

ORIGINAL ARTICLE

Anemia

Roxadustat Versus ESA Therapy for Sustained Hemoglobin Response in ESA-Hyporesponsive Hemodialysis Patients

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ABSTRACT

Background: In Erythropoiesis-Stimulating Agent (ESA)-hyporesponsive hemodialysis patients, hemoglobin (Hb) change from baseline may not fully capture durable treatment response. This secondary analysis evaluated sustained Hb ≥ 10 g/dL achievement and month-to-month Hb variability with roxadustat versus continued ESA therapy.

Methods: This multicenter retrospective secondary analysis included adult maintenance hemodialysis patients with ESA-hyporesponsive anemia and complete monthly Hb data from Months 1–6. Sustained target achievement was defined as Hb ≥ 10 g/dL in at least 3 of 6 months. Hb variability was assessed using within-patient Hb SD, coefficient of variation, range, mean absolute monthly change, and maximum absolute change. Predictors were evaluated using logistic and linear regression.

Results: Among 108 patients, 78 received roxadustat and 30 continued ESA therapy. Sustained Hb ≥ 10 g/dL achievement occurred in 52 patients. Roxadustat was associated with higher adjusted odds of sustained target achievement versus ESA therapy (adjusted OR: 4.44, 95% CI: 1.24–15.84; $p = 0.022$). Higher baseline Hb was also independently associated with sustained response (adjusted OR: 2.95 per 1 g/dL, 95% CI: 1.57–5.55; $p < 0.001$). By Month 6, Hb ≥ 10 g/dL was achieved by 50.0% of roxadustat-treated patients versus 33.3% of ESA-treated patients. Hb variability metrics were numerically lower with roxadustat but were not significantly different between groups.

Conclusions: In ESA-hyporesponsive hemodialysis patients, roxadustat was associated with higher adjusted odds of sustained Hb ≥ 10 g/dL achievement but did not clearly reduce month-to-month Hb variability over 6 months. These retrospective findings support sustained target achievement as a clinically relevant response metric and warrant prospective validation.

1 | Introduction

In our primary multicenter retrospective study, we evaluated roxadustat as an alternative to continued high-dose Erythropoiesis-Stimulating Agent (ESA) therapy in ESA-hyporesponsive maintenance hemodialysis patients with persistent hemoglobin (Hb) < 10 g/dL. That analysis showed a significant six-month-Hb increase after switching to roxadustat, but also demonstrated that final Hb was strongly influenced by baseline Hb, underscoring the complexity of response assessment in this high-risk population [1].

However, in dialysis anemia care, the clinical question is not only whether Hb increases, but whether patients reach and maintain a therapeutically meaningful threshold. Kidney Disease Improving Global Outcomes (KDIGO) 2026 considers Hb $\leq$ 9–10 g/dL a reasonable threshold for ESA initiation in maintenance dialysis and recommends avoiding maintenance Hb $\geq$ 11.5 g/dL, with usual adult treatment targets generally around 10–11.5 g/dL [2]. Similarly, Turkish Social Security reimbursement criteria permit erythropoietin, darbepoetin, methoxy polyethylene glycol-epoetin beta, and roxadustat for Chronic Kidney Disease (CKD)-related anemia when iron parameters are adequate and Hb remains below 10 g/dL, with maintenance directed toward 11–12 g/dL and interruption above 12 g/dL [3]. Therefore, Hb $\geq$ 10 g/dL represents a clinically and policy-relevant treatment boundary rather than an arbitrary analytic cut-off.

Roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), has demonstrated Hb-correcting efficacy in dialysis-dependent CKD trials, but guideline recommendations remain cautious regarding HIF-PHI use, particularly in ESA-hyporesponsive patients where long-term safety and patient-centered outcome data remain limited [2, 4–9]. Because end-point Hb change alone may not capture durable treatment success, we performed this secondary analysis to evaluate sustained Hb $\geq$ 10 g/dL achievement and month-to-month Hb variability in ESA-hyporesponsive hemodialysis patients treated with roxadustat versus continued ESA therapy.

We hypothesized that roxadustat would be associated with more frequent sustained Hb target achievement and potentially lower Hb variability. These findings may help clarify whether sustained target achievement is a clinically useful response metric in this difficult-to-treat population.

2 | Methods

2.1 | Study Design and Population

This was a secondary analysis of a multicenter, retrospective observational cohort of adult maintenance hemodialysis patients with ESA-hyporesponsive anemia. Eligible patients had persistent Hb < 10 g/dL despite intravenous ESA therapy administered up to the Turkish Social Security Institution reimbursement upper limit, corresponding to epoetin alfa/beta/zeta 150 IU/kg/week where applicable. Therefore, “high-dose ESA therapy” in this study refers to the maximum reimbursed ESA dosing framework in Türkiye rather than a universal international definition of ESA resistance.

