Article

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Impact of Altitude on Erythrocyte Sedimentation Rate: A Cross-Sectional Study Using National Laboratory Data from Saudi Arabia

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Background: The erythrocyte sedimentation rate (ESR) is a widely used haematological test that indirectly measures inflammation in the body. It is influenced by various factors, including age, sex, and physiological condition. Altitude is another critical factor due to its impact on red blood cell physiology and plasma protein composition. This study aims to evaluate how altitude influences ESR values in the Saudi Arabian population, considering demographic and clinical variables.

Methods: This cross-sectional study analyzed data from 158,539 participants collected from 42 commercial laboratory branches across 13 administrative regions in Saudi Arabia from 1 January 2015 to 31 December 2022. Participants were categorized based on city altitude and demographic characteristics including body mass index (BMI), alanine transaminase (ALT), chronic kidney disease (CKD), glycated haemoglobin (HbA1c), and thyroid-stimulating hormone (TSH) level. Univariate and multivariate logistic regression models were used to assess the factors influencing elevated ESR.

Results: The study analyzed 158,539 participants, with an equal sex distribution (49.9%) and a mean age of 40 years. The adjusted model results showed a CKD prevalence of 3%, with a higher prevalence at lower altitudes (3.8% at 0–500 meters). ESR levels were significantly influenced by sex, age, altitude, and clinical measurements. Males were less likely to have elevated ESR than females (odds ratio (OR) = 0.470, 95% confidence interval (CI): 0.440–0.510, $p < 0.001$). Older age was a strong predictor of elevated ESR, with those aged 90+ at a fourfold higher risk (OR = 4.540, 95% CI: 1.410–14.548, $p = 0.011$). Higher altitude was associated with reduced ESR, with an odds ratio of 0.660 (95% CI: 0.560–0.769, $p < 0.001$) above 2000 meters.

Conclusion: Altitude significantly impacts ESR values, highlighting the need for altitude-specific reference ranges to improve diagnostic accuracy in high-altitude regions. The results also emphasize the importance of considering demographic and clinical factors when interpreting ESR. These findings can guide clinicians in refining diagnostic algorithms and optimizing patient management strategies in diverse geographical settings.

Keywords: erythrocyte sedimentation rate; altitude; cross-sectional study; Saudi Arabia

Introduction

Erythrocyte sedimentation rate (ESR), also known as sedimentation rate, is a commonly utilized haematological test that measures the rate at which red blood cells (erythrocytes) settle in a vertical column of anticoagulated blood over a specific period [1]. This test is based on the principle that inflammatory proteins, including fibrinogen and globulins, promote the aggregation of red blood cells, leading to faster settling in response to inflammatory processes [2,3]. That is, as these proteins increase during systemic inflammation, they alter the physical properties of red blood cells, causing the formation of rouleaux, or stacks, which settle more rapidly. Consequently, the rate at which the red blood cells settle, measured in millimetres per hour (mm/h), serves as an indirect marker of the degree of inflammation present in the body [4].

While ESR offers valuable insights into the overall inflammatory burden, it may lack specificity and is influenced by various non-inflammatory factors [5,6]. Therefore, in clinical practice, ESR is often used in combination with other diagnostic tests to provide a comprehensive assessment of inflammatory status [7]; in particular, C-reactive protein (CRP), white blood cell count (WBC), and imaging studies are used to corroborate findings and aid in differential diagnosis [8]. By integrating multiple diagnostic

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Table 1. Altitude-based classification of Saudi Arabian cities.

Altitude category	Cities
0–500 meters (m)	Aljobeil, Dammam, Khobar, Yanbu, Jeddah, Jazan, Hassa, and Makkah
501–1000 m	Sakaka, Riyadh, Madina, Bisha, Qassim, Tabouk, and Hail
1001–1500 m	Najran
1501–2000 m	Taif and Muhail Asir
More than 2000 m	Khamis Mushait, Abha, and Albaha

modalities, clinicians can obtain a more accurate assessment of the underlying pathology, refine diagnostic algorithms, and optimize patient management strategies.

