Clin. Lab. 2026;72:XXX-XXX

ORIGINAL ARTICLE

Effect of Moderate Altitude Short Stay on Complete Blood Count Parameters

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ABSTRACT

Background: **High-altitude habitation is known to impose physiological stress, notably affecting red blood cells and hemoglobin concentration. The effects of moderate altitude exposure on leukocytes and platelets remain less well-characterized. This study aimed to longitudinally evaluate hematological adaptations, focusing on leukocyte and platelet dynamics, in sea-level residents exposed to moderate altitude.**
Methods: **A prospective cohort of 45 healthy male international students from West Africa was followed over six months after their arrival at 2,270 meters above sea level (Southwestern Saudi Arabia). Complete blood count (CBC) was measured within 48 hours of arrival, at two months, and at six months. Longitudinal changes in hematological parameters were assessed using mixed-effects linear regression.**
Results: **Exposure of healthy sea-level residents to moderate altitude (2,270 m) led to significant hematological adaptation. Hemoglobin, red blood cells (RBC), and hematocrit increased at two and six months (all $p < 0.05$), while red cell distribution width (RDW-CV) decreased, indicating more uniform erythropoiesis. Mean corpuscular indices (MCV, MCH, MCHC) remained unchanged. Leukocyte counts were overall stable, but neutrophils declined significantly at both time points ($p < 0.01$). Lymphocytes rose transiently at two months ($p = 0.022$), and monocytes increased modestly by six months ($p = 0.046$). Platelet counts did not change significantly, but platelet volume indices (MPV, PDW) rose consistently ($p < 0.001$), suggesting altered platelet activation.**
Conclusions: **Moderate altitude exposure triggers increased erythropoiesis, mild neutropenia, and platelet activation without altering platelet count. These changes reflect complex hypoxia-driven mechanisms and highlight the need for altitude-specific CBC reference ranges. Further research is needed to explore their clinical significance.**
(Clin. Lab. 2026;72:xx-xx. DOI: 10.7754/Clin.Lab.2025.251018)

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KEYWORDS

moderate altitude, hematological adaptation, platelet activation

INTRODUCTION

High-altitude habitation is associated with added stress to body physiology, with the effects on red blood cells (RBCs) and hemoglobin (Hb) concentration being well documented. Meanwhile, the influence of moderate altitude exposure on leukocytes and platelets (PLTs) remains less thoroughly explored. Prolonged altitude exposure is known to impact white blood cell count, potentially due to alterations in bone marrow function or

Manuscript accepted October 20, 2025

immune cell trafficking. In particular, chronic altitude exposure is reportedly associated with mild to moderate neutropenia [1-3]. Hypoxic stress may also cause shifts in the population dynamics of leukocytes, key players in immune defense. Even acute high-altitude exposure can lead to shifts in immune cell populations, including decrease in classical monocytes and increases in intermediate monocytes and B cells [4].

Research on the effects of altitude on platelet counts and volume has returned mixed results. Acute high-altitude exposure (1 - 14 days) generally does not significantly affect platelet count [5], but some studies have reported that altitude-associated increases in erythropoietin (EPO) and Hb mass are also associated with increases in thrombopoietin (TPO) and PLT count [6]. These changes are driven by the hypoxia-inducible factor (HIF) pathway, which stimulates EPO production and enhances erythropoiesis. Altitude exposure can activate platelets, leading to increased aggregation and consumption [7]; chronic exposure (≥ 1 month) is associated with decreased platelet count and increased mean platelet volume [5,8]. Overall, the relationship between altitude, platelet count, and volume appears complex and may depend on factors such as exposure duration and individual physiology.

Most existing studies have focused on high altitude (above 3,000 meters), but moderate altitudes (approximately 2,000 - 2,500 meters) are inhabited by millions worldwide and frequently visited by travelers, including students, military personnel, and tourists. Understanding hematological adaptations at moderate altitude is therefore essential for accurate clinical assessment and health management in these populations [9].