Inclusion criteria were: age $\geq$ 18 years, receipt of maintenance hemodialysis, ESA-hyporesponsive anemia defined as persistent Hb < 10 g/dL despite intravenous ESA therapy up to the Turkish reimbursement upper-limit dose, classification into either the roxadustat group or the continued ESA group, and availability of monthly Hb measurements from Month 1 through Month 6 after the index date [3]. Patients were excluded if treatment-group coding was missing or invalid, if monthly Hb data during the six-month follow-up were incomplete, or if they did not meet the above eligibility criteria.

Patients were classified according to their real-world treatment course as either switched to roxadustat or continued on ESA therapy. Roxadustat was prescribed three times weekly according to routine clinical practice, with subsequent dose adjustments at the discretion of the treating physician.

Baseline data were defined as values recorded before treatment transition or the matched index date for controls. Follow-up extended through 6 months after the index date. Monthly Hb values from Month 1 through Month 6 were used to evaluate target achievement and Hb variability. Clinical and laboratory variables included demographic characteristics, dialysis vintage, dialysis adequacy, baseline Hb, transfusion status, ferritin, albumin, C-reactive protein (CRP), intact parathyroid hormone (iPTH), and comorbidities.

2.2 | Outcomes

The primary objective of this secondary analysis was to compare sustained Hb target achievement between patients treated with roxadustat and those who continued ESA therapy. Secondary objectives were to compare monthly Hb target achievement, target-month count, and month-to-month Hb variability between treatment groups.

The primary outcome of this secondary analysis was sustained Hb target achievement, defined as Hb $\geq$ 10 g/dL in at least three of six post-index monthly measurements. Secondary outcomes included monthly target achievement, defined as Hb $\geq$ 10 g/dL at each post-index month, and the target-month count was defined as the total number of months, from 0 to 6, in which Hb was $\geq$ 10 g/dL.

Hb variability was assessed using within-patient Hb standard deviation across Months 1–6. Additional variability metrics included Hb coefficient of variation, Hb range, mean absolute month-to-month Hb change, maximum absolute month-to-month Hb change, and the number of months within prespecified Hb zones.

This retrospective observational cohort study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for cohort studies [10].

2.3 | Statistical Analysis

The analytic cohort for the secondary Hb analyses included patients with valid treatment-group coding and complete Hb measurements from post-index Month 1 through Month 6.

Continuous variables were summarized as mean $\pm$ standard deviation or median [interquartile range], according to distributional assessment. Categorical variables were summarized as n/N (%) using non-missing denominators. Between-group comparisons used Welch's *t*-test for approximately symmetric continuous variables, Mann-Whitney *U* test for skewed or ordinal variables, and Pearson's chi-squared or Fisher's exact test for categorical variables according to expected cell counts.

Predictors of sustained Hb target achievement were evaluated using logistic regression. Univariable models were fitted for candidate predictors. The pathophysiology-informed multivariable model included treatment group, baseline Hb, baseline transfusion status, ferritin, albumin, and iPTH. Ferritin and iPTH were modeled per 100-unit increase. A sensitivity model replaced albumin with log-transformed CRP, defined as $\log(1 + \text{CRP})$. Results are reported as odds ratios with 95% confidence intervals and *p* values.

Predictors of Hb variability were evaluated using linear regression models for within-patient Hb standard deviation and mean absolute month-to-month Hb change. These models used the same pathophysiology-informed covariate set. Regression coefficients are reported with 95% confidence intervals and *p* values; heteroskedasticity-robust standard errors were used where specified by the R analysis script.

Missing data were not imputed. Descriptive summaries used available non-missing data, whereas regression models used

complete-case analysis for variables included in each model. All *p* values were two-sided, and *p* values < 0.001 were reported as $p < 0.001$. Because this was a retrospective observational secondary analysis, findings were interpreted as associative and hypothesis-generating rather than causal. All tables, figure source values, model outputs, validation checks, and reproducible R scripts were archived. Analyses were performed at the patient level using R software (R 4.6.0).

3 | Results

The secondary analytic cohort included 108 patients with valid treatment-group coding and complete Hb measurements from post-index Month 1 through Month 6; 78 treated with roxadustat and 30 who continued ESA therapy (Figure 1). Sustained Hb target achievement, defined as $\text{Hb} \geq 10 \text{ g/dL}$ in at least three of six post-index months, was observed in 52 patients; 56 patients did not meet this criterion (Table 1).