Several factors can influence the results of ESR, emphasizing the need for careful interpretation and consideration of patient-specific characteristics. One such factor is age, as ESR tends to increase with advancing age due to age-related changes in plasma proteins and erythrocyte properties [9,10]. Additionally, it can be impacted by sex, with generally higher values observed in females, partly attributable to hormonal influences [11]. Finally, factors such as anaemia, pregnancy, and certain medications may also influence ESR levels, necessitating a comprehensive evaluation of clinical and contextual factors when interpreting test results [12,13].

In addition to physiological variables, altitude exerts a crucial influence on ESR due to its ability to affect the physiology of red blood cells and the composition of plasma proteins. Specifically, at higher altitudes, where atmospheric pressure is lower and oxygen tension diminishes, erythropoiesis is stimulated as a compensatory response to hypoxia [14,15]. This increased erythropoietin production leads to a rise in red blood cell mass, which can influence ESR values [16]. Additionally, the decreased oxygen tension at higher altitudes may affect erythrocyte morphology and rheological properties, potentially influencing their sedimentation characteristics [4,17,18].

Investigation of the correlation between altitude and ESR in Saudi Arabia is crucial due to the country's diverse geography. Accordingly, this study aims to explore the association of ESR with different demographics (age, sex, altitude, body mass index (BMI)) and clinicopathological variables (Diabetes Miletus (DM), chronic kidney disease (CKD) and abnormal thyroid status) in order to explore the derivation of a modified reference range for ESR that can be applied at high altitude in Saudi Arabia.

Materials and Methods

Study Design and Inclusion & Exclusion Criteria

This cross-sectional was conducted in accordance with the ethical Principles as outlined in the Declaration of Helsinki. Patient consent was waived off due to retrospective nature of the study based on the request of the research team, ethical approval was received from the King Khalid University Committee of Research Ethics, under approval number ECM#2024-215. Additionally, ethical clearance was obtained from the Unit of Biomedical Ethics at Al-Borg Laboratory under IRB Approval Number No08/23.

Table 2. Variance inflation factor (VIF) analysis for selected features in this study.

Feature	VIF
Sex	2.004482
Age	4.956555
Region altitude	4.550557
ALT	3.512925
BMI	4.079993
CKD	1.976984
HbA1c	2.72991
TSH	3.041353

ALT, alanine transaminase; BMI, body mass index; CKD, chronic kidney disease; HbA1c, glycosylated haemoglobin; TSH, thyroid-stimulating hormone. Chronic kidney disease is identified by a decrease in estimated glomerular filtration rate to less than 60 mL/min per 1.73 m^2.

This study utilized national data collected from 1 January 2015 to 31 December 2022 at 42 branches of Al-Borg Laboratories located across all 13 administrative regions of Saudi Arabia. The regions included in the study are Albaha, Aljouf, Almadina, Alqasim, Asir, Eastern Region, Hail, Jazan, Makkah, Najran, Northern Borders, Riyadh, and Tabouk. Data from the Northern Borders was available only for the year 2022, while data from Tabouk spanned the years 2018 to 2022. Cities within these regions range in altitude from sea level to more than 2000 meters above sea level, and were categorized into five distinct groups (Table 1).

Normal hemoglobin levels were locally validated and are defined at 13–17.5 g/dL for men and 12–17 g/dL for women at sea level, while at altitudes >2000 meters, these levels increase to 13.5–18.1 g/dL for men and 12.5–17.5 g/dL for women [19]. For altitudes less than 2000 meters above sea level, the effect on hemoglobin is minimal, and no adjustment to reference values is required [19,20].

The study included individuals who visited Al-Borg Laboratories and had data available for the parameters of interest. Specifically, the inclusion criteria mandated patients with comprehensive data during their initial visit, without any subsequent data duplication, irrespective of the visit

