Altitude and All-Cause Mortality in Incident Dialysis Patients

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Context Patients undergoing dialysis at higher altitude receive lower erythropoietin doses, yet achieve higher hemoglobin concentrations. Increased iron availability caused by activation of hypoxia-induced factors at higher altitude may explain this finding. Hypoxia-induced factors are also involved in other pathways that may affect morbidity and mortality.

Objective To study whether mortality differed by altitude in patients initiating dialysis.

Design, Setting, and Participants Retrospective cohort of patients initiating dialysis in the United States between 1995 and 2004. Patients were stratified by the average elevation of their residential zip code. Covariates included age, sex, race, Medicaid coverage, dialysis modality, comorbidities, and reported laboratory measurements. We constructed proportional hazards models of all-cause mortality, stratifying by year, and censoring patients at 5 years from first dialysis, at the end of the database (December 31, 2004), or loss to follow-up. We also compared age- and sex-adjusted standardized mortality rates of US patients receiving dialysis with the general population.

Main Outcome Measure Mortality from any cause.

Results A total of 804 812 patients initiated dialysis and were followed up for a median of 1.78 years. Crude mortality rates per 1000 person-years were 220.1 at an altitude lower than 76 m (<250 ft), 221.2 from 76 through 609 m (250-1999 ft), 214.6 from 610 through 1218 m (2000-3999 ft), 184.9 from 1219 through 1828 m (4000 to 5999 ft), and 177.2 at an altitude higher than 1828 m (>6000 ft). After multivariable adjustment, compared with patients living at an altitude of lower than 76 m, the relative mortality rates were 0.97 (95% confidence interval [CI], 0.96-0.98) for those living from 76 through 609 m; 0.93 (95% CI, 0.91-0.95), from 610 through 1218 m; 0.88 (95% CI, 0.84-0.91), from 1219 through 1828 m, and 0.85 (95% CI, 0.79-0.92) higher than 1828 m. Age- and sex-standardized mortality decreased more with altitude in patients receiving dialysis than in the general population.

Conclusions Altitude was inversely associated with all-cause mortality among US patients receiving dialysis.

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IT WAS RECENTLY REPORTED THAT patients with end-stage renal disease (ESRD) living at higher altitude achieved greater hemoglobin concentrations while receiving lower doses of erythropoietin.[1] This study raised the possibility that certain biological factors that are induced by hypoxia may be responsible for this finding. Hypoxia-induced factors, whose transcriptional activities may be increased at higher altitude in patients with ESRD, have been shown to improve iron availability, which may lead to more efficient erythropoiesis.[2,3] Hypoxia-induced factors also regulate many enzymes that could affect cardiovascular risk, such as vascular endothelial growth factor, heme oxygenase-1, inducible nitric oxide synthase, and cyclooxygenase 2.[4,5]

From these theoretical effects of hypoxia–induced factor activation at higher altitude, we hypothesized that increased altitude would be associated with reduced mortality risk among patients initiating chronic dialysis in the United States, and that this association would be more pronounced than in the US general population due to the blunted erythropoietin response to hypoxia-induced factors activation in patients with ESRD.

METHODS

Data Sources

This study used data from the United States Renal Data System (USRDS) and the US Geological Survey (USGS). The USRDS contains detailed data on all patients in Medicare's ESRD program. The Medical Evidence Form contains demographic data; the likely cause of ESRD; some clinical baseline data such as weight and height; and certain laboratory measurements, such as serum albumin, creatinine, and hematocrit concentrations. In addition, the USRDS contains all Medicare Part A and B claims that include information on diagnoses and procedures recorded for all hospitalizations and outpatient visits.

As described previously, we used data from the USGS and each patient's residential zip code to define the altitude of each study patient's residence.[1]

The Brigham and Women's Hospital Institutional Review Board approved this research.

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Patient Selection

From the USRDS standard analytic files, we selected all adult patients (≥18 years) who initiated dialysis treatment between January 1, 1995, and December 31, 2004. We excluded all patients who underwent preemptive kidney transplantation as primary ESRD treatment. Patients whose age, sex, or race was missing or implausible were also dropped from study. Follow-up began at the first reported date of renal replacement therapy.