In this study, we prospectively investigated the effects of a six-month stay at moderate altitude (2,270 meters) on complete blood count (CBC) parameters in healthy young males who were lifelong sea-level residents. By analyzing longitudinal trends in erythrocytes, leukocytes, and platelets, we aimed to elucidate the time course and nature of the hematological changes induced by moderate hypobaric hypoxia, with a particular focus on leukocyte subsets and platelet activation markers. Our findings provide insights into physiological adaptation and have implications for clinical practice and future research on moderate-altitude-related hematological responses.

MATERIALS AND METHODS

Study design

A prospective study was conducted to measure blood volumes (total blood volume, RBC volume, plasma volume) and Hb mass using the carbon monoxide rebreathing technique in sea level residents visiting moderate altitude. Ethical approval was obtained from the ethical committee at King Khalid University, Abha, Saudi Arabia (ECM#2023-105). As part of the study, CBC was also obtained. Measurement points consisted of within 48 hours of arrival, after two months, and after six months of continuous stay at altitude (2,270 meters above sea level). Informed consent was obtained from all participants. Each participant was assigned a research ID and all data were transferred to an Excel sheet anonymously.

CBC was performed on EDTA-anticoagulated samples using an automated hematology analyzer (Yumazin H500, HORIBA ABX SAS) within 4 hours of collection.

Statistical analysis

Statistical analysis was conducted using the STATA 19.5 program. Mixed-effects linear regression was applied to evaluate longitudinal changes in CBC parameters, accommodating unbalanced data and missing values via maximum likelihood. To address non-normality and heteroscedasticity, variables were log-transformed based on objective criteria (e.g. skewness > 2, CV > 1), resulting in ten log-transformed and six untransformed variables. Log-transformed results were expressed as percentage change $100 \times (e\beta - 1)$ and untransformed results as absolute change, all with 95% CIs. A significance level of 0.05 was used without multiplicity correction due to the study's exploratory nature. Paired *t*-test was used to compare longitudinal CBC values.

RESULTS

A total of 45 people participated in this study (40 in the second visit, 37 in the third visit). All participants were male international students at King Khalid University, Abha, Saudi Arabia and all originated from West African countries. The mean age of participants is 26.8 ± 5.2 years.

Table 1 summarizes the descriptive and comparative analysis of CBC parameters. Hemoglobin levels increased from baseline (15.0 ± 1.3 g/dL) at both two months (16.0 ± 1.3 g/dL, $p < 0.001$) and six months (15.7 ± 1.2 g/dL, $p < 0.001$). Similarly, RBC counts rose modestly ($5.4 \pm 0.8 \times 10^{12}$/L to $5.7 \pm 0.6 \times 10^{12}$/L at two months, $p = 0.022$; and to $5.7 \pm 0.4 \times 10^{12}$/L at six months, $p = 0.043$). Hematocrit also increased significantly at both follow-ups (45.6 ± 5.6% to 48.0 ± 3.7% at two months, $p = 0.017$; 48.0 ± 3.5% at six months, $p = 0.014$). Mean corpuscular indices (MCV, MCH, MCHC) showed no significant change. RDW-CV declined significantly from baseline (13.8 ± 1.0%) to two months (13.2 ± 0.9%, $p < 0.001$) and remained reduced at six months (13.4 ± 0.9%, $p = 0.002$), although this statistical change is not clinically significant.

Total WBC counts remained stable across time points. However, differential analysis revealed a transient decline in absolute neutrophil count (ANC) at two months ($2.1 \pm 1.0 \times 10^9$/L → $1.6 \pm 0.6 \times 10^9$/L, $p = 0.005$), persisting at six months ($1.6 \pm 0.5 \times 10^9$/L, $p = 0.004$). Absolute lymphocyte count increased modestly at two months ($p = 0.022$) but not at six months. Absolute

Table 1. Longitudinal analysis of hematological parameters at baseline, two-month, and six-month follow-up.