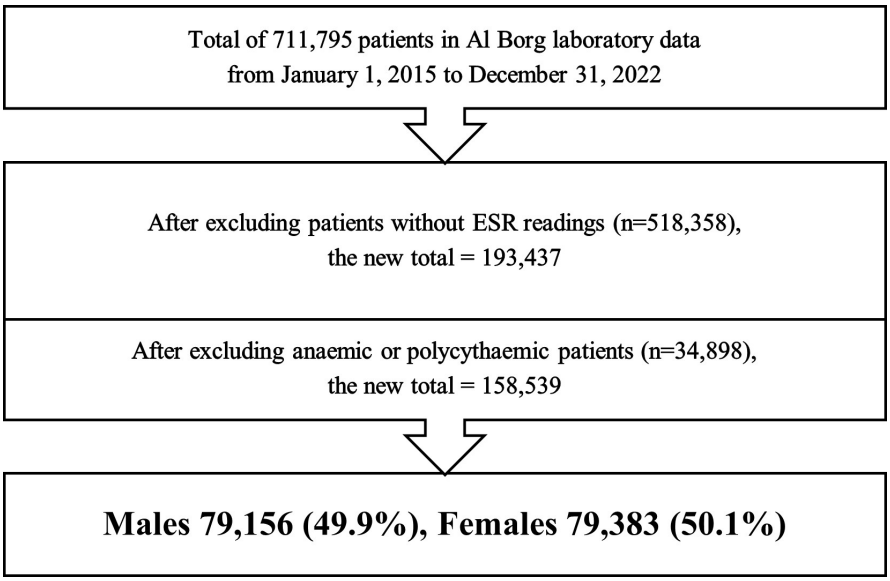

Fig. 1. Flowchart of cohort selection. There was a total of 711,795 patients, of which 158,539 met the criteria for inclusion in the study. ESR, erythrocyte sedimentation rate. Fig. 1 is drawn by Microsoft Word version 2409 (Microsoft Corporation, Redmond, WA, USA).

year. The exclusion criteria were established to exclude patients who did not have ESR readings and those who were diagnosed with anaemia or polycythaemia. At sea level (0–500 m), the typical range for normal haemoglobin level is 13–17.5 g/dL for men and 12–17 g/dL for women. However, at higher altitudes (>2000 m), the normal level changes to 13.5–18.1 g/dL for men and 12.5–17.5 g/dL for women. Haemoglobin levels below these ranges indicate anaemia, while levels above suggest polycythaemia.

Dependent and Independent Variables

The dependent variable was the occurrence of elevated ESR, which was defined as ESR values over 20 mm/hr for men and 30 mm/hr for women. The independent variables encompassed demographic characteristics, including age (grouped into ten-year intervals), sex, and city altitude, as well as clinical laboratory measurements such as BMI, alanine transaminase (ALT), CKD defined as an estimated glomerular filtration rate below 60 mL/min per 1.73 m^2, glycated haemoglobin (HbA1c), and thyroid-stimulating hormone (TSH) level.

Statistical Analysis

Univariate and multivariate logistic regression models were used to determine the factors that influence greater ESR levels, including the impact of city altitude. Variables that had a p-value of 0.25 or less from the univariate analysis were included in the multivariate logistic regression model. The findings were reported as odds ratios (ORs) together with their matching 95% confidence intervals (CIs) and p-values. A significance level of $p < 0.05$ was used to determine statistical significance. The amount of missing data, which was determined to be Missing Completely at Random (MCAR) based on Little's test ($p = 0.11$), varied from 2.5% to 18.42%. To handle these missing values, we performed multiple imputations (25 iterations) using SPSS v29 (IBM Corporation, Armonk, NY, USA). Analyses of the combined data following imputation were compared to the original dataset and found to be statistically similar at common significance levels (0.01, 0.05, 0.1). Multicollinearity was evaluated using variance inflation factors (VIF), all of which were less than 5, indicating an absence of multicollinearity problems (Table 2). Data cleaning and management were conducted using SPSS version 29.0.2.0 (IBM Corporation, Armonk, NY, USA), Microsoft Excel version 2409 (Microsoft Corporation, Redmond, WA, USA), and R version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographic Characteristics of the Participants

The original dataset consisted of 711,795 patients from the Al-Borg Laboratory records, from visits spanning 1 January 2015 to 31 December 2022. After eliminating 518,358 patients who did not have ESR measurements, the eligible cohort was reduced to 193,437 individuals. After excluding an additional 34,898 individuals diagnosed with anaemia or polycythaemia, the cohort was finalised to a sample size of 158,539 participants (Fig. 1). Among these were 79,156 men, which accounted for 49.9% of the total. The average age of the participants was 40 years, with a standard deviation of 15.23 years. The age group of 30–39 years was the most prevalent, comprising 42,120 individuals, 26.6% of the total. Regarding city altitude categories, the largest proportion of the population, 66,038 individuals (41.7%), lived at altitudes between 0 and 500 meters above

Table 3. Demographic information of the participants (entire cohort = 158,539).