3.1 | Baseline Characteristics by Sustained Response Status

Compared with non-responders, sustained responders had higher baseline Hb (9.1 ± 0.6 vs. $8.3 \pm 1.2 \text{ g/dL}$; $p < 0.001$), lower ferritin (457.0 [$330.5, 616.0$] vs. 584.5 [$432.5, 837.5$] ng/mL; $p = 0.014$), and a higher prevalence of diabetes mellitus (48.1% vs. 26.8% ; $p = 0.022$). The proportion treated with roxadustat was numerically higher among sustained responders,

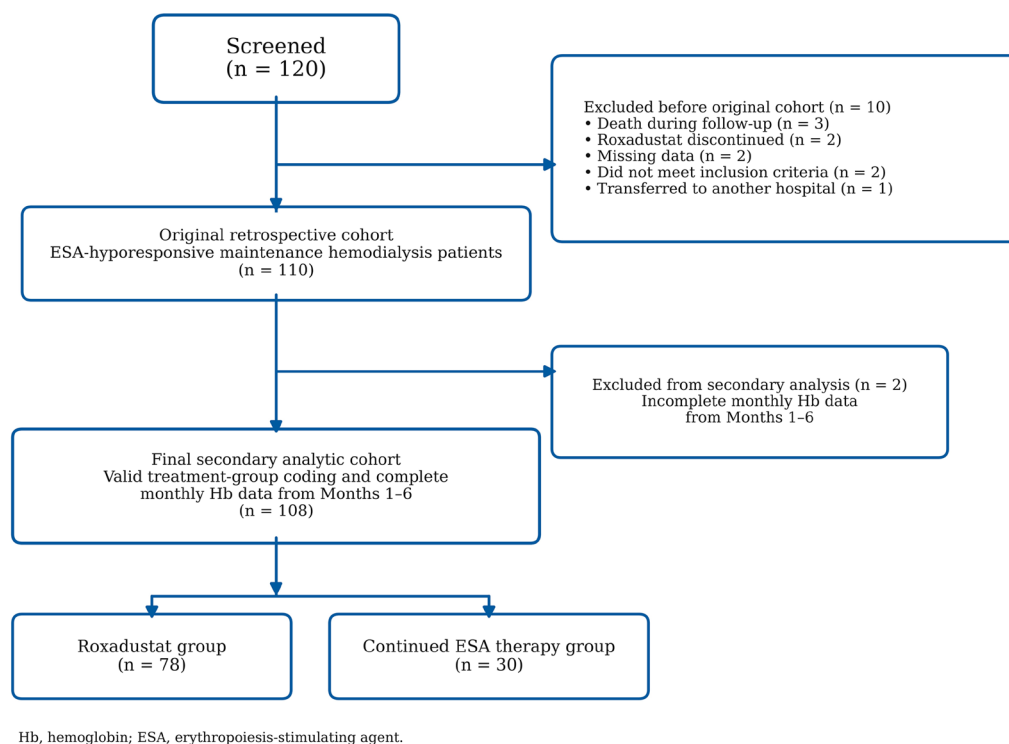


FIGURE 1 | The original multicenter retrospective cohort included 110 ESA-hyporesponsive maintenance hemodialysis patients. Two patients were excluded from this secondary analysis because complete monthly Hb follow-up data from Month 1 through Month 6 were unavailable. The final analytic cohort included 108 patients with valid treatment-group coding and complete monthly Hb measurements. Hb, hemoglobin; ESA, erythropoiesis-stimulating agent.

TABLE 1 | Baseline characteristics by sustained Hb target achievement status.

Characteristic	No sustained Hb > 10 g/dL (n = 56)	Sustained Hb > 10 g/dL (n = 52)	p
Roxadustat treatment, n/N (%)	38/56 (67.9)	40/52 (76.9)	0.293
Age, years	51.9 ± 16.9	51.9 ± 12.9	0.996
Male sex, n/N (%)	24/56 (42.9)	23/52 (44.2)	0.886
HD vintage, months	46.0 [26.0, 60.0]	48.0 [32.0, 72.0]	0.501
Dry weight, kg	66.6 ± 16.5	67.6 ± 14.5	0.737
Baseline Hb, g/dL	8.3 ± 1.2	9.1 ± 0.6	<0.001
Baseline transfusion, n/N (%)	20/56 (35.7)	14/52 (26.9)	0.326
Ferritin, ng/mL	584 [432, 837]	457 [330, 616]	0.014
Albumin, g/dL	3.6 ± 0.6	3.7 ± 0.4	0.661
CRP, mg/L	10.5 [5.0, 18.0]	8.0 [4.0, 16.0]	0.279
iPTH, pg/mL	641 [259, 1195]	481 [275, 797]	0.118
spKt/V	1.5 ± 0.3	1.5 ± 0.3	0.943
Diabetes mellitus, n/N (%)	15/56 (26.8)	25/52 (48.1)	0.022
AVF thrombosis history, n/N (%)	12/48 (25.0)	10/43 (23.3)	0.846