Parameter	Baseline	Two months		Six months	
	Mean (SD)	Mean (SD)	p-value (vs. baseline)	Mean (SD)	p-value (vs. baseline)
Hb (g/dL)	15.0 (1.3)	16.0 (1.3)	< 0.001	15.7 (1.2)	< 0.001
RBC (× 10^{12}/L)	5.4 (0.8)	5.7 (0.6)	0.022	5.7 (0.4)	0.043
Hct (%)	45.6 (5.6)	48.0 (3.7)	0.017	48.0 (3.5)	0.014
MCV (fL)	84.3 (6.4)	84.6 (6.7)	0.498	84.7 (6.4)	0.062
MCH (pg)	27.8 (3.0)	28.2 (2.8)	0.172	27.8 (2.4)	0.803
MCHC (g/dL)	33.0 (1.8)	33.3 (1.0)	0.272	32.8 (0.7)	0.608
RDW-CV (%)	13.8 (1.0)	13.2 (0.9)	< 0.001	13.4 (0.9)	0.002
WBC (× 10^9/L)	5.2 (1.4)	4.9 (1.2)	0.202	5.0 (1.1)	0.121
ANC (× 10^9/L)	2.1 (1.0)	1.6 (0.6)	0.005	1.6 (0.5)	0.004
ALC (× 10^9/L)	2.3 (0.7)	2.5 (0.7)	0.022	2.6 (0.7)	0.089
AEC (× 10^9/L)	0.2 (0.2)	0.2 (0.2)	0.189	0.2 (0.1)	0.845
AMC (× 10^9/L)	0.5 (0.2)	0.5 (0.2)	0.514	0.5 (0.2)	0.046
ABC (× 10^9/L)	0.1 (0.0)	0.1 (0.0)	0.217	0.1 (0.0)	0.675
PLT (× 10^9/L)	225.4 (71.1)	237.6 (53.1)	0.272	237.9 (56.5)	0.179
MPV (fL)	9.1 (0.9)	9.6 (1.0)	< 0.001	9.6 (1.1)	< 0.001
PDW (%)	15.1 (2.6)	15.9 (2.7)	0.051	16.2 (3.1)	< 0.001

[*] **p-values from paired t-tests comparing each time point to baseline.**

monocyte count rose slightly by six months (0.5 ± 0.2 × 10^9/L → 0.5 ± 0.2 × 10^9/L, p = 0.046). Other subsets (eosinophils, basophils) showed no significant alterations.

Platelet counts trended upward but did not reach significance. Notably, platelet volume indices increased consistently: MPV rose from 9.1 ± 0.9 fL at baseline to 9.6 ± 1.0 fL at two months and 9.6 ± 1.1 fL at six months (both p < 0.001). PDW also increased significantly by six months (15.1 ± 2.6%→ 16.2 ± 3.1%, p < 0.001).

Longitudinal changes in CBC parameters expressed as absolute and percent change from baseline, estimated using linear mixed-effects models with restricted maximum likelihood (REML) were presented in Supplemental Tables S1 and S2.

Figure 1 represents a forest plot of absolute and percent changes in CBC parameters from baseline. Moderate altitude exposure was associated with increased hemoglobin, hematocrit, and RBC counts, alongside reduced RDW, modest neutrophil decline, and rises in lymphocytes (transient) and monocytes (late). Platelet counts remained stable, but indices of platelet size (MPV, PDW) increased consistently, reflecting both erythropoietic and broader hematological remodeling.

DISCUSSION

This prospective analysis investigated the effects of moderate altitude (2,270 meters above sea level) on CBC parameters over a six-month period in previously sea-level-dwelling, healthy male international students. Our findings provide novel insights into the time course and nature of hematological adaptations to moderate hypobaric hypoxia and underscore the nuanced interplay between red cell production, leukocyte dynamics, platelet physiology, and cytokine-mediated regulation in the context of altitude exposure.

We observed a significant rise in RBC, Hb, and HCT within the first two months of arrival at altitude, with sustained levels at six months. These findings align with well-documented altitude physiology, where reduced oxygen availability leads to stabilization of HIFs, particularly HIF-1α and HIF-2α, which upregulate EPO expression and stimulate erythropoiesis [10,11]. The stabilization of red cell parameters across months two through six suggests that erythropoietic adaptation reaches a homeostatic threshold by the second month, consistent with previous findings at similar altitudes [12]. The concomitant lack of significant change in MCV, MCH, and MCHC indicates that erythropoiesis occurred without a shift toward macrocytosis or microcytosis, suggesting efficient, normocytic red cell production.