Age group (total visits)				City altitude	
Mean age = 40.40 (SD = 15.23)					
Less than 18 years	6792 (4.3%)	60–69 years	13,105 (8.3%)	0–500 m	66,038 (41.7%)
18–29 years	33,708 (21.3%)	70–79 years	5391 (3.4%)	501–1000 m	65,917 (41.6%)
30–39 years	42,120 (26.6%)	80–89 years	1582 (1%)	1001–1500 m	3095 (2%)
40–49 years	32,540 (20.5%)	90 years	199 (0.1%)	1501–2000 m	5273 (3.3%)
50–59 years	23,102 (14.6%)			More than 2000 m	18,216 (11.5%)
Participant distribution by city					
Abha	6169 (3.9%)	Dammam	5804 (3.7%)	Khamis Mushait	8748 (5.5%)
Albaha	3299 (2.1%)	Hail	4353 (2.7%)	Khobar	2469 (1.6%)
Aljobeil	772 (0.5%)	Hassa	5243 (3.3%)	Madina	5408 (3.4%)
Arar	32 (0%)	Jazan	1174 (0.7%)	Makkah	7501 (4.7%)
Bisha	210 (0.1%)	Jeddah	41,248 (26%)	Muhail Asir	57 (0.03%)
Najran	3095 (2%)	Yanbu	2717 (1.7%)	Taif	5216 (3.3%)
Qassim	8682 (5.5%)	Riyadh	43,023 (27.1%)	Tabouk	3124 (2%)

SD, standard deviation.

Table 4. Participants' clinical characteristics are based on available laboratory readings and stratified by altitude category.

Measurement mean (SD)	Entire cohort (n = 158,539)	0–500 m (n = 66,038)	501–1000 m (n = 65,917)	1001–1500 m (n = 3095)	1501–2000 m (n = 5273)	More than 2000 m (n = 18,216)
CKD (n, %)	4745 (3%)	2481 (3.8%)	1473 (2.2%)	48 (1.6%)	169 (3.2%)	574 (3.2%)
TSH (mIU/L)	2.31 (4.59)	2.24 (4.36)	2.30 (4.61)	2.64 (4.88)	2.18 (3.84)	2.61 (5.41)
BMI (kg/m^2)	28.78 (5.15)	28.85 (5.17)	28.60 (5.10)	26.24 (4.48)	29.13 (5.55)	29.32 (5.15)
ALT (U/L)	30.76 (298.63)	32.37 (441.23)	29.85 (132.49)	37.12 (100.42)	29.38 (122.25)	27.76 (89.85)
HbA1c (%)	5.40 (1.45)	5.43 (1.46)	5.35 (1.41)	5.55 (1.54)	5.58 (1.58)	5.59 (1.55)

sea level. This was closely followed by those residing at altitudes of 501–1000 meters, with a total of 65,917 individuals (41.6%) (Table 3).

Clinical Characteristics of the Study Participants

As presented in Table 4, among the 158,539 individuals included in the study, the overall prevalence of CKD was 3%. Table 5 presents the distribution of patients with elevated ESR across different altitude ranges, showing the highest proportion at lower altitudes (0–500 m) with a decreasing trend as altitude increases. The prevalence of CKD was greater at lower altitudes, with a rate of 3.8% at altitudes from 0 to 500 meters, while it remained constant at 3.2% at altitudes over 1500 meters. The level of TSH showed minimal fluctuation across altitudes, with an average value of 2.31 mIU/L. Regarding BMI, values were highest among individuals residing at altitudes greater than 2000 meters, with a mean of 29.32 kg/m^2. Conversely, the lowest BMI values were seen among those living at altitudes of 1001 to 1500 meters, with a mean of 26.24 kg/m^2. The average ALT level was highest at altitudes between 1001–1500 meters, with a mean value of 37.12, notably above the general mean of 30.76 for the entire group. Finally, HbA1c exhibited a slight increase as altitude increased, with the total group having an average of 5.40% (Table 4).