Note: Values are n/N (%), mean ± SD, or median [IQR], selected from code-generated distribution checks. Sustained response is Hb ≥ 10 g/dL in at least three of six post-index months. Continuous variables were compared with Welch *t*-test when approximately symmetric and Mann-Whitney *U*/Wilcoxon rank-sum otherwise. Categorical variables were compared with Pearson chi-squared or Fisher's exact test according to expected cell counts. Percentages use non-missing denominators. Abbreviations: AVF, arteriovenous fistula; CRP, C-reactive protein; Hb, hemoglobin; HD, hemodialysis; iPTH, intact parathyroid hormone; spKt/V, single-pool Kt/V.

but the difference was not statistically significant (76.9% vs. 67.9%; $p = 0.293$). Other baseline variables, including age, sex, dialysis vintage, dry weight, transfusion status, albumin, CRP, iPTH, single pool Kt/V (spKt/V), and arteriovenous fistula (AVF) thrombosis history, were not clearly different between groups (Table 1).

3.2 | Predictors of Sustained Hb Target Achievement

In univariable logistic regression, roxadustat treatment was not significantly associated with sustained Hb target achievement (OR: 1.58, 95% CI: 0.67–3.71; $p = 0.295$). Higher baseline Hb was associated with greater odds of sustained response (OR: 2.44 per 1 g/dL higher, 95% CI: 1.52–3.92; $p < 0.001$). Ferritin and iPTH were inversely associated with sustained response in univariable models, while diabetes mellitus was positively associated (Table 2).

In the pathophysiology-informed multivariable model, roxadustat treatment was associated with higher adjusted odds of sustained response compared with continued ESA therapy (adjusted OR: 4.44, 95% CI: 1.24–15.84; $p = 0.022$). Baseline Hb also remained independently associated with sustained response (adjusted OR: 2.95 per 1 g/dL higher, 95% CI: 1.57–5.55; $p < 0.001$). Baseline transfusion status, ferritin, albumin, and iPTH were not independently associated with sustained response. In the sensitivity model replacing albumin with log-transformed CRP, CRP was not independently associated with sustained response (Table 2).

3.3 | Monthly Hb Target Achievement

Monthly Hb ≥ 10 g/dL achievement was descriptively higher in the roxadustat group during later follow-up. At Month 1, target achievement was 33.3% in the ESA group and 24.4% in the roxadustat group. By Month 6, target achievement was 33.3% and 50.0%, respectively (Figure 2A; Table S1). The distribution of the total number of target-achieving months is shown in Figure 2B.

3.4 | Hb Variability by Treatment Group

Hb variability did not differ significantly between treatment groups. Within-patient Hb SD was 1.1 ± 0.5 g/dL in the ESA group and 1.0 ± 0.4 g/dL in the roxadustat group ($p = 0.160$). Hb coefficient of variation, Hb range, mean absolute monthly Hb change, maximum absolute monthly Hb change, and the number of months with Hb ≥ 10 g/dL were numerically favorable for roxadustat but were not statistically different between groups (Table 3).

