UNIVERSIDAD DE INVESTIGACIÓN DE TECNOLOGÍA EXPERIMENTAL YACHAY TECH

Escuela de Ciencias Biológicas e Ingeniería

TÍTULO: RETROSPECTIVE GROUP STUDY OF RISK FACTORS FOR DEVELOPING EXCESSIVE ERYTHROCYTOSIS ON THE ECUADORIAN POPULATION LIVING IN THE SIERRA REGION

Trabajo de integración curricular presentado como requisito para la obtención del título de Ingeniero Biomédico

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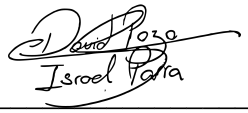

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DEDICATION

I want to dedicate this thesis to all the people that support me. My father Byron whose is not here anymore and my mother Marisol who give me the strength to achieve this goal in my life. To my brothers Pablo and Daniel whom help me despite the difficulties in the last few years. Finally, to the rest of my family specially my uncle Patricio and my grandparents Nelson and Maria without them this will be not possible.

"David Israel Pozo Parra"

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"David Israel Pozo Parra"

Abstract

Living at high altitude is related to the development of adaptive mechanisms in humans, high altitude (HA) diseases occur in areas greater than 2.500 m.a.s.l. where oxygen levels decrease to 75% in relation to sea level. This O_2 deficiency causes an activation of chain mechanisms for adaptability to the environment. Millions of people around the world live at HA and can develop diseases due to a malfunction of the body, mainly caused by hypoxia, among these are chronic mountain disease (CMS) and excessive erythrocytosis (EE). The Andean population does not assimilate hypoxia induced by HA as do other mountaineers around the world (e.g. Tibetans). Appropriate medical information from EE is necessary to provide proper diagnosis and medical care for high-altitude people. The objective of this project is to investigate the risk factors for the development of EE based on the degree of HA. Taking this into consideration, two groups of patients will be examined, each of them inhabitants of different altitude regions (2.800 - 3.200 m medium HA (NA); and $>$ 3.600 m HA) who will be scrutinized for the following selected variables: demography (sex, age and weight); health status variables (vital signs) and blood count variables (hematology). Cramer's V statistical analysis, simple and multiple logistic regression will be carried out to reveal the presumed risk factors that sustain the EE.

Keywords: EE, Hemoglobin, High-altitude, Andean.

Resumen

Vivir a gran altura, esta relacionado con el desarrollo de mecanismos adaptativos en el ser humano, las enfermedades de gran altitud (GA) se producen en zonas mayores a 2.500 m.s.n.m donde los niveles de oxígeno disminuyen al 75% en relación a nivel del mar. Esta deficiencia de O_2 ocasiona la activación de una serie de mecanismos para la adaptabilidad al medio. Millones de personas en todo el mundo viven a gran GA y pueden desarrollar enfermedades debido a un mal funcionamiento del organismo, principalmente ocasionados por la hipoxia, entre estas se presentan la enfermedad crónica de montaña (ECM) y la eritrocitosis excesiva (EE). La población Andina no asimila la hipoxia inducida por GA como lo hacen otros montañeses alrededor del mundo (ej. Tibetanos). La información médica apropiada de EE es necesaria para dar un diagnóstico y atención medica adecuados para las personas que habitan a GA. El objetivo de este proyecto es investigar los factores de riesgo para el desarrollo de EE en función del grado de GA. Tomando esto en consideración, se examinarán dos grupos de pacientes, cada uno de ellos habitantes de diferentes regiones de altitud (2.800 – 3.200 m.s.n.m.) media GA (NA); y (> 3.600 m.s.n.m. GA) que serán escudriñados para las siguientes variables seleccionadas: demografía (sexo, edad y peso); variables de estatus de salud (signos vitales) y variables de conteo sanguíneo (hematología). Análisis estadistico por V de Cramer, regresión logística simple y múltiple se llevarán a cabo para revelar los supuestos factores de riesgo que sustenta el EE.

Palabras Clave: EE, Hemoglobina, Gran-altura, Andino.