Table 5. Distribution of elevated ESR cases by altitude range.

Total number of patients with elevated ESR in this study	19,895 out of 158,539 (12.5%)
0–500 m	9536 out of 66,038 (14.44%)
501–1000 m	7521 out of 65,917 (11.40%)
1001–1500 m	336 out of 3095 (10.85%)
1501–2000 m	607 out of 5273 (11.51 %)
More than 2000 m	1895 out of 18,216 (10.40%)

Univariate Analysis

As listed in Table 6, the univariate analysis indicated that sex was a significant predictor, with males having a 50% lower likelihood of increased ESR compared to females (OR = 0.500, 95% CI: 0.480–0.510, $p < 0.001$); this association was marginally greater in the adjusted model (OR = 0.470, 95% CI: 0.440–0.510, $p < 0.001$). Age was also a consistently important factor, with the likelihood of having increased ESR increasing significantly in each successive age category. The univariate OR for individuals aged over 90 years was 10.330 (95% CI: 7.660–13.940), indicating a strong association. This association remained significant, although weakened, in the adjusted model, with an OR of 4.540 (95% CI: 1.410–14.548, $p = 0.011$).

Table 6. Variables linked to elevated ESR in the Al-Borg Laboratory database in Saudi Arabia.

Variable	(β values), (SE values), and (Wald) (for the univariate model)	OR (for the univariate model)	95% CI	*p*-value	(β values), (SE values), and (Wald) (for the adjusted model)	OR (for the adjusted model)	95% CI	*p*-value
Sex (male vs the (reference = female))	(–0.694), (0.016), (1931.267)	0.500	(0.480–0.510)	<0.001	(–0.746), (0.039), (364.871)	0.470	(0.440–0.510)	<0.001
18–29 years	(0.076), (0.055), (1.952)	1.070	(0.970–1.200)	0.162	(–0.096), (0.469), (0.042)	0.910	(0.360–2.279)	0.838
30–39 years	(0.457), (0.053), (74.785)	1.580	(1.420–1.750)	<0.001	(0.335), (0.467), (0.514)	1.400	(0.560–3.486)	0.473
40–49 years	(0.730), (0.053), (189.909)	2.070	(1.870–2.300)	<0.001	(0.501), (0.466), (1.152)	1.650	(0.660–4.116)	0.283
50–59 years	(1.128), (0.053), (449.950)	3.080	(2.780–3.420)	<0.001	(0.832), (0.466), (3.180)	2.300	(0.920–5.729)	0.075
60–69 years	(1.514), (0.054), (777.349)	4.540	(4.080–5.050)	<0.001	(1.050), (0.467), (5.053)	2.860	(1.140–7.142)	0.025
70–79 years	(1.876), (0.058), (1034.662)	6.520	(5.820–7.310)	<0.001	(1.479), (0.470), (9.911)	4.390	(1.750–11.017)	0.002
80–89 years	(2.195), (0.072), (922.542)	8.970	(7.790–10.340)	<0.001	(1.906), (0.480), (15.789)	6.720	(2.630–17.213)	<0.001
More than or equal to 90 years	(2.336), (0.153), (233.705)	10.330	(7.660–13.940)	<0.001	(1.512), (0.595), (6.461)	4.540	(1.410–14.548)	0.011
Regions altitude (measured in meters (m))								
0–500 m					Ref			
501–1000 m	(–0.270), (0.017), (268.062)	0.760	(0.730–0.780)	<0.001	(–0.228), (0.041), (31.120)	0.800	(0.730–0.862)	<0.001
1001–1500 m	(–0.326), (0.059), (30.763)	0.720	(0.640–0.810)	<0.001	(0.490), (0.396), (1.532)	1.630	(0.750–3.547)	0.216
1501–2000 m	(–0.260), (0.045), (34.153)	0.770	(0.700–0.840)	<0.001	(–0.517), (0.243), (4.532)	0.600	(0.370–0.960)	0.033
More than 2000 m	(–0.374), (0.027), (196.616)	0.680	(0.650–0.720)	<0.001	(–0.424), (0.082), (26.666)	0.660	(0.560–0.769)	<0.001
Lab measurements								
ALT (U/L)	(0.01), (0.001), (32.920)	1.010	(1.001–1.040)	<0.001	(0.010), (0.005), (6.540)	1.060	(1.001–1.090)	0.011
BMI (Kg/m^2)	(0.080), (0.003), (559.668)	1.084	(1.077–1.091)	<0.001	(0.053), (0.004), (176.486)	1.060	(1.050–1.063)	<0.001
CKD presence (ref = no CKD)	(1.373), (0.031), (1901.337)	3.940	(3.710–4.200)	<0.001	(0.646), (0.073), (78.398)	1.910	(1.650–2.200)	<0.001
HbA1c (%)	(0.234), (0.006), (1705.183)	1.260	(1.250–1.270)	<0.001	(0.109), (0.012), (85.406)	1.120	(1.090–1.141)	<0.001
TSH (mIU/L)	(0.010), (0.010), (1.500)	1.015	(0.990–1.030)	0.221	(0.005), (0.015), (0.110)	1.010	(0.990–1.020)	0.740