Patient Characteristics

We classified all patients into 5 strata based on the elevation above sea level based on their zip code of residence: lower than 76 m (<250 ft), from 76 through 609 m (250-1999 ft), from 610 through 1218 m (2000-3999 ft), from 1219 through 1828 m (4000-5999 ft), and higher than 1828 m (>6000 ft). Covariates included demographic data as reported in the Medical Evidence Form such as age at first dialysis, sex, race (white, black, Asian, Native American, other), and Medicaid coverage as a proxy for socioeconomic status. Comorbidities were also derived from the Medical Evidence Form and included diabetes, hypertension, congestive heart failure, ischemic heart disease or myocardial infarction, cerebrovascular disease, peripheral arterial vascular disease, cardiac arrest, arrhythmia, chronic obstructive pulmonary disease, and cancer. We also noted whether a patient was unable to ambulate or transfer, whether a patient used hemodialysis or peritoneal dialysis, and whether a patient had received erythropoietin treatment prior to initiation of dialysis. From height and weight, we determined each patient's body mass index (BMI), calculated as weight in kilograms divided by height in meters squared. Baseline laboratory measurements included albumin, hemoglobin, creatinine, estimated glomerular filtration rate (GFR), and hematocrit.

Outcome

Death from any cause was the outcome of interest in this study, and each patient's date of death was ascertained from the USRDS data set.

Statistical Analyses

We calculated means and frequencies of patient characteristics by elevation group. We constructed Cox proportional hazards models for the time from first dialysis to death from any cause, stratifying by year, and censoring patients at 5 years after their first dialysis, at the end of database (December 31, 2004), or loss to follow-up; those living at an elevation of lower than 76 m served as reference category for all analyses.

We sequentially built increasingly adjusted models to understand the forces driving any possible confounding: (1) crude; (2) adjusted for demographic factors; (3) additionally adjusted for comorbid conditions including the inability to ambulate or transfer and dialysis modality; and (4) additionally adjusted for BMI, estimated GFR, and hemoglobin and albumin concentration. We conducted these analyses in the overall sample as well as in subgroups defined by age, sex, and race.

We provided the relative rate (RR) of death for each elevation group accompanied by its 95% confidence interval (CI). An $\alpha < .05$ constituted statistical significance. All statistical analyses were conducted using SAS version 9.1. (SAS Institute Inc, Cary, North Carolina).

We also obtained from the Centers for Disease Control and Prevention data on the county-specific mortality rates for the US general population for the years 1999-2005.[6] Each county was assigned an average elevation from the USGS. We then generated age- and sex-specific mortality rates for each altitude stratum, which were then used for age- and sex-standardization to the lowest altitude stratum in the Centers for Disease Control and Prevention data; using the same standard, age- and sex-standardized mortality rates were also calculated for the USRDS population for direct comparison with findings from the general population.

RESULTS

We identified 804 812 patients with ESRD who initiated hemodialysis or peritoneal dialysis between 1995 and 2004 and who met the study entry requirements. Most patients resided below an altitude of 76 m (40.5%) or between 76 and 609 m (54.4%). Only 1.9% of incident dialysis patients lived between 1219 and 1828 m and 0.4% higher than 1828 m. These patients' characteristics at initiation of renal replacement therapy are shown in TABLE 1, stratified by elevation group. Patients living at higher altitude tended to be slightly younger, more likely to undergo peritoneal vs hemodialysis, and more likely to have hypertension or diabetes. Other comorbid conditions were slightly less common at higher altitude, such as congestive heart failure or ischemic heart disease. The most obviously imbalanced characteristic was race. Although blacks constituted 37.6% of patients with incident dialysis at an elevation of lower than 76 m, only 4.2% of patients were black in the highest altitude group. Asians were also more common at lower altitude. Native Americans, however, constituted only 0.4% of incident patients at or near sea level, whereas nearly one-quarter of patients living at an altitude higher than 1828 m were Native American. Among the biometric measurements available, BMI, albumin levels, and estimated GFR at initiation of dialysis tended to be slightly lower at higher altitude.

Over a median follow-up of 1.78 years and 1.99 million person-years available for analysis, 436 772 patients died (crude mortality rate, 219.7 per 1000 person-years). Crude mortality differed across elevation groups and was monotonically lower at higher altitude (Wilcoxon rank sum, $P < .001$): 220.1 per 1000 person-years (95% CI, 219.1-221.2) at less than 76 m, whereas it was 177.2 per 1000 person-years (95% CI, 169.0-185.7) at an altitude higher than 1828 m, for an unadjusted incidence rate ratio of 0.81 (95% CI, 0.78-0.85; TABLE 2). Actuarial 5-year survival

was 34.8% for patients living at or near sea level but was 42.7% among those living at an altitude higher than 1828 m; patients in the highest elevation group experienced a 7.9% greater absolute or 22.7% greater relative 5-year survival. Median survival after initiation of dialysis was 3.1 years for those living lower than 76 m but was 4.0 years for those living at an altitude higher than 1828 m, for a difference in median survival of 0.9 years between these 2 groups.