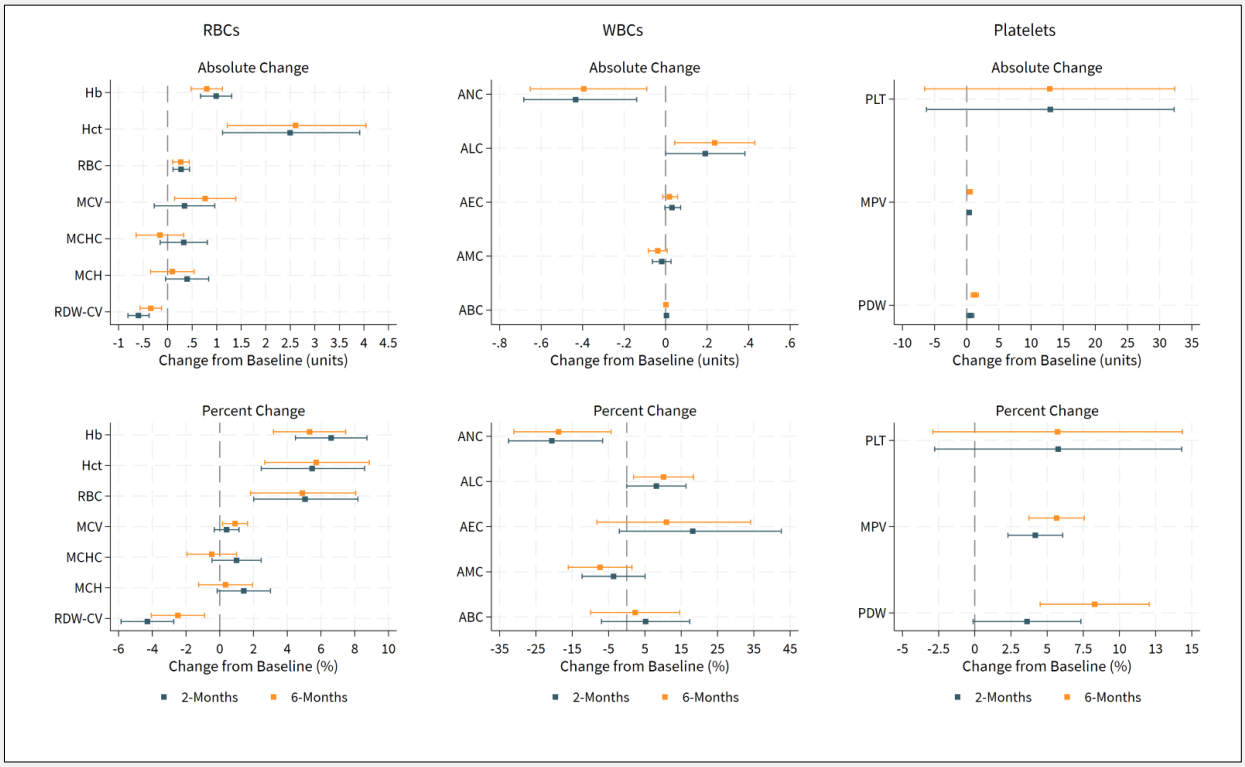

Figure 1. CBC parameter changes from baseline at two months (blue) and six months (orange).

Hb hemoglobin, Hct hematocrit, RBC red blood cell count, MCV mean cell volume, MCHC mean cell hemoglobin concentration, MCH mean cell hemoglobin, RDW-CV red cell distribution width-coefficient of variation, ANC absolute neutrophil count, ALC absolute lymphocyte count, AMC absolute monocyte count, AEC absolute eosinophil count, ABC absolute basophil count, PLT platelets, MPV mean platelet volume, PDW platelet distribution width.