β values, Beta values (regression coefficients); SE values, Standard Error values; Wald, Wald Chi-Square statistic; OR, odds ratio; CI, confidence interval.

With regard to city altitude, individuals residing at altitudes between 501–1000 meters had a lower likelihood of having high ESR. In the univariate model, the OR was 0.760 (95% CI: 0.730–0.780) with a *p*-value of less than 0.001. After a modest adjustment in the multivariate model, the OR was 0.800 (95% CI: 0.730–0.862) with a *p*-value of less than 0.001. The pattern of decreasing likelihood with increased altitude continued in the higher-altitude groups throughout the univariate analysis, and it remained statistically significant in the adjusted model for altitudes above 1500 meters (OR = 0.600, 95% CI: 0.370–0.960, $p = 0.033$) and above 2000 meters (OR = 0.660, 95% CI: 0.560–0.769, $p < 0.001$) (Table 6).

In laboratory tests, each incremental unit rise in ALT was shown to be linked with a 1% greater likelihood of elevated ESR when analyzed independently (OR = 1.010, 95% CI: 1.001–1.040, $p < 0.001$). This association increased to 6% in the adjusted model (OR = 1.060, 95% CI: 1.001–1.090, $p = 0.011$). There was also a clear association between higher BMI and increased likelihood of elevated ESR, with univariate OR 1.084 (95% CI: 1.077–1.091, $p < 0.001$) and adjusted OR 1.060 (95% CI: 1.050–1.063, $p < 0.001$). Additionally, the presence of CKD was a robust indicator of elevated ESR, with an OR of 3.940 (95% CI: 3.710–4.200) in the univariate analysis and 1.910 (95% CI: 1.650–2.200) after accounting for other factors ($p < 0.001$). Likewise, increased HbA1c was strongly linked to greater ESR in both univariate (OR = 1.260, 95% CI: 1.250–1.270, $p < 0.001$) and adjusted models (OR = 1.120, 95% CI: 1.090–1.141, $p < 0.001$) (Table 6).

These findings indicate that sex, age, and certain laboratory measurements, such as ALT, BMI, CKD presence, and HbA1c, are significantly connected to the likelihood of high ESR. Additionally, altitude has a noteworthy impact on ESR level (Table 6).

Discussion

As ESR is a key inflammatory marker, it is crucial to understand how this parameter is influenced by environmental factors such as altitude. Various studies have reported that ESR value decreases with increased altitude because the amount of oxygen available is correspondingly reduced [21,22]. In healthy subjects living at high altitudes, this reduction results in increased production of red blood cells, indirectly inducing a fall in ESR reference values [23]. High altitudes are known to be potent stressors that spur alterations in physiological and metabolic functions as the body tries to restore homeostasis in the face of hypoxia disbalance. Multiple studies have noted that acute or chronic exposure to altitudes between 2500 and 5000 m stimulates the sympathoadrenal system and leads to numerous changes in metabolic pathways that, in turn, could affect various other systems, ultimately leading to an increase in ESR [24,25].

