The Effect of Altitude on Erythropoiesis-Stimulating Agent Dose, Hemoglobin Level, and Mortality in Hemodialysis Patients

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Introduction

- Previous studies have demonstrated that hemodialysis (HD) patients residing at higher altitudes:
  - Utilize less erythropoiesis-stimulating agent (ESA) and have higher hemoglobin (Hb) concentrations [1,2]
  - Have lower all-cause mortality and fewer cardiovascular events [3,4,5]
- It is suggested that these effects may be due to regulation of hypoxia-responsive genes.[6]
- There has been a fundamental change in anemia management in end-stage renal disease (ESRD) patients since 2011. It is therefore important to understand the effects of altitude on patient outcomes in a contemporary population of ESRD patients.
  - Confirmation would lend support to the effect of altitude being the consequence of a real biological mechanism, as opposed to an artifact of the previous standard of care.

Objective

To better understand the impact of altitude on utilization of anemia medications and mortality following the 2011 changes to the US epoetin alfa label and reimbursement policy.

Methods

Data Source and Population

- The study was a retrospective observational analysis. Data were derived from the electronic health records of a large dialysis organization (LDO) for the 2012 calendar year.
- Patients included in the analysis were, as of 01 January 2012, ≥18 years old, non-US veterans, and receiving hemodialysis at the LDO with a dialysis vintage of at least 6 months.

Analysis

- The exposure of interest was altitude, which was determined by clinic ZIP code. Outcomes were assessed over the 2012 calendar year.
- ESA hyporesponse was defined as 2 consecutive bimonthly Hb measures <10 g/dL with ESA dose >7700 U/treatment at baseline.
- Erythropoietin resistance index (ERI) was defined as the mean monthly ESA dose divided by the mean monthly Hb during the study period.
- ESA and intravenous (IV) iron utilization were calculated as the proportion of patient use (yes/no) and dose among users (ie, non-users excluded).
  - Associations with altitude categories were estimated using mixed linear models.
  - Models were adjusted for covariates that differed significantly across altitude categories at baseline ($P<0.10$).
- Mortality and missed dialysis treatment rates were calculated as the number of events divided by time at risk.
  - Associations with altitude categories were estimated using mixed models assuming Poisson and negative binomial outcome distributions.
  - Models were adjusted for covariates that differed significantly at baseline ($P<0.10$).
  - Confidence intervals (95% CI) were determined by generating bootstrap estimates with 100 replicates, using unrestricted replacement sampling.