We sequentially introduced possible confounders into the unadjusted mortality model: (1) demographics; (2) comorbidities, inability to ambulate, inability to transfer, predialysis erythropoietin use, and dialysis modality; and (3) BMI and selected laboratory measurements. As can be seen in Table 2, the results changed only slightly and were essentially identical between the last 2 analyses (only 61.8% of patients had complete information on laboratory values and BMI and were included in the last analyses). Compared with patients living near sea level, mortality was reduced for patients living from 76 through 609 m by 3% (95% CI, 2%-4%); from 610 m through 1218 m, by 7% (95% CI, 5%-9%), from 1219 through 1828 m, by 12% (95% CI, 9%-16%), and higher than 1828 m, by 15% (95% CI, 8%-21%). Whether we included predialysis erythropoietin use, baseline hemoglobin concentration, or both in these analyses did not influence these findings.

These results were also virtually unchanged in subgroups defined by age, sex, Medicaid coverage, presence of diabetes, ischemic heart disease, or congestive heart failure (not shown).

In the general US population, we also found a small reduction in age- and sex-standardized mortality at higher altitudes. On the relative scale, compared with individuals living at or near sea level, those living at higher

Table 1. Baseline Characteristics by Elevation Group

	Residential Elevation, m				
	<76	76-609	610-1218	1219-1828	>1828
Patients, No. (%)	325 722 (40.5)	437 855 (54.4)	22 556 (2.8)	15 110 (1.9)	3569 (0.4)
Age, mean (SD), y	61.9 (15.5)	62.0 (15.3)	61.4 (14.8)	60.6 (15.3)	60.2 (15.2)
Male sex, No. (%)	174 336 (53.5)	234 227 (53.5)	12 304 (54.6)	8418 (55.7)	1946 (54.5)
Race, No. (%)					
White	187 055 (57.4)	301 145 (68.8)	19 245 (85.3)	12 138 (80.3)	2544 (71.3)
Black	122 543 (37.6)	121 784 (27.8)	1699 (7.5)	946 (6.3)	148 (4.2)
Asian	14 845 (4.6)	9898 (2.3)	250 (1.1)	393 (2.6)	55 (1.5)
Native American	1279 (0.4)	5028 (1.2)	1362 (6.0)	1633 (10.8)	822 (23.0)
Medicaid coverage, No. (%)	81 195 (24.9)	95 848 (21.9)	5281 (23.4)	2969 (19.7)	806 (22.6)
Hemodialysis (vs peritoneal), No. (%)	300 875 (92.4)	394 721 (90.2)	19 545 (86.7)	13 680 (90.5)	3106 (87.0)
Reported comorbidities, No. (%)					
Hypertension	237 842 (73.0)	329 515 (75.3)	17 116 (75.9)	11 520 (76.2)	2764 (77.4)
Congestive heart failure	98 718 (30.3)	138.125 (31.6)	6541 (29.0)	3876 (25.7)	989 (27.7)
Myocardial infarction	24 984 (7.7)	39 063 (8.9)	1762 (7.8)	1287 (8.5)	306 (8.6)
Ischemic heart disease	72 839 (22.4)	107 264 (24.5)	4690 (20.8)	2928 (19.4)	609 (17.1)
Cardiac dysrhythmia	17 450 (5.4)	26.331 (6.0)	1026 (4.6)	741 (4.9)	174 (4.9)
Cardiac arrest	2187 (0.7)	3660 (0.8)	157 (0.7)	112 (0.7)	24 (0.7)
Cerebrovascular disease	27 424 (8.4)	40 442 (9.2)	1659 (7.4)	1033 (6.8)	254 (7.1)
PAVD	43 531 (13.4)	62.247 (14.2)	2832 (12.6)	1809 (12.0)	494 (13.8)
Diabetes mellitus	147 488 (45.3)	211 429 (48.3)	12 247 (54.3)	8193 (54.2)	2011 (56.4)
COPD	19 778 (6.1)	34.968 (8.0)	1544 (6.9)	910 (6.0)	208 (5.8)
HIV	4258 (1.3)	9670 (2.2)	259 (1.1)	24 (0.2)	2 (0.1)
Cancer	15 972 (4.9)	24 859 (5.7)	1083 (4.8)	664 (4.4)	168 (4.7)
Inability to transfer	4397 (1.4)	5975 (1.4)	235 (1.0)	125 (0.8)	25 (0.7)
Inability to ambulate	12 471 (3.8)	17 078 (3.9)	690 (3.1)	453 (3.0)	92 (2.6)
Baseline rhEPO use	91 910 (29.2)	118 649 (27.1)	5084 (22.5)	3265 (21.6)	773 (21.7)
BMI, mean (SD)	26.7 (7.1)	27.1 (7.1)	26.8 (6.9)	26.6 (6.4)	26.1 (5.9)
Clinical values, mean (SD)					
Serum hemoglobin, g/dL	9.7 (1.8)	9.8 (1.6)	10.0 (1.8)	10.2 (1.8)	10.3 (1.9)
Serum creatinine, mg/dL	7.8 (3.8)	7.5 (3.6)	7.1 (3.4)	7.6 (3.4)	7.8 (3.5)
Estimated GFR, mL/min/1.73 m^2	8.9 (4.9)	9.3 (5.1)	9.4 (5.0)	8.6 (4.2)	8.2 (4.0)
Serum albumin, g/dL	3.2 (0.7)	3.2 (0.7)	3.1 (0.7)	3.1 (0.7)	3.1 (0.7)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate, calculated; HIV, human immunodeficiency virus; PAVD, peripheral arterial vascular disease; rhEPO, recombinant human erythropoietin.
SI conversion factor: to convert from meters to feet, divide by 0.3; creatinine from mg/dL to mmol/L, multiply by 88.4.