3.5 | Predictors of Hb Variability

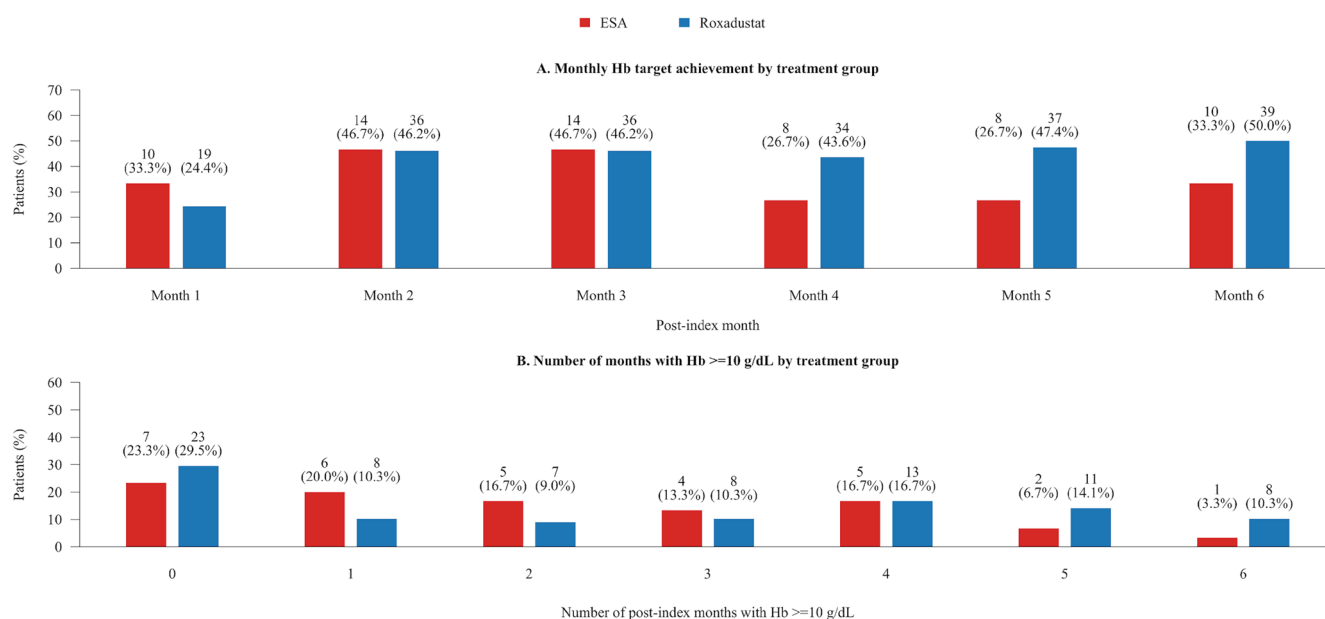
In adjusted linear regression models, roxadustat was not independently associated with within-patient Hb SD (coefficient -0.16 , 95% CI: -0.41 to 0.08 ; $p = 0.189$) or mean absolute month-to-month Hb change (coefficient -0.16 , 95% CI: -0.40 to 0.07 ; $p = 0.163$). Baseline transfusion status was associated with greater mean absolute month-to-month Hb change (coefficient 0.23 , 95% CI: 0.02 to 0.44 ; $p = 0.032$), but not with within-patient Hb SD (Table 4).

TABLE 2 | Univariable and pathophysiology-informed multivariable predictors of sustained Hb target achievement.

Predictor	Univariable OR (95% CI)	Univariable <i>p</i>	Multivariable OR (95% CI)	Multivariable <i>p</i>
Roxadustat versus ESA	1.58 (0.67–3.71)	0.295	4.44 (1.24–15.8)	0.022
Baseline Hb, per 1 g/dL higher	2.44 (1.52–3.92)	<0.001	2.95 (1.57–5.55)	<0.001
Baseline transfusion	0.66 (0.29–1.51)	0.327	1.14 (0.42–3.12)	0.793
Ferritin, per 100 ng/mL higher	0.88 (0.78–0.98)	0.022	0.93 (0.81–1.06)	0.271
Albumin, per 1 g/dL higher	1.18 (0.56–2.46)	0.661	0.76 (0.27–2.11)	0.600
iPTH, per 100 pg/mL higher	0.92 (0.86–0.99)	0.021	0.96 (0.89–1.04)	0.306
CRP, log(1 + <i>x</i>)	0.75 (0.48–1.16)	0.197	Sensitivity: 0.80 (0.48–1.34)	0.399
Age, per 10 years	1.00 (0.78–1.29)	0.996	—	—
Male sex	1.06 (0.49–2.26)	0.886	—	—
Diabetes mellitus	2.53 (1.13–5.65)	0.024	—	—
spKt/V, per 1.0 higher	1.05 (0.29–3.78)	0.942	—	—

Note: Logistic regression outcome is Hb ≥ 10 g/dL for at least three of six post-index months. The main multivariable model included treatment group, baseline Hb, baseline transfusion, ferritin per 100 ng/mL, albumin, and iPTH per 100 pg/mL. ORs > 1 indicate higher odds of sustained target achievement. Main model *N* = 108; events = 52. The CRP model is a sensitivity model replacing albumin with log(1 + CRP). Wald 95% CIs and *p* values are shown.

Abbreviations: CRP, C-reactive protein; ESA, Erythropoiesis-Stimulating Agent; Hb, hemoglobin; iPTH, intact parathyroid hormone; spKt/V, single-pool Kt/V.

**FIGURE 2** | (A) Monthly hemoglobin target (at least 10 g/dL) achievement by treatment group. (B) Number of months with at least 10 g/dL hemoglobin by treatment group.

4 | Discussion

In this secondary analysis of ESA-hyporesponsive maintenance hemodialysis patients, roxadustat treatment was associated with higher adjusted odds of sustained Hb ≥ 10 g/dL achievement compared with continued ESA therapy. Baseline Hb remained an important determinant of response, and target achievement was still incomplete overall. Hb variability metrics were numerically favorable with roxadustat but did not differ significantly between treatment groups. We extended the primary report from end-point Hb change to

sustained achievement of a clinically meaningful treatment threshold. This threshold is aligned with guideline-based and reimbursement-relevant decision-making in dialysis anemia care. These findings suggest that roxadustat may improve the probability of reaching a clinically meaningful Hb threshold in selected ESA-hyporesponsive patients, while durable correction remains constrained by baseline anemia severity and real-world clinical heterogeneity.