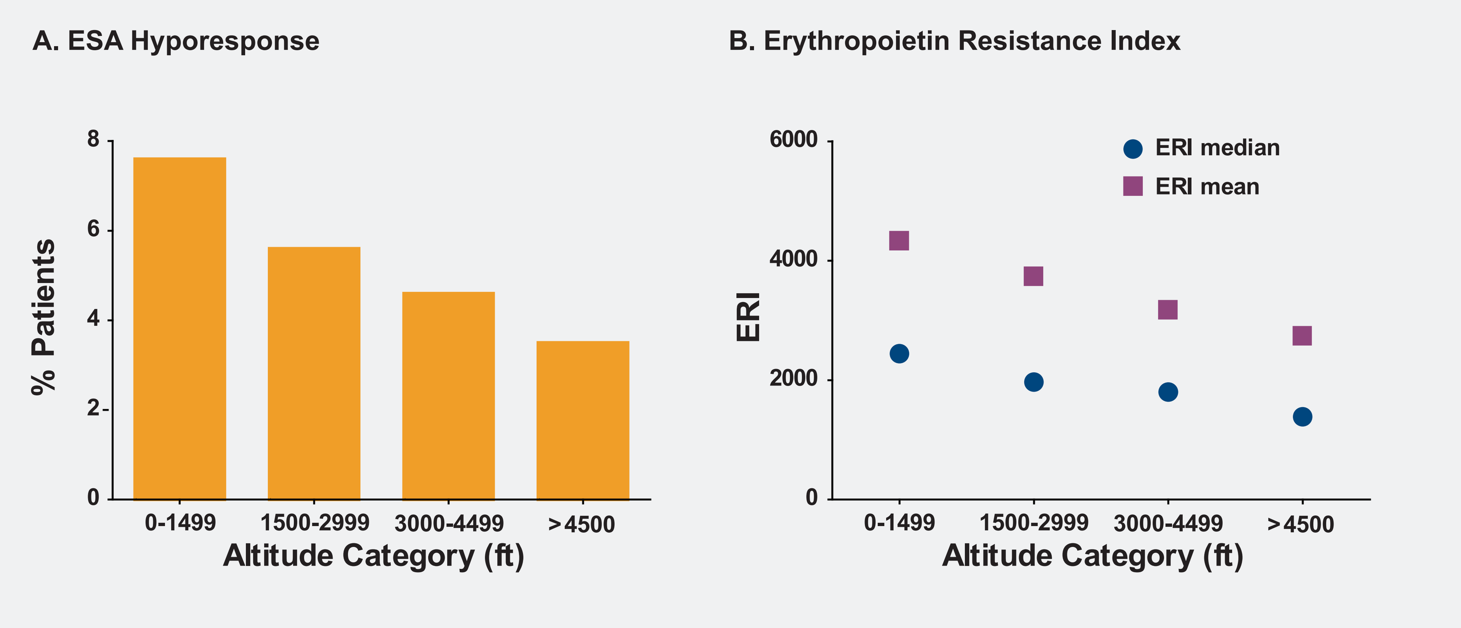
Results

Table 1. Baseline Patient Characteristics by Altitude Category

		Altitude Category 0-1499 N = 92,490	1500-2999 N = 3118	3000-4499 N = 1659	>4500 N = 2027	*P*-Value
Age, years,	mean ± SD	61.6 ± 14.9	61.9 ± 14.6	62.3 ± 14.0	63.0 ±14.8	< 0.001
Sex						0.41
Male		54.5%	53.1%	55.3%	54.2%	
Female		45.5%	46.9%	44.7%	45.8%	
Race						< 0.001
White		33.7%	49.4%	21.6%	40.5%	
Black		41.6%	14.3%	4.2%	12.1%	
Hispanic		17.3%	19.5%	69.1%	19.2%	
Asian		3.8%	4.4%	1.0%	2.2%	
Other/Unknown		3.7%	12.4%	4.2%	26.0%	
Etiology ESRD						< 0.001
Diabetes		44.5%	50.6%	59.8%	54.1%	
Hypertension		31.9%	25.2%	21.0%	15.1%	
Other/Unknown		23.5%	24.3%	19.2%	30.7%	
Postdialysis weight, kg	mean ± SD	80.4 ± 22.7	80.8 ± 22.7	77.5 ± 20.1	77.9 ± 21.4	< 0.001
Vintage, months	median [p25, p75]	38 [20, 68]	36 [19, 63]	46 [22, 74]	43 [23, 76]	< 0.001
Vascular access						< 0.001
Fistula		64.5%	67.9%	76.3%	76.0%	
Graft		22.7%	19.2%	15.1%	16.0%	
Catheter		12.8%	12.8%	8.6%	7.9%)	
Diabetes		68.8%	69.7%	81.1%	73.8%	< 0.001
Congestive heart failure		12.8%	11.4%	6.1%	7.8%	< 0.001
Coronary artery disease		7.9%	8.2%	10.9%	6.9%	< 0.001
Cerebrovascular disease		0.8%	1.0%	0.4%	0.5%	0.03
Cancer		2.0%	2.5%	1.4%	2.5%	0.03
Infection		0.7%	0.7%	0.4%	0.5%	0.25
Peripheral vascular disease		2.0%	4.0%	2.7%	2.0%	< 0.001
GI bleed		1.2%	1.1%	0.9%	1.5%	0.38
Charlson comorbidity index,	mean ± SD	5.49 ± 1.93	5.57 ± 1.93	5.74 ± 1.75	5.68 ± 1.84	< 0.001
Ferritin, ng/mL	median [p25, p75]	790 [549, 1032]	841 [592, 1094]	831 [610, 1088]	694 [417, 943]	< 0.001
TSAT, %	mean ± SD	31.7 ± 14.3	32.5 ± 14.6	33.4 ± 14.8	31.9 ± 14.2	< 0.001
PTH, pg/mL	median [p25, p75]	360 [225, 563]	335 [210, 519]	315 [199, 463]	316 [201, 493]	< 0.001
Kt/V	mean ± SD	1.61 ± 0.32	1.68 ± 0.33	1.71 ± 0.32	1.75 ± 0.35	< 0.001
Albumin, g/dL	mean ± SD	3.96 ± 0.41	3.95 ± 0.41	3.98 ± 0.40	3.94 ± 0.38	< 0.001