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Chapter 1

Introduction

1.1 Background

1.1.1 Erythrocytes

Erythrocytes are blood cells, their main function is oxygen transportation through different tissues of the body (Arderiu, 1997). In humans, there are around 4.5 million (women) and 5.4 million (men) cells per microliter of blood (Bianconi et al., 2013). When significantly lower ranges of these cells are present, it is known as anemia ($<$ 4.2 million cell/uL in women and $<$ 4.7 million cell/uL), the excess of erythrocytes is known as polycythemia ($>$ 5.4 million cell/uL in women and $>$ 6.1 million cell/uL in men) (Hall, 2016).

1.1.2 Erythropoietin

Erythropoietin, erythropoietic stimulating factor, or EPO. Is a growth hormone, their principal function is the response to changes on oxygen level in the blood. In the case of hypoxia, that occurs at HA, oxygen level decrease to less than 75% available at sea level. It triggers an erythropoietin response that stimulates erythrocyte production (erythropoiesis) to increase red cell mass therefore enhancing oxygen reception and transportation. (Elliott et al., 2008).

1.1.3 Hemoglobin

Hemoglobin (HGB) is a red-colored hemoprotein, which carries O_2, CO_2 and is also related to the regulation of blood pH. It has a quaternary structure, with a heme group (stores a Fe^+ atom) in each of its four subunits (Arderiu, 1997). Attached by weak bonds to an oxygen molecule, each hemoglobin carries eight oxygen atoms (Maschio et al., 2010).

1.1.4 Hematocrit

Hematocrit (HCT) is the solid portion percentage in a blood sample, consists almost entirely of the volume occupied by red blood cells. Its value in women is between 36%

and 46%, for men between 41% and 53%. Values will depend on age, physical condition, altitude, and habits (diet, smoking) (Chernecky and Berger, 2012).

1.1.5 High altitude hypoxia

At HA, more than 2.500 m.a.s.l., the human body is in a hypoxic state. The increase in erythrocytes at HA also causes a decrease in the saturation degree, producing less hemoglobin that carries oxygen (Reeves and Leon-Velarde, 2004). As a compensation process, an increasing amount of hemoglobin is produced, which increases the oxygen transport capacity and is modified to adequately contribute its content to the body's tissues (Basnyat and Murdoch, 2003; Fandrey et al., 2006; Franke et al., 2013). There are three mechanisms in the body that response to being in a hypoxic state due to height. Accommodation is the initial response to this condition, there are an increase of ventilation and heart rate. Acclimatization is a certain degree of tolerance to low oxygen levels after staying for a period of time at HA and will see the effects of erythropoietic action (Gonzales and Tapia, 2007). Lastly, adaptation allows people living under hypoxic and hyperbaric conditions. Through genetic variations and a suitable acclimatization process, the body can maintain at HA permanently. This last mechanism generally requires a process that occurs through hundreds or thousands of years after several generations.

1.1.6 Secondary erythrocytosis

Erythrocytosis is an erythrocyte mass increase, usually adjusted to values that depend on the laboratory measurement method, altitude, and sex (Greer et al., 2014). As a diagnosis method, hematocrit values grater than 50% are used to diagnose polycythemia (Villafuerte and Corante, 2016; Zubieta-Castillo et al., 2006). It usually will present as a comorbidity of different chronic respiratory diseases: cyanotic congenital heart disease, chronic alveolar hypo ventilation, or poor adaptation to altitude (Álvarez-Sala Walther, 1989).

1.1.7 What is high altitude erythrocytosis?

For secondary erythrocytosis, presenting more frequently in hypoxic origin, generally in cases of decrease in oxygen saturation ($SatO_2$), or arterial oxygen pressure (PaO). It has been suggested an acclimatization mechanism to improve the function of erythrocytosis, without being adaptive. By maintaining a constant high level of red blood cells, a heated person will, over time, begin to show signs of CMS (Gregorietti Di Nella et al., 2018). Hypoxemia weakly induces an erythrocyte production, therefore, acts as a mediator to the EPO response. The hypoxia-inducible factor (HIF) works as the most relevant mediator in erythropoietic response at low oxygen levels, absorption increase, and iron utilization. An adequate spinal response to hypoxemia depends on hemoglobin, a correct oxygen distribution depends on its synthesis, which is not guaranteed by increasing the volume of erythrocytes in the blood (Haase, 2010; Stradling and Lane, 1981).