Roxadustat may improve Hb response in ESA-hyporesponsive patients through mechanisms beyond direct erythropoietin

TABLE 3 | Month-to-month Hb variability metrics by treatment group.

Metric	ESA (<i>n</i> = 30)	Roxadustat (<i>n</i> = 78)	<i>p</i>
Within-patient Hb SD, g/dL	1.1 ± 0.5	1.0 ± 0.4	0.160
Hb coefficient of variation, %	10.8 [8.2, 14.3]	9.1 [6.8, 13.0]	0.102
Hb range, g/dL	2.9 ± 1.2	2.5 ± 1.1	0.101
Mean absolute monthly Hb change, g/dL	1.1 ± 0.4	0.9 ± 0.4	0.162
Maximum absolute monthly Hb change, g/dL	2.2 ± 0.9	1.9 ± 0.9	0.165
Months with Hb ≥ 10 g/dL	2.1 ± 1.8	2.6 ± 2.2	0.279
Months with Hb < 10 g/dL	3.9 ± 1.8	3.4 ± 2.2	0.279
Months in Hb 10–11.5 g/dL	1.5 ± 1.3	1.9 ± 1.7	0.251
Months with Hb > 11.5 g/dL	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.807

Note: Values are mean ± SD or median [IQR] according to code-generated distribution checks. Metrics use Month 1 through Month 6 post-index Hb values. Hb coefficient of variation = within-patient Hb SD/mean post-index Hb × 100. Group comparisons used Welch *t*-test for approximately symmetric metrics and Mann–Whitney *U*/Wilcoxon rank-sum otherwise.

Abbreviations: ESA, Erythropoiesis-Stimulating Agent; Hb, Hemoglobin; SD, standard deviation.

TABLE 4 | Pathophysiology-informed predictors of Hb variability.

Predictor	Hb SD coefficient (95% CI)	Hb SD <i>p</i>	Mean absolute change coefficient (95% CI)	Mean absolute change <i>p</i>
Roxadustat vs. ESA	−0.16 (−0.41 to 0.08)	0.189	−0.16 (−0.40 to 0.07)	0.163
Baseline Hb, per 1 g/dL higher	0.01 (−0.09 to 0.10)	0.897	0.02 (−0.07 to 0.10)	0.694
Baseline transfusion	0.11 (−0.09 to 0.32)	0.268	0.23 (0.02 to 0.44)	0.032
Ferritin, per 100 ng/mL higher	0.00 (−0.02 to 0.02)	0.842	0.00 (−0.02 to 0.03)	0.851
Albumin, per 1 g/dL higher	−0.01 (−0.17 to 0.16)	0.951	−0.03 (−0.21 to 0.15)	0.736
iPTH, per 100 pg/mL higher	−0.01 (−0.02 to 0.00)	0.060	−0.01 (−0.02 to 0.01)	0.285

Note: Linear regression models used Hb SD and mean absolute month-to-month Hb change as dependent variables. Covariates were treatment group, baseline Hb, baseline transfusion, ferritin per 100 ng/mL, albumin, and iPTH per 100 pg/mL. Coefficients are reported with 95% CIs and *p* values using HC3 heteroskedasticity-robust standard errors. Hb SD model *N* = 108; mean absolute change model *N* = 108. Negative coefficients indicate lower variability.

Abbreviations: ESA, Erythropoiesis-Stimulating Agent; Hb, hemoglobin; iPTH, intact parathyroid hormone; SD, standard deviation.

replacement [11, 12]. As a hypoxia-inducible factor prolyl hydroxylase inhibitor, roxadustat stabilizes HIF signaling, thereby promoting endogenous erythropoietin production and coordinated erythropoiesis-related iron handling [11, 13]. Importantly, roxadustat has been shown to reduce hepcidin and improve iron availability, including increases in transferrin and total iron-binding capacity, which may enhance mobilization and utilization of stored iron in patients with inflammation-related functional iron restriction [11, 13]. These effects provide a plausible biological rationale for improved Hb target achievement in ESA-hyporesponsive hemodialysis patients, although mechanistic confirmation was beyond the scope of the present retrospective analysis.

Hb ≥ 10 g/dL is a clinically meaningful end-point because it corresponds to both guideline and reimbursement thresholds. KDIGO 2026 places ESA initiation in dialysis around Hb ≤ 9–10 g/dL, recommends avoiding maintenance Hb ≥ 11.5 g/dL, and positions HIF-PHIs as selective options in ESA hyporesponsiveness rather than routine ESA replacements [2]. Turkish

reimbursement rules similarly define treatment eligibility around Hb < 10 g/dL and include roxadustat within the reimbursed CKD-anemia treatment framework [3].

