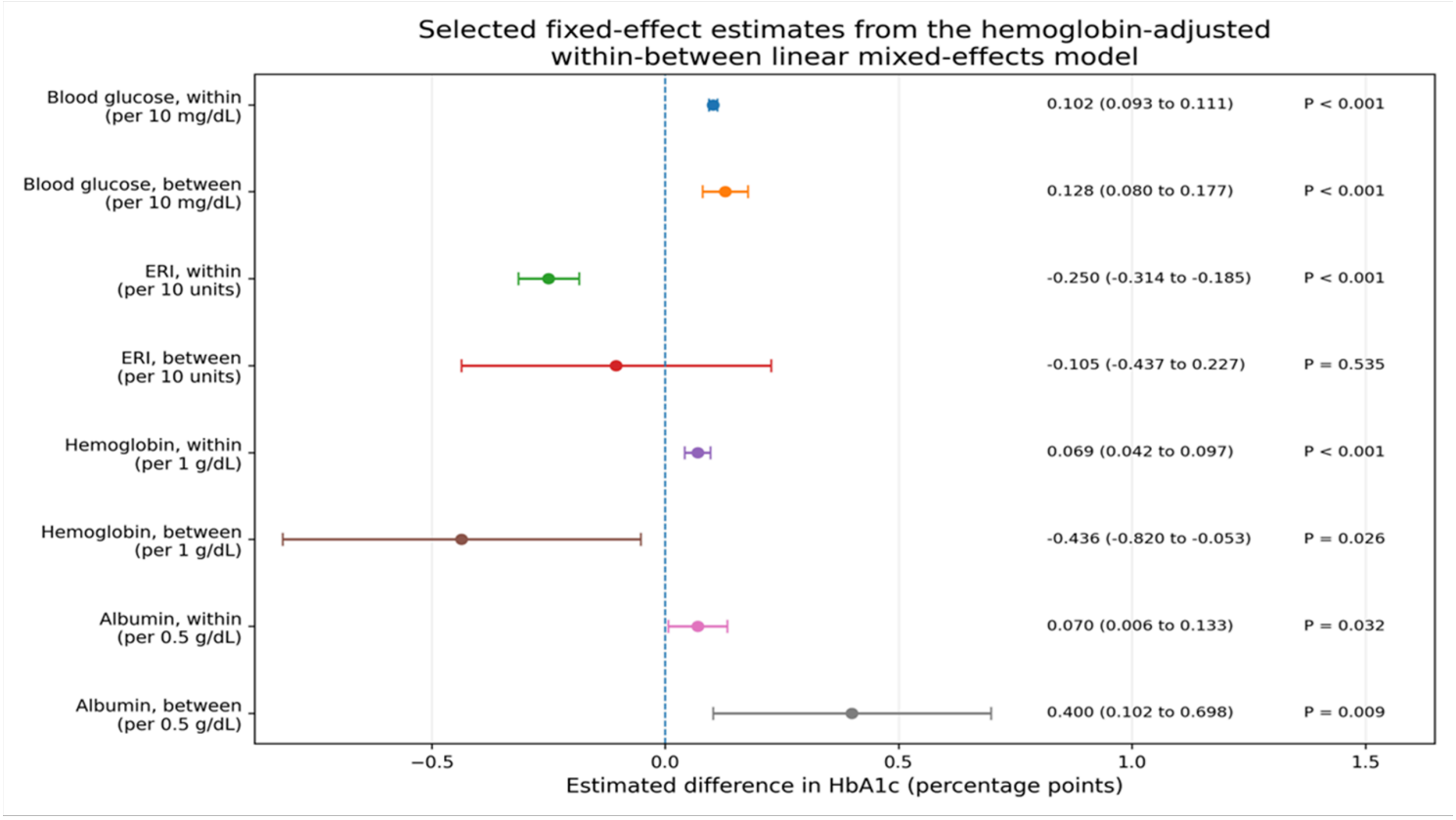


Figure 5

Selected fixed-effect estimates from the hemoglobin-adjusted within-between linear mixed-effects model

Points indicate regression coefficients and horizontal bars indicate 95% confidence intervals. Blood glucose effects are expressed per 10 mg/dL, ERI effects per 10 units, hemoglobin effects per 1 g/dL, and albumin effects per 0.5 g/dL. The vertical reference line indicates no association (β = 0). Within-patient estimates reflect temporary deviations from an individual's usual level, whereas between-patient estimates reflect differences in patient-specific mean levels. ERI, erythropoietin resistance index; HbA1c, hemoglobin A1c.