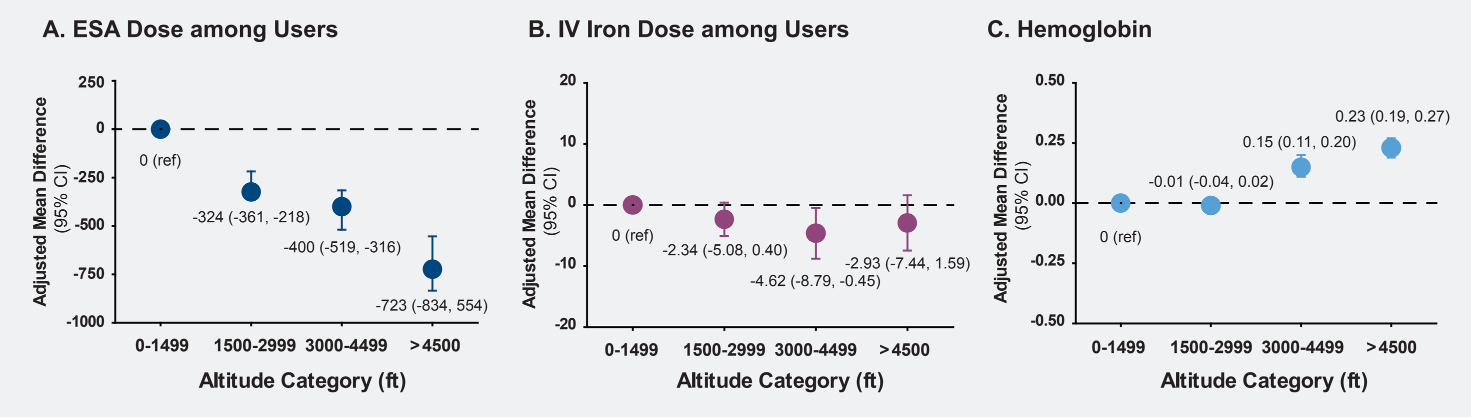
Abbreviations: ESA, erythropoiesis-stimulating agent; ESRD, end-stage renal disease; GI, gastrointestinal; IV, intravenous; TSAT, transferrin saturation; PTH, parathyroid hormone, SD, standard deviation

Figure 1. ESA Hyporesponse and Erythropoietin Resistance Index Score by Altitude Category