Beyond erythropoiesis, we observed a significant and sustained decline in absolute neutrophil count at both two and six months, while WBC count and other leukocyte subtypes remained largely unchanged. This mild neutropenia has been reported in other altitude studies and is thought to reflect either decreased granulopoiesis or enhanced margination and tissue sequestration of neutrophils [13,14]. Chronic hypoxia can downregulate granulopoiesis through the bone marrow niche's response to low oxygen tension and cytokine signaling. Elevated levels of cytokines such as interleukin-10 (IL-10) and tumor necrosis factor-alpha (TNF-α), both of which have been shown to increase in hypoxic environments, may inhibit neutrophil proliferation or promote apoptosis [15].

In addition to impacting neutrophil abundance, alterations in cytokine profiles under hypoxic stress may shift immune cell priorities. Hypoxia has been shown to elevate IL-6 and IL-1β, which in acute exposure stimulate neutrophilia, but with chronic exposure may lead to immune suppression or altered leukocyte distribution [16]. Conversely, lymphocyte counts remained stable in our cohort, and the relative lymphocytosis observed was attributable to neutrophil decline. This shift suggests a tilt toward adaptive immunity, possibly mediated by increased levels of IL-2 and interferon-gamma, which support lymphocyte activation and proliferation in response to chronic low-grade inflammatory signaling at altitude [17].

A distinctly different pattern was observed in platelet dynamics. While total platelet count did not significantly change over the study period, both MPV and PDW increased significantly at two and six months. These changes are indicative of platelet activation and increased size heterogeneity, which are known to reflect the presence of younger, more reactive platelets in circulation [18]. The increase in MPV and PDW without an accompanying rise in platelet count suggests that hypoxia influences platelet turnover and function, rather than simply increasing their number. TPO, which is in-

creased in response to hypoxia, can enhance megakaryocyte maturation and result in the production of larger platelets [19]. HIF-1α is also implicated in megakaryocyte development and platelet activation through regulating genes involved in cytoskeletal remodeling and adhesion [20].

The prothrombotic implications of these findings are clinically relevant. Even at moderate altitudes, enhanced platelet activation could predispose susceptible individuals to thrombotic events, especially those with underlying cardiovascular or hematologic conditions. Prior studies have suggested an association between altitude exposure and increased risk of venous thromboembolism, although findings are mixed and may depend on duration and altitude level [21]. While our cohort did not experience any clinical thrombotic events, the hematological shifts we observed support the need for further investigation, particularly in higher-risk populations.

These findings additionally emphasize the need for altitude-adjusted reference intervals when interpreting CBC results. Mild neutropenia or increased MPV may not necessarily reflect pathology in individuals residing at altitude but rather physiological adaptations to hypoxic stress. For clinicians working in highland regions or with populations that frequently transition between sea level and altitude, understanding these patterns is essential for accurate diagnosis and management.

This study has several limitations, including a sample restricted to healthy, young males of West African descent, which limits generalizability. Additionally, the absence of baseline sea level hematological parameters prevents definitive linking of the observed changes to altitude exposure. Key physiological and molecular markers such as serum EPO and HIF expression were not measured, and cytokine profiling along with platelet function testing were also not performed. Future research should address these gaps by including more diverse populations, incorporating sea level controls, and performing comprehensive molecular and functional assessments to better elucidate underlying mechanisms and evaluate clinical implications, particularly in at-risk groups.

In conclusion, moderate altitude exposure induces a multifaceted hematological response characterized by increased erythropoiesis, persistent mild neutropenia, and platelet activation without thrombocytosis. These changes are likely mediated by complex interactions between hypoxia, cytokines, and hematopoietic signaling pathways. Further research is warranted to investigate the functional consequences of these changes and their potential clinical implications in diverse and at-risk populations.

Acknowledgment:
The authors extend their appreciation to the Deanship of Research and Graduate Studies at King Khalid University for funding.

Source of Funds:
This work was funded through a Small Group Research Project under grant number RGP.1/82/46.

Data availability statement:
The dataset used during this study is available upon reasonable request.

Declaration of Generative AI in Scientific Writing:
The authors declare that generative AI tools were not used to assist in the preparation of this manuscript.

Informed Consent:
Informed consent was obtained from all participants.

Declaration of Interest:
No potential conflict of interest was reported by the author(s).

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