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Impact of Haemoglobin and Haematocrit on the Incidence of Thrombosis in the Individuals Exposed to High-Altitude

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ABSTRACT

Objective: To investigate the association among high haemoglobin (Hb), high hematocrit (HCT), and thrombosis in individuals exposed to high-altitude (HA) environments, contributing to our understanding of haematological changes and thrombotic risk associated with HA exposure.

Study Design: Retrospective longitudinal study

Place and Duration of Study: High Altitude Medical and Research Cell (HALMARC) Pakistan, from Jan 2021 and Dec 2022.

Methodology: The total number of 91 participants who were exposed to high-altitude were included. All age groups were included. Participants were categorized based on altitude, stay duration, Hb, and HCT levels. All types of thrombotic events were recorded.

Results: Participants were exposed to altitudes ranging from less than 15,000 feet to greater than 18,000 feet, with varying durations of stay. The majority of the male participants were non-smokers. The mean Hb was 16.76±2.03 g/dl, and the mean HCT was 52.17±6.1%. More than half (53%) of the participants experienced thrombosis, with most cases involving brain thrombosis. However, there was no significant effect of elevated Hb (p=0.10) or HCT (p=0.75) on the incidence of thrombosis.

Conclusion: Extended stays at high altitudes were associated with elevated hematocrit levels. However, no direct association was found between high Hb and HCT levels and the incidence of thrombosis. Thrombotic events at high altitudes are likely influenced by multifactorial factors beyond haematological parameters, including individual variations in blood coagulation, genetics, and environmental influences.

Keywords: Haemoglobin, Haematocrit, High-altitude, Thrombosis.

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INTRODUCTION

Worldwide, exposure to high-altitude (HA) environments presents a unique set of physiological challenges to the human body. The relationship between haematological changes, specifically Hb and HCT levels, and thrombotic events in HA populations remains poorly understood.[1,2] Globally, it was reported that over 140 million people permanently live at altitudes greater than 2500 meters above sea level.[3] Low ambient temperature and hypobaric hypoxia are two challenges to life at HA, with an increased risk of thrombotic diseases. In the developed world, there is a lack of correlation between Hb and HCT levels and basic coagulation parameters in HA populations.[4]

Additionally, the predictive value of HGB and HCT for HA-induced thrombotic disease may be relatively independent. In China, the results revealed that plasmin production decreased and secondary fibrinolysis increased in individuals exposed to HA conditions. Surprisingly, there were no notable distinctions in fibrinolytic parameters between healthy volunteers living at HA and patients with HA polycythemia. This suggested that alterations in fibrinolysis may not be the main factor contributing to thrombosis due to elevated blood viscosity observed in patients with HA polycythemia.[5,6]

Data from South Asia reports that clinically apparent thrombotic events, particularly venous events rather than arterial events, were significantly higher at altitudes above 15000 feet compared to what has been reported at sea level. These findings suggested that altitudes exceeding 15000 feet could be an independent risk factor for thrombosis, even among healthy individuals.[7] Moreover, the individuals who have resided at low altitudes for more than 50 years exhibit significantly reduced red blood cell count, HCT, Hb, mean corpuscular Hb (MCH), mean corpuscular Hb concentration (MCHC) and increased mean corpuscular volume (MCV) compared to their HA counterparts. These findings suggested that these

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haematological changes are likely a result of adaptive responses to the relatively higher oxygen levels in low-altitude regions.[8]

In Pakistan, due to high Peaks, a high number of individuals are exposed to HA.[9] Thrombotic episodes, although uncommon, carry significant morbidity and mortality, and Although thrombotic episodes are uncommon, they carry significant morbidity and mortality and need further evaluation to ensure preventive strategies and timely management. This study investigated the correlation between Hb and HCT levels and the occurrence of thrombosis in individuals exposed to HA. They can aid in developing risk assessment tools and preventive strategies for HA exposure, helping healthcare professionals identify at-risk individuals and implement targeted interventions. The study's insight can also formulate public health policies and guidelines for HA residents or travellers, improving overall health outcomes in these populations.

METHODOLOGY

The retrospective longitudinal study was conducted at the High Altitude Medical and Research Cell (HALMARC), Pakistan, from January 2021 to December 2022 after approval from Institutional Review Board (HALMARC/2023/1-1). The sample size was calculated using the WHO sample size calculator, taking the reported prevalence of thrombosis incompatibility at 8%.[10] Data were collected from the HALMARC registry.