As shown in Table 3, among the 158,539 individuals included in the study, the overall prevalence of CKD was 3%, with a higher prevalence observed at lower altitudes. This is not in accordance with another study, which found a higher prevalence of CKD among residents of the Tibetan Plateau [26]. It has been reported that increased blood pressure caused by chronic hypoxia, endothelial cell debilitation, elevated cellular proliferation combined with more collagen biosynthesis, and elevated production of uric acid all lead to increased occurrence of CKD at high altitudes [26,27]. However, the studies in question focused on data from altitudes over 2400 meters, which might have been the reason for this discrepancy. In another study, Harhay MN *et al.* [28] detected various altitude-associated and regional dissimilarities in CKD prevalence in Costa Rica that were not properly explained by the typical CKD risk factors [29]. Therefore, it can be hypothesized that CKD patients with longer exposure to high altitude may display faster progression to end stage kidney disease than those who live at sea level, reflected in the CKD rate of 3.8% for the lowest altitude category (0 to 500 meters) versus the constant rate of 3.2% at altitudes over 1500 meters.

TSH level showed minimal fluctuation across altitudes, with an average value of 2.31 mIU/L. A cross-sectional study by Singh *et al.* [30] found that with long-term high altitude exposure, free thyroid hormone is independent of the thyroid stimulating hormone [30]. Inhabitants living at high altitudes (above 3000 meters) may present different clinical values compared to those living in lowland areas, and diagnosing thyroid diseases in these populations remains a challenge. TSH concentration is one of the most sensitive indicators of hypothalamic–pituitary–thyroid (HPT) axis function [31]. Various studies have demonstrated that the thyroid, adrenal, and gonadal axes are altered by increases in altitude, and these changes manifest in the HPT axis as it adjusts to hypoxia [32,33]. Gong B *et al.* [34] found that as altitude descended from above 3000 meters to sea level, the prevalence of thyroid nodules increased, while the prevalence of subclinical hypothyroidism, goiter, and overt hypothyroidism decreased (first region: above 3000 meters; second region: 3000 meters to 500 meters; third region: 500 meters to sea level). After adjusting for confounding factors, no significant associations were observed between thyroid disorders and these altitude categories. Similarly, no such significant relationship was found between the altitude category and the prevalence of subclinical or overt hyperthyroidism [34].

In the present study, BMI values were found to be highest among individuals residing at altitudes beyond 2000 meters, with a mean of 29.32 kg/m^2. This could be due to physiological adaptations to hypoxia at high altitudes, where the body increases energy expenditure to compensate for lower oxygen levels, potentially leading to increased caloric intake or metabolic changes. Conversely, the lowest BMI values were seen among those living at altitudes

ranging from 1001 to 1500 meters, with a mean of 26.24 kg/m^2. At these moderate altitudes, oxygen levels are not low enough to induce significant metabolic changes, and individuals may engage in more physical activity, contributing to lower BMI. In addition to elevation in BMI at higher altitudes, elevation in leptin levels has also been observed, which leads to lower energy intake due to appetite loss. This causes a negative energy balance leading to weight loss. However, findings concerning this aspect of leptin regulation have been inconsistent [35,36].

The average ALT was highest at altitudes of 1001–1500 meters, with a mean value of 37.12 compared to the general mean of 30.76 for the entire group. ALT is aggregated primarily in the cytosol of hepatocytes and is detectable in serum at low concentrations (typically <30 IU/L) [37]. However, any process that leads to loss of hepatocyte membrane integrity or necrosis results in the release of high amounts of ALT into the plasma [38]. A study by Mera JR *et al*. [39] found that ALT is higher in males when compared to females, a gender-based variation attributed to hormonal differences. Earlier research did not find any association between hypoxia-inducible factors and ALT [40]. Previously, Feng yun Liu *et al*. [41] found that yaks living at 4000 and 4300 m had appreciably increased ALT levels compared with other groups. Therefore, this finding reported here can be a significant step in high altitude.

HbA1c exhibited a slight increase as altitude increased, with the total group having an average of 5.40% (Table 3). In people living at high altitudes, the number of erythrocytes naturally increases to compensate for the depleted availability of oxygen, a condition known as polycythaemia. Therefore, many clinicians have cautioned against the use of HbA1c as a diagnostic measure for prediabetes or diabetes in persons living at high altitudes, since people with polycythaemia can exhibit a pseudo-increase in HbA1c that might lead to false diagnosis. A proper adjustment should be considered when using HbA1c to diagnose diabetes in a patient living at an altitude above 2500 m [42]. Elevated levels of hemoglobin and glucose metabolism alterations have long been reported in people living at high altitude, and may have affected the observed value of HbA1c. One study that explored the relationship between fasting plasma glucose (FPG) and HbA1c in populations living at altitudes >3000 metres and at sea level determined these parameters to have a complex relationship that is much less clear at high altitudes than at sea level [42].