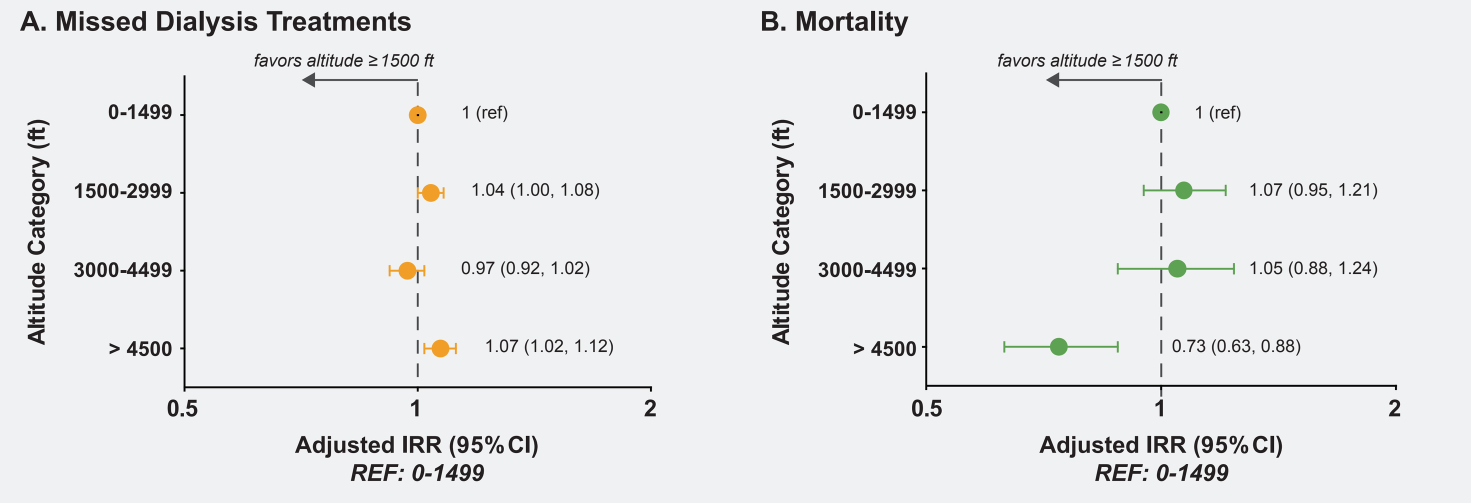
Abbreviations: ESA, erythropoiesis-stimulating agent; ERI, erythropoietin resistance index

Figure 2. Differences in ESA and IV Iron Dose and Hemoglobin Level by Altitude Category



Abbreviations: CI, confidence interval; ESA, erythropoiesis-stimulating agent; IV, intravenous
Adjustments were made for covariates that were imbalanced ($P<0.1$) across groups at baseline.

Figure 3. Incidence Rate Ratios for Missed Dialysis Treatments and Mortality by Altitude Category



Abbreviations: CI, confidence interval; IRR, incidence rate ratio; ref, referent
Adjustments were made for covariates that were imbalanced ($P<0.1$) across groups at baseline.