Inclusion Criteria: Individuals of any age groups who were exposed to high altitude were included.

Exclusion Criteria: Individuals who did not sign the consent were excluded.

High altitude was defined as an elevation of 8000-13000 feet; very HA was considered more than 13000-18000 feet, and extremely HA was defined as above 18000 feet. The participants were categorized into three groups based on their stay duration: <45 days, 45-100 days, and >100 days.[11] Three Hb groups were also established: less <13 g/dl, 13-18 g/dl, and >18 g/dl. The study cohort was divided into two HCT groups: <52% and 52 % or more.

In the descriptive analysis, quantitative data was presented with Mean± standard deviation (SD) and median (interquartile range), while qualitative data was presented with frequency and percentage. Chi-square test and Independent sample t-test were applied to explore the inferential statistics. The *p*-value of ≤0.05 was set as the cut-off value for significance.

RESULTS

Ninety-one participants were male, with a mean age of 31.97±6.07. 50(55%) male participants were from Punjab, 25(27.5%) Khyber Pakhtunkhwa, 7(8%) Gilgit Baltistan and remaining participants were from Azad Kashmir 5(5.5%) and Sindh 4(4%).84(92%) of the participants were non-smokers and 18(20%) had a previous hospital stay.

Median height that individuals were exposed to was, 17400 feet (interquartile range: 14000- 19300 feet). 26(29%) participants went to less than 15000 feet, 25(27%) went from 15000 to 18000 feet, and 40(44%) went to greater than 18000 feet. The median duration of stay at HA was 34 days (interquartile range: 0-90 days) in which 24(26%) of the participants had a stay of fewer than 45 days, 20(22 %) had a stay of 45 to 100 days, 22(24%) had a stay of more than 100 days, and 25(28%) had a stay of few hours within a day. At the same time, there was no prior history of HA illness in 82(90%) patients.

Table-I: Association of Age, Smoking and Family History of disorders with Thrombosis (n=91)

		Thrombosis		*p*-value
		Yes, n(%)	No, n(%)	
Age (years)	< 20	0(0)	1(100)	0.47
	20-35	37(55)	30(45)	
	> 35	11(48)	12(52)	
Smoking	Yes	2 (29)	5(71)	0.18
	No	46(55)	38(45)	
Family Hx of Comorbids	Yes	2(33)	4(66)	0.32
	No	46(54)	39(46)	
Previous Hospital Stay	Yes	9(50)	9(50)	0.79
	No	39(53)	34(46)	
History of Respiratory Disorder	OSA	1(50)	1(50)	0.56
	Allergic Cough	0(0)	1(100)	
	No	47(53)	41(47)	
History of Cardiac Disease	Yes	1(100)	0(0)	0.34
	No	47(52)	43(48)	
History of Neurological Disorders	Yes	0(0)	2(100)	0.13
	No	48(54)	41(46)	
Hemoglobin	(Mean±SD)	16.43 ± 2.01	17.13±2.02	0.10
Hematocrit	(Mean±SD)	51.94 ± 5.68	52.42 ± 6.61	0.75

The data revealed that 2(2%) of the participants had less than 13 g/dl of Hb, 63(69%) had 13-18 g/dl, 26(29%) had greater than 18 g/dl with mean 16.76±2.03 g/dL. Once studied for raised HCT, 29(45%) participants had less than 52% HCT, while 36(55%) had greater than 52% HCT with a mean of 52.17±6.10 %. The data indicated that 48(53%) of the participants had a thrombotic episode in which

34(37%) of the thrombosis cases occurred in the brain, 11(12%) in the lungs, 3(3%) in the heart and 1(1%) in the liver. Additionally, 42(46%) participants have not reported thrombosis. There was no significant association of age, smoking, previous hospital stays, or previous cardiorespiratory disease with thrombosis. We did not find any relationship between Hb (p=0.10) and HCT (p=0.75) and thrombosis (Table-I). We found a significant association of Hb and HCT with altitude (Table II).