However, the roxadustat signal should not be overinterpreted, because response remained incomplete and Hb stability was not clearly improved. Only 52 of 108 patients achieved sustained Hb ≥ 10 g/dL, and only 50.0% of roxadustat-treated patients were at or above this threshold at Month 6. Moreover, Hb variability metrics were numerically favorable but not statistically different, and adjusted models showed no independent association between roxadustat and lower Hb SD or lower mean absolute monthly Hb change. Given that Hb variability has been linked to adverse outcomes in hemodialysis, albeit with some conflicting evidence, these findings suggest that roxadustat improved target achievement more than Hb stability [14–16].

The present findings are directionally consistent with Phase 3 dialysis-dependent CKD trials showing that roxadustat can

correct or maintain Hb compared with ESA therapy. In the Chinese Phase 3 dialysis trial, roxadustat was non-inferior to epoetin alfa for anemia treatment in patients undergoing long-term dialysis [4]. In the ROCKIES Phase 3 trial, roxadustat was likewise non-inferior to epoetin alfa for Hb increase and was associated with reduced red blood cell transfusion and intravenous iron supplementation [17]. Our cohort differs from these trials because all patients had real-world ESA-hyporesponsive anemia with persistent Hb <10 g/dL despite high-dose ESA therapy, making sustained Hb ≥10 g/dL achievement a more stringent and clinically difficult end-point.

Evidence in ESA-hyporesponsive dialysis patients remains limited, but available studies support roxadustat's hematologic activity while mainly assessing Hb rise or target attainment at fixed follow-up points. In a prospective 24-week study of 30 ESA-hyporesponsive hemodialysis patients, Song et al. reported a mean Hb increase of 2.5 ± 1.3 g/dL, with 93.3% achieving >1 g/dL Hb rise and 56.7% reaching mean Hb ≥10 g/dL at Weeks 20–24 [18]. Our analysis extends this literature by evaluating sustained Hb ≥10 g/dL achievement across six monthly measurements rather than relying only on end-point Hb response. This distinction is clinically relevant because ESA hyporesponsiveness identifies a high-risk dialysis phenotype; Cizman et al. reported higher mortality, cardiovascular hospitalization, and healthcare costs in ESA-hyporesponsive versus

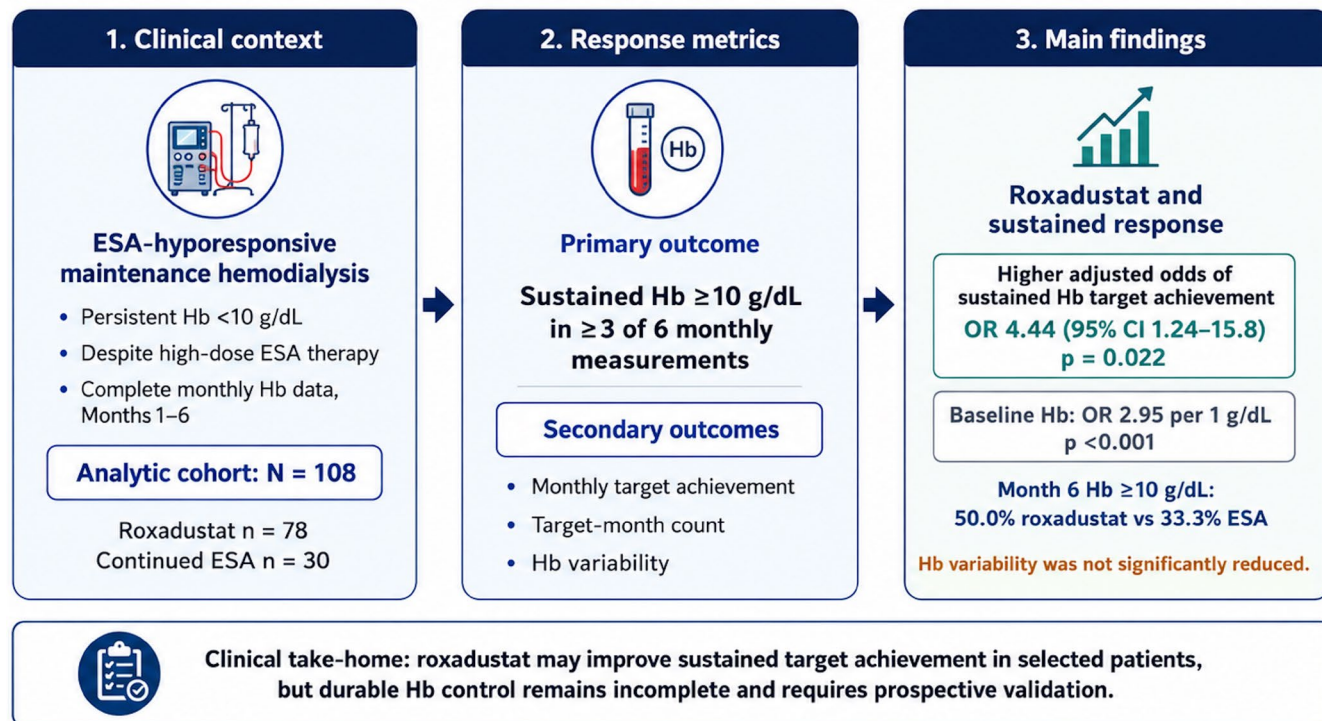
ESA-normoresponsive dialysis patients, and ASCEND-D analyses similarly found baseline ESA hyporesponsiveness to be a strong predictor of major adverse cardiovascular events [19, 20].