Table 2. Description of Outcomes by Altitude Category

	Altitude Category 0-1499 N = 92,490	1500-2999 N = 3118	3000-4499 N = 1659	>4500 N = 2027
ESA				
Utilization, U/treatment [a]				
Mean ± SD	3517 ± 3994	3063 ± 3701	2456 ± 3099	2257 ± 3191
Median [p25, p75]	2200 [1015, 4492]	1729 [769, 3977]	1523 [677, 3046]	1257 [0, 2800]
Users (%)	88.3%	85.0%	82.0%	74.2%
Dose among Users, U/treatment				
Unadjusted modeled mean (95% CI) [b]	2599 (2585, 2613)	2278 (2206, 2351)	2002 (1932, 2074)	1871 (1795, 1949)
Adjusted modeled mean (95% CI) [b]	2907 (2553, 3311)	2615 (2288, 2989)	2495 (2180, 2854)	2182 (1905, 2501)
IV Iron				
Utilization, mg/month [a]				
Mean ± SD	162 ± 159	162 ± 150	138 ± 152	135 ± 159
Median [p25, p75]	200 [0, 200]	200 [0, 200]	150 [0, 200]	100 [0, 200]
Users (%)	73.2%	74.6%	65.6%	62.8%
Dose among Users, mg/month				
Unadjusted modeled mean (95% CI) [b]	222 (221, 222)	218 (215, 221)	211 (207, 215)	214 (210, 219)
Adjusted modeled mean (95% CI) [b]	260 (245, 275)	257 (242, 272)	255 (240, 271)	257 (241, 272)
Hemoglobin, g/dL				
Mean ± SD	10.89 ± 1.15	10.91 ± 1.17	11.12 ± 1.19	11.14 ± 1.29
Median [p25, p75]	10.90 [10.20, 11.50]	10.90 [10.20, 11.50]	11.10 [10.40, 11.70]	11.10 [10.40, 11.80]
Unadjusted modeled mean (95% CI) [b]	10.89 (10.88, 10.89)	10.91 (10.88, 10.94)	11.12 (11.07, 11.16)	11.14 (11.10, 11.19)
Adjusted modeled mean (95% CI) [b]	10.83(10.74, 10.92)	10.82 (10.73, 10.91)	10.98 (10.88, 11.07)	11.06 (10.96, 11.15)
Missed Dialysis Treatments				
At-risk time (patient-years)	80,873	2653	1481	1821
Number of missed treatments	976,200	31,707	15,321	21,924
Unadjusted modeled rate (95% CI) [b]	12.07 (11.98, 12.15)	11.94 (11.45, 12.45)	10.33 (9.78, 10.91)	12.05 (11.45, 12.69)
Adjusted modeled rate (95% CI) [b]	10.70 (8.95, 12.79)	11.14 (9.29, 13.37)	10.38 (8.61, 12.50)	11.44 (9.51, 13.77)
Mortality				
At-risk time (patient-years)	80,873	2653	1481	1821
Number of deaths	7837	292	134	140
Unadjusted rate (95% CI) [b]	0.096 (0.095, 0.099)	0.11 (0.098, 0.123)	0.09 (0.076, 0.107)	0.08 (0.065, 0.091)
Adjusted rate (95% CI) [b]	0.08 (0.05, 0.13)	0.09 (0.06, 0.14)	0.09 (0.05, 0.14)	0.06 (0.04, 0.10)

[a] Includes non-users.
[b] CI were generated using a bootstrapping method. Adjustments were made for covariates that were imbalanced ($P<0.1$) across groups at baseline.
Abbreviations: CI, confidence interval; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; IV, intravenous; p25, 25th percentile; p75, 75th percentile; pt, patient; SD, standard deviation.

- Compared to patients in the lowest altitude category, patients in the highest altitude category were older with lower dry weight, longer dialysis vintage, and higher Kt/V; were more frequently white and/or diabetic; were less likely to have a history of hypertension or congestive heart failure; and had lower ferritin values (Table 1).
- The frequency of ESA hyporesponse and ERI scores decreased with higher altitude (Figure 1).
- Patients at higher altitude were less likely to receive ESA treatment (range, 88.3% to 74.2%). Per treatment ESA dose among users decreased with increasing altitude category: the adjusted mean difference in dose between the lowest and highest altitude categories was -723 U/treatment (Figure 2A and Table 2).
- The proportion of patients using IV iron decreased incrementally with increasing altitude category (range, 74.6% to 62.8%) but there was no difference in mean monthly IV iron utilization across categories (Figure 2B and Table 2).
- Hb concentration increased incrementally with higher altitude; patients in the 2 highest altitude categories had greater mean Hb values (+0.15 and +0.23 g/dL, respectively) than patients in the lowest altitude category.
- Patients in the highest altitude category had a higher rate of missed dialysis treatments compared to those in the lowest altitude category (incidence rate ratio [IRR], 1.07; Figure 3A and Table 2).
- Mortality was lower for patients in the highest altitude category compared to those in the lowest altitude category (IRR, 0.73; Figure 3B and Table 2).

Conclusions

- Among contemporary HD patients, higher altitude was associated with higher Hb levels despite lower ESA doses and comparable IV iron utilization. Frequency of ESA hyporesponse and ERI scores both decreased with increasing altitude.
- Compared to altitude <1500 ft, altitude >4500 ft was independently associated with 26% lower mortality risk but a 7% greater rate of missed dialysis treatments.
- These findings confirm that the positive association between higher altitude and patient outcomes is still evident in the context of current anemia management.

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