Table-II: Association of Hemoglobin and Hematocrit with Altitude (n=91)

		Altitude			*p*-value
		<15000 Feet n(%)	15-18000 Feet n(%)	>18000 Feet n(%)	
Hemoglobin	<13gm/dl	1(4)	1(4)	0(0)	0.03
	13-18gm/dl	21(81)	20(80)	22(55)	
	>18gm/dl	4(15)	4(16)	18(45)	
Hematocrit	<52%	12(71)	10(67)	7(21)	0.001
	>52%	5(29)	5(33)	26(79)	

DISCUSSION

This study offered valuable insights into the intricate influence of HA exposure on haematological changes and thrombosis risk among male participants. The findings revealed a compelling association between extended durations spent at HA and heightened HCT levels. However, the relationship between Hb, HCT, and thrombosis incidence remained inconclusive. In contrast to Aaron R. Folsom *et al*. research on a general middle-aged population, our study did not find a definite link between Hb, HCT, and thrombosis incidence. Aaron R. Folsom *et al*. showed a significant 72% increase in provoked venous thromboembolism (VTE) risk associated with elevated HCT levels in the general population. The disparities in findings may be attributed to differences in study populations, exposure durations, and physiological adaptations to hypoxia experienced at Has.[11,12]

The study unveiled a diverse spectrum of altitudes explored by the participants, with nearly half of them venturing beyond 18,000 feet. It was observed that ascending to higher altitudes corresponded to heightened levels of Hb and HCT. This finding aligned with a study by Windsor *et al*.[13] which indicated that prolonged exposure to HA was also linked to increased HCT levels. These findings suggested that both altitude and duration of exposure influence haematological parameters, potentially due to the physiological adaptation to hypoxia, consequently leading to an augmentation in red blood cell production. The findings from Gassman *et al*.[14] supported our research, which found that both altitude and duration of exposure influenced haematological parameters due to physiological adaptation to hypoxia, resulting in increased red blood cell production. The study's equations for estimating Hb values at different altitudes aligned with our observations of Hb increasing with altitude. Overall, these congruent findings contributed to our understanding of how haematological parameters responded to HA conditions and reinforced the importance of physiological adaptations in red blood cell production.

Our study produced contrasting findings compared to Malenica *et al*.[15] concerning the impact of smoking on haematological parameters. Malenica et al. emphasized the severe detrimental effects of continuous cigarette smoking on various haematological parameters, potentially increasing the susceptibility to specific diseases. Conversely, our study revealed a significant association between non-smokers and high Hb levels. The plausible reason was that disparities in results may be attributed to variations in study design, participant characteristics and potential genetic or environmental factors [16]. Our study focused solely on male individuals and found a significant association between smoking and Hb levels, indicating potential adverse effects on Hb production or regulation in smokers. In contrast, Sharma *et al*. included both preschool-age children and women of reproductive age and reported a positive association between smoking and higher Hb levels in women.[17]

Our study investigated the impact of HA exposure on haematological changes and thrombotic risk. Interestingly, we observed a higher incidence of thrombotic events, particularly brain thrombosis, among participants than the Singh *et al*. study had Indian soldiers. Surprisingly, we did not find a direct association among Hb, HCT, and thrombosis, indicating potential additional factors at play. These disparities imply that thrombotic events at HA involved

more than just haematological parameters. Individual variations in blood coagulation, genetic predispositions, underlying medical conditions, and environmental influences could be contributing factors. Further in-depth research is warranted to fully comprehend the mechanisms behind these events.[18,19]

In conclusion, this study shed light on haematological changes and thrombotic risk associated with HA exposure in males. The findings suggested that HA travel and prolonged exposure were linked to increased HCT levels. Insights gained from such research could contribute to developing preventive strategies and interventions to mitigate thrombotic risk in individuals exposed to HA.

LIMITATIONS OF STUDY

Our study focused on specific altitude ranges and durations of exposure, and there may be variations in haematological parameters and thrombotic risk at different altitudes and durations. Additionally, we did not explore other potential factors, such as genetic predispositions or specific medical conditions. Also, several other factors were not done even though blood sampling was carried out, like nitric oxide levels in the blood, VEGF, TRBC, etc., possibly because of retrospective design and/or cost limitations that could contribute to thrombotic events at high altitudes. Further research with larger and more diverse cohorts is needed to address these limitations comprehensively.

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CONCLUSION

Extended stays at high altitudes were associated with elevated hematocrit levels. However, no direct association was found between high Hb and HCT levels and the incidence of thrombosis. Thrombotic events at high altitudes are likely influenced by multifactorial factors beyond haematological parameters, including individual variations in blood coagulation, genetics, and environmental influences.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

MA & HS: Data acquisition, data analysis, critical review, approval of the final version to be published.

RI & SS: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

HT & FS: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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