These findings have both clinical and methodological implications. Clinically, roxadustat may be considered a targeted option for selected ESA-hyporesponsive patients in whom the practical goal is to achieve Hb ≥10 g/dL after reversible causes of anemia have been addressed, consistent with KDIGO's cautious positioning of HIF-PHIs in ESA hyporesponsiveness rather than as routine first-line ESA replacement [2]. This is relevant because ESA hyporesponsiveness identifies a high-risk hemodialysis phenotype, with recent USRDS data showing higher rates of transfusion, major cardiovascular events, hospitalization, and mortality compared with the broader hemodialysis population [21]. Methodologically, our analysis supports moving beyond mean Hb change alone toward patient-level durability endpoints because Hb target maintenance is difficult even in stable ESA-treated hemodialysis patients, and higher Hb time-in-range has been associated with lower transfusion frequency, healthcare utilization, and costs [22, 23].

This study is limited by its retrospective observational design, non-randomized treatment allocation, modest ESA-control group, and six-month follow-up, which limit causal inference and precision. Residual confounding and confounding by indication

Central Illustration. Roxadustat and Sustained Hemoglobin Response

Secondary analysis in ESA-hyporesponsive maintenance hemodialysis



Hb, hemoglobin; ESA, erythropoiesis-stimulating agent; OR, odds ratio; CI, confidence interval.

FIGURE 3 | Central illustration. Roxadustat and sustained hemoglobin response in ESA-hyporesponsive hemodialysis. The illustration summarizes the study population, response metrics, main findings, and clinical interpretation. Roxadustat was associated with higher adjusted odds of sustained Hb ≥10 g/dL achievement, while baseline Hb remained an important determinant of response and Hb variability was not significantly reduced.

remain possible despite adjustment. The adjusted association between roxadustat and sustained Hb target achievement was significant but imprecise, with a wide confidence interval, supporting the direction more than the exact effect size. In addition, some potentially relevant variables for ESA hyporesponsiveness and anemia management, including oral anticoagulant use, antiplatelet therapy, history of malignancy, history of gastrointestinal bleeding, and patient-level intravenous iron administration, were not included among the variables analyzed in this secondary dataset. Complete monthly Hb data were required, which may introduce selection bias. Strengths include a clearly ESA-hyporesponsive cohort, a concurrent ESA comparator, monthly Hb assessment, and evaluation of both sustained Hb target achievement and Hb variability.

The Central Illustration summarizes the study population, sustained Hb response metric, main adjusted findings, and clinical interpretation, emphasizing that roxadustat may improve sustained Hb target achievement in selected ESA-hyporesponsive patients, while durable Hb control remains incomplete (Figure 3).

5 | Conclusions

In this secondary analysis, roxadustat was associated with higher adjusted odds of sustained Hb ≥ 10 g/dL achievement in ESA-hyporesponsive hemodialysis patients, while baseline Hb remained an important determinant of response. This benefit was not accompanied by a clear reduction in month-to-month Hb variability, and sustained target achievement remained incomplete. Overall, these findings suggest that roxadustat may help selected ESA-hyporesponsive patients reach a clinically meaningful Hb threshold, but durable Hb control remains challenging and should be confirmed in prospective studies.

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The authors have nothing to report.

Ethics Statement

The study was approved by the Harran University Ethics Committee (No. 24.09.07; 01.07.2024). Informed consent was waived due to the retrospective design. All procedures complied with the Declaration of Helsinki.

Conflicts of Interest

T.S. reports receiving speaker honoraria from AstraZeneca, Amgen, Sanofi, Nobel Ilac, Baxter, Boehringer Ingelheim, Astellas, Alexion, and Abdi Ibrahim-Otsuka outside the submitted work. The authors declare

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Monthly Hb target achievement and mean Hb by treatment group.