Table 2. Unadjusted and Adjusted Relative Mortality in US Patients Receiving Dialysis[a]

	Residential Elevation, m				
	<76	76-609	610-1218	1219-1828	>1828
No. of deaths	177 412	238 214	12 046	7380	1720
Mortality rate (95% CI)					
Per 1000 person-years	220.1 (219.1-221.2)	221.2 (220.3-222.1)	214.6 (210.8-218.5)	184.9 (180.7-189.1)	177.2 (169.0-185.7)
Unadjusted	1.0 [Reference]	1.00 (1.00-1.01)	0.97 (0.96-0.99)	0.85 (0.83-0.87)	0.81 (0.78-0.85)
Adjusted for age, sex, race, Medicaid coverage	1.0 [Reference]	0.99 (0.98-1.00)	0.95 (0.93-0.97)	0.85 (0.83-0.87)	0.83 (0.79-0.87)
Additionally adjusted for comorbidities, inability to ambulate, inability to transfer, baseline rhEPO use, and dialysis modality	1.0 [Reference]	0.97 (0.97-0.98)	0.96 (0.94-0.97)	0.86 (0.84-0.88)	0.85 (0.81-0.89)
Additionally adjusted for BMI, estimated GFR, hemoglobin, and serum albumin[b]	1.0 [Reference]	0.97 (0.96-0.98)	0.93 (0.91-0.95)	0.88 (0.84-0.91)	0.85 (0.79-0.92)

Abbreviations: BMI, body mass index; CI, confidence interval; GFR, glomerular filtration rate; rhEPO, recombinant human erythropoietin.
Metric conversion factor: to convert meters to feet, divide by 0.3.
[a] All analytical models were stratified by year of initiation of dialysis treatment.
[b] Restricted to the 496 984 patients (61.8% of the overall sample) for whom complete information on weight, height, serum creatinine, hemoglobin, and albumin concentrations were available.

than 1828 m experienced a 7% lower mortality, but the reduction in age-sex-standardized mortality in patients with ESRD between these 2 altitude groups was more than 2-fold greater (15%; TABLE 3). Of note, the 95% CIs for the hazard ratio (HR) between the extreme altitude groups in patients receiving dialysis (HR, 0.85; 95% CI, 0.80-0.91) and in the general population (HR, 0.93; 95% CI, 0.92-0.93) did not overlap, thus indicating that the observations from the general and the ESRD populations are different. Comparing the lowest and highest altitude strata on the absolute scale provided an even starker contrast. Although there are 83 (95% CI, 76-91) fewer deaths per 100 000 age- and sex-standardized person-years at the highest altitude in the general population, there were 2336 (95% CI, 1512-3160) fewer than expected deaths among patients with ESRD living at an altitude higher than 1828 m compared with those living lower than an altitude of 76 m.