Oxidative stress is another factor that should be considered. Oxidative stress is elevated at higher altitudes, and this elevation may persist until the person returns to sea level. Not only is endothelial cell function affected by hypoxia and oxidative stress, but enduring diminishment or loss of vascular function or ability has been seen in lowlanders after exposure to high altitude, a phenomenon that is in part attributed to increased oxidative stress [43,44].

People living for a long time in hypoxic environments found at high altitudes not only experience an increase in erythrocyte formation but also might suffer from problems in erythrocyte volume and inhibition of the suicidal death (eryptosis) of mature erythrocytes. It has been suggested that a longer erythrocyte lifespan may lead to the prolongation of haemoglobin exposure to blood glucose and therefore to the elevation of HbA1c [45,46].

Table 4 presents the association analysis results. In the univariate analysis, sex was a significant predictor, with males having a 50% lower likelihood of increased ESR compared to females (OR = 0.50, $p < 0.001$); this association was marginally greater in the adjusted model (OR = 0.470, $p < 0.001$). Similarly, age was a consistently important factor, with the likelihood of increased ESR increasing with each successive age category; ultimately, the OR for individuals aged over 90 years was 10.330, indicating a strong association. This association remained significant, although weakened, in the adjusted model, with an OR of 4.540 and a *p*-value of 0.011. These results are consistent with previous studies where ESR tends to be more elevated in women than in men, and to increase steadily with age. It has been reported that the median ESR of females was almost 2-fold higher than that of males, and the median ESR of individuals aged >65 years was 2-fold higher than that of individuals in the youngest category (ages 18–35 years) [2,11,47]. These differences are significant enough to propose establishing different reference values. Simplistic approaches that only establish an average reference value for males and females may therefore be inaccurate [2].

This study has some limitations. We have no access to clinical data that may influence the ESR. Factors such as genetic variation, lifestyle differences, and unmeasured confounders like hydration and diet were not assessed. Additionally, the study did not examine other critical health markers, such as cardiovascular and pulmonary function, which could provide a more complete understanding of altitude's effects on health. Therefore, future research should expand the scope to include additional health indicators and genetic factors, which will provide a more robust understanding of altitude-related adaptations. Moreover, the creation of altitude-specific diagnostic reference ranges is essential for improving the accuracy of disease detection and management in high-altitude populations. Incorporating these insights into AI-driven healthcare systems can further refine risk predictions and treatment approaches for these regions.

Conclusion

In conclusion, altitude has a notable impact on key physiological markers, including ESR, CKD, and levels of TSH, BMI, and ALT. The results revealed that ESR significantly decreases with increasing altitude, likely due to elevated red blood cell counts in response to hypoxia. Con-

versely, CKD prevalence rises at higher altitudes, influenced by chronic hypoxia and metabolic changes. TSH levels remain stable, while BMI peaks and ALT levels increase at moderate elevations.

These findings highlight the need to adapt diagnostic reference ranges for ESR, CKD, TSH, BMI, and ALT for populations living at different altitudes to ensure accurate disease detection and management, preventing potential misdiagnoses in conditions related to inflammation, renal function, and metabolic health.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

AAM, KO, MAls, AAD, MAlg, ZA, and HA analysed results and made the figures. AAM and HA designed the research. AAM and HA wrote the paper. All authors contributed significantly to editorial changes of important content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This cross-sectional was conducted in accordance with the ethical Principles as outlined in the Declaration of Helsinki. Patient consent was waived off due to retrospective nature of the study based on the request of the research team, ethical approval was received from the King Khalid University Committee of Research Ethics, under approval number ECM#2024-215. Additionally, ethical clearance was obtained from the Unit of Biomedical Ethics at Al-Borg Laboratory under IRB Approval Number No08/23.

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Conflict of Interest

The authors declare no conflict of interest.

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