1.1.8 CMS

Chronic mountain sickness, also known as Monge's disease or CMS, is a maladaptive disease, occurs in people who have a prolonged residence in high altitude sites ($>$ 2.500 m.a.s.l). Its signs and symptoms are headache, tinnitus, shortness of breath, cyanosis, sleep disturbances, vein dilation, right ventricular hypertrophy, and fatigue (Wu et al., 2005). The diagnosis came from laboratory indicators, HGB 21 g/dL in men, HGB 19 g/dL in women, HCT $>$ 65%, and $SatO_2 < 85\%$ in both genders (West, 2010), also, a diagnostic method that includes symptoms known as "Qinghai Score".
This disease shows clear polycythemia and hypoxemia, the excessive production of red blood cells due to erythropoietic action, increases the blood viscosity, making it difficult to cross the thinnest blood vessels. The treatment can be taken by different approaches, each with its own inconvenience, through phlebotomies (not very practical); acetazolamide as a pharmacological agent (side effects) (Swenson, 1998; Pichon et al., 2012; Richalet et al., 2005, 2008; Rivera-Ch et al., 2007) and displacement of residence at sea level (inconvenient due to socio-economic aspects).

1.1.9 Illness related with EE

High levels of erythrocytes are related to cardiovascular diseases develop, as the erythrocyte mass increases, blood viscosity increases. HCT levels also increase and, therefore, there is an increased risk of coronary heart disease, occlusive vascular disease and decreased cerebral blood flow (Corante et al., 2018; Thomas et al., 1977). Also, as a consequence of EE, a relationship with renal failure has been found in animal models, causing chronic failure, possibly due to the increase on the filtration fraction and renal plasma flow reduction (Davis et al., 2015; Lozano and C., 1965; Shih and Huang, 1998). Another consequence found in animal studies is a tissue endothelial system marked response causing increased mortality after blocking vasodilation mediated by nitric oxide (Quaschning et al., 2003).
The mechanisms that cause the increase in red cell mass are not understood completely. Erythropoietic activity mediates generation of new erythrocytes, a malfunction of this in response to various stimuli (transplantation, anemia, stress) results in erythropoiesis, which can occur in the spleen or liver, increasing erythrocyte levels (Franke et al., 2013).

1.1.10 Studies in South America

Several studies have been developing on HA inhabitants. Nearly 140 million people live in these conditions worldwide. Differences in adaptation have been evidenced, in Tibetans and Sherpas that show oxygen saturation and hematocrit similar to the reference values observed in residents at sea level (Beall, 2006; Bigham, 2016; Bhagi et al., 2014; Crawford et al., 2017; Hainsworth and Drinkhill, 2007; Jacovas et al., 2018; Moore, 2017; Painschab et al., 2015; Peng et al., 2011; Simonson et al., 2015). On the other hand, in American continent populations, especially in the Andean countries, a clear maladaptation to HA is evidenced (Beall et al., 2002; León-Velarde et al., 2005; Monge et al., 1992). This difference in results could be associated with evolutionary trends and the history period in which populations have been established at HA (Beall et al., 2002; Moore et al., 2007). Most of the studies in Andean countries have been carried out in Peru and Bolivia (Painschab

et al., 2015), also, although to a lesser extent, studies from other countries in this region (Fernández et al., 2006; Rodríguez MA, Schlottfeldt V, Inchaustegui JL, Herrera C, 2007; Gonzales and Tapia, 2007) and a few related with HA in Ecuador (Davis et al., 2015; Sáenz et al., 2008).

1.2 Problem statement

In Ecuador, an Andean country, several cities are ubicated in HA, which cover approximately 6.6 million inhabitants, with permanent residence in altitudes higher than 2.500 m.a.s.l (Villacís B., 2011). Due to the lack of resources and mobility restriction, the most remote populations cannot get access to a proper health treatment. Which is why, for visitors and residents of HA, the prevention and information are utmost important, specially in the study of factors related to polycythemia development. Few epidemiological studies have been carried out on HA diseases in Ecuador, compared to Peru and Bolivia, despite the ethnic diversity of each region (Gutiérrez et al., 2014; Naeije and Vanderpool, 2013; Painschab et al., 2015; Sáenz et al., 2008; Zubieta-Castillo et al., 2006; Zubieta-Calleja et al., 1995).