Table 3. Age- and Sex-Standardized Mortality Rates in the US General and Dialysis Populations

Residential Elevation, m	General Population	United States Renal Data System
Standardized mortality rates (95 CI)[a]		
Rates per year		
<76	0.01131 (0.01130 to 0.01132)	0.15793 (0.15699 to 0.15886)
76-609	0.01188 (0.01187 to 0.01189)	0.15476 (0.15397 to 0.15554)
610-1218	0.01153 (0.01150 to 0.01156)	0.15406 (0.15050 to 0.15762)
1219-1828	0.01108 (0.01105 to 0.01112)	0.13474 (0.13074 to 0.13874)
>1828	0.01048 (0.01041 to 0.01056)	0.13456 (0.12637 to 0.14275)
Rate ratios		
<76	1.0 [Reference]	1.0 [Reference]
76-609	1.050 (1.049 to 1.051)	0.980 (0.972 to 0.988)
610-1218	1.019 (1.016 to 1.021)	0.976 (0.952 to 0.999)
1219-1828	0.980 (0.977 to 0.983)	0.853 (0.828 to 0.879)
>1828	0.927 (0.920 to 0.933)	0.852 (0.802 to 0.906)
Rate differences per 100 000 person-years		
<76	1.0 [Reference]	1.0 [Reference]
76-609	57 (55 to 58)	–317 (–194 to –439)
610-1218	21 (18 to 25)	–386 (–18 to –755)
1219-1828	–23 (–19 to –26)	–2319 (–1908 to –2729)
>1828	–83 (–76 to –91)	–2336 (–1512 to –3160)

Abbreviation: CI, confidence interval.
Metric conversion factor: to convert from meters to feet, divide by 0.3.
[a] All mortality rates were age- and sex-standardized to the general US population living at altitude lower than 76 m.

COMMENT

We used the comprehensive US dialysis registry to examine differences in survival across elevation groups defined by patients' residential zip codes. We found a monotonic increase in survival across elevation, with patients initiating dialysis treatment at an altitude higher than 1828 m experiencing a 15% reduced mortality compared with similar patients who began dialysis living near sea level. These findings were present in crude analyses and did not change meaningfully after controlling for demographic characteristics, several comorbid conditions, and biometric measurements or after stratification on important variables. Furthermore, while a decrease in age- and sex-standardized mortality at higher altitude was also observed in the general population, the magnitude of the risk reduction was half of that observed in the ESRD population.

The present study was hypothesis-driven by previous observations of greater erythropoietin response in patients receiving dialysis who resided at higher altitude. It was suspected that such an observation could be explained by greater activation of hypoxia-inducible factors, which may increase erythropoietin effectiveness and availability of stored iron in patients living at higher altitude. Hypoxia-induced factors, however, are involved with the regulation of many other biological pathways that might affect morbidity and mortality. The dialysis population was thought to be an interesting model population for studying potential effects of hypoxia-induced factor activation. Erythropoietin production in the failed kidney is mostly absent, and the natural feedback loop leading to down regulation of hypoxia–induced activated systems is only partly operational and dependent on exogenous erythropoietin administration by dialysis providers. Thus, to juxtapose the association of altitude and mortality in patients receiving dialysis and in the general population, where this feedback loop is closed, is crucial to support the validity of our hypothesis.

To our knowledge, this study also appears to be the first to systematically describe an association between altitude and age- and sex-standardized mortality in the overall US general population. Smaller-scale studies have previously described such associations in more selected populations.[7,8] These epidemiological associations between altitude and mortality may be confounded,[9] for example in that sicker patients may systematically migrate to lower altitudes at various points during their lifetime.[10] Such behavior, however, increases the apparent mortality gradient across altitude in the general population, and controlling for it would further augment the contrast with our findings from the dialysis population.

One important limitation of the present work is the possibility that our results could be due to uncontrolled patient characteristics or environmental factors correlated with altitude rather than an independent effect of altitude.[11] Thus, we cannot be certain whether the observed association between altitude and mortality is causal. It is encouraging, however, that multivariable adjustment for observed characteristics had only a small effect on the associations found and, furthermore, that the association between altitude and mortality risk was observed within all subgroups that we examined. Further research with more detailed clinical data could help rule out unmeasured confounding as an explanation of our results.

In conclusion, we found a graded reduction in mortality from any cause in ESRD patients residing at greater altitude, a finding that was not explained by differences in observed patient characteristics. The magnitude of this observation was markedly greater than the observed small reduction in mortality at higher altitude in the general population. We propose that hypoxia-inducible factors are persistent at high altitude in patients with ESRD and may confer protective effects.

Author Contributions: Dr Winkelmayer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Winkelmayer, Brookhart.
Acquisition of data: Winkelmayer, Brookhart.
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