1.3 Objectives

1.3.1 General Objective

- Finding risk factors for developing EE in patients living in Zumbahua (Cotopaxi) during the 2007 - 2018 period.

1.3.2 Specific Objectives

- Establish the prevalence of EE patients compared to inhabitants $>$ 3.600 m.a.s.l. and people living at $<$ 2.300 m.a.s.l..
- Determine the relationship between demographic, environmental, health, blood test, and prevalence variables in EE.
- Compare the prevalence of EE at different altitudes and analyze the influence of some variables.
- Compare the relative impact of health variables and blood tests on the development of EE.
- Build a model capable of predicting the EE development with the most correlated variables.

Chapter 2

Methodology

2.1 Description

2.1.1 Study Zone

In this study, we compared two cohorts of patients between 2007-2018 years, the first with patient's resident at > 3.600 m.a.s.l and the second < 2.300 m.a.s.l. In both cases, we will perform a statistical study of patients with evident EE signs (HGB > 21 g/dL in men, HGB > 19 g/dL in women, HCT > 51% in men, and > 46% in women). Subsequently, in HA group 1, risk factors will be identified for those with EE compared to those with normal ranges levels. A retrospective cohort analysis was carried out in two groups of patients. The first, whose information stored in the Claudio Benati hospital, located in Zumbahua city (Cotopaxi) established at 3.600 m.a.s.l. And the second group from Ibarra city (Imbabura) at 2.220 m.a.s.l.
Due to the HA location and at the same time geographic remote ubication, more analyzes were carried out in the first group, since, in case of emergencies, the inhabitants of Zumbahua and their visitors must approach the hospital in search of basic medical treatment. For specialized medical treatment the patient should be transported to another hospital 60 km away. This study was carried out under the "Ley Orgánica de Protección de Datos Personales" (Asamblea Nacional Republica del Ecuador, 2019) for scientific research purposes only. The information used is entirely anonymous and not identifies one or a group of people.

2.1.2 Data collection and Categorization

The information on the patients was obtained from the database for the years 2007 to 2018. A total of 915 clinical files were analyzed, from hospitals located at 2.200 - 2.300 m.a.s.l. and 3.600 - 4.400 m.a.s.l. The scrutiny of 721 patients, of which 452 were women and 269 men. A total of 480 patients were HA dwellers and 241 were dwellers at altitudes of 2.200 - 2.300 m.a.s.l. The patients were between the ages of 1 to 96 years. The EE categorization came from the red blood cells levels, for women, is positive when are obtained values greater than 5.4 x 10 E6 cells/uL, in the case of men with values greater than 6.1 x 10 E6 cells/uL.

The conceptualization of the variables are the follow:

Demographic variables

Categorized as: residents of high altitude (3.600 - 4.400 m.a.s.l.) Or inhabitants of normal altitude (2.200 - 2.300 m.a.s.l.), sex categorized as men and women; body mass index (BMI) categorized as underweight (< 18.5), normal (18.5 - 24.9) and over-weight (> 24.9); age categorized as children (1 - 14 years), young (15 - 25 years), adult (26 - 64 years), or elderly (> 65 years). Age and BMI variables were established according to reference values (American Cancer Society, nd; Government of Canada, 1998).

Vital variables

For this section we have: systolic pressure (SP), diastolic pressure (DP), heart rate (HR), breathing frequency (BF), oxygen saturation in the blood ($SatO_2$), and axillary temperature (℃). This information was classified as low, normal, and high according to Real First Aid information(Real First Aid, ndb,n).

Blood variables

Categorized as: hemoglobin (HGB), hematocrit (HCT), red blood cells (RBC), white globes (WBC), platelets (PLT), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC) and Creatinine. The variables were grouped as: low, normal, high according to the reference value of Marshfield Labs and Alberta Health Service (Alberta Health Service, 2018; Marshfield Labs, 2013).

2.1.3 Problem analysis

Statistics

Continuous variables were compared with the t-student test (health status and blood variables among patients with or without EE). Contingency tables and associations by Cramer V statistical analysis were used in the variables. Step wise multiple linear regression to determine significant blood and health variables. Using multiple logistic regression (MLR) a model was established with the variables significantly associated in the previous analyzes. For data analysis, SPSS software version 25 for Windows, all analyzes were carried out with a two-tailed test with an Alpha value of 0.05 as an indicator of statistical significance.

Chapter 3

Results and Discussion

3.1 Results

3.1.1 Missing data in clinical records

For demographic variables, there is no loss of data, except for BMI with a loss of 5.4%. For vital variables, there are different percentages of loss, all of them less than 15%. For blood variables, loss is not greater than 2%, except for creatinine with 30.9% loss. Only variables with at least 80% of the data were taken into account in the binary logistic regression model.

3.1.2 Analysis of risk factors for CMS associated with EE

This work studies 721 patients (452 women and 269 men), taking as a diagnosis for EE the high-level parameter (Mean + 2 SD) of RBC in blood, 139 (12.28%) patients showed levels above the limit (EE) and 582 (80.72%) showed lower or in range values (No EE). The possible risk variables divide into three categories: demographic, vital signs, and blood. For continuous variables, separated into different groups, a division was made into three sections (low, normal, high), considering in the division: age and sex of the patient. Each category is represented by a number 1 for low, 2 for normal, and 3 for high.

Demographic variables characteristics are shown in Table 3.1. Altitude group and sex show a significant P-value, both with $P < 0.001$. Both age variable and BMI did not show a level of significance for their analysis.

Variable	**EE**	**No EE**	***P*-value 2-tailed**
Group altitude No. (%)			**<0.001**
High-altitude	131 (94.2)	349 (60.0)	
Medium-altitude	8 (5.8)	233 (40.0)	
Sex: No. (%)			
Women	114 (82.0)	338 (58.1)	**<0.001**
Men	25 (18.0)	244 (41.9)	
Age (years) Mean ± SD	37.66 (23.02)	35.69 (19.57)	0.353
BMI No. (%)			0.260
Underweight	22 (17.2)	83 (15.0)	
Normal weight	56 (43.8)	223 (40.3)	
Overweight	50 (39.1)	248 (44.8)	

Significant P-values are in bold letter

Table 3.1: Demographic characteristics of the patients in the EE cohort against No EE cohort.

Variable	EE			No EE			*P*-value
	n	Mean	SD	n	Mean	SD	
Hemogram:							
RBC (10^12 cells/uL)	114	5.86	0.57	338	4.88	0.34	**<0.001**
HCT (%)	114	49.31	6.67	338	42.70	3.43	**<0.001**
HGB (g/dL)	114	16.33	2.07	338	14.41	1.57	**<0.001**
MCV (fL)	114	84.10	7.46	337	87.35	6.94	**<0.001**
MCHC (g/dL)	114	33.01	1.87	337	32.79	3.66	0.536
PLT (10^9/ L)	112	264.77	90.07	332	275.11	71.43	0.217
WBC (10^9/L)	114	9.66	3.81	335	8.24	3.57	**0.001**
Creatinine (mg/dL)	63	1.02	0.49	227	0.86	0.20	**0.017**
Health signs:							
Systolic pressure (mm Hg)	94	108.77	17.62	297	105.66	15.14	0.097
Diastolic pressure (mm Hg)	93	72.19	13.36	297	68.25	11.18	**0.011**
Heartbeat (beats/min)	113	86.87	22.98	335	84.51	21.84	0.329
Breathing frequency (breaths/min)	101	23.97	6.07	300	22.51	6.44	**0.046**
O_2 saturation (%)	109	89.99	7.47	322	91.80	5.96	**0.011**
Temperature (C)	109	37.03	0.78	321	36.83	0.79	**0.021**

Significant *P*-values are in bold letter

Table 3.2: Contingency tables of contrast between blood variables and vital variables in the EE cohort compared to the No EE cohort in the women group.

Table 3.2 shows the significance in the case of the vital and blood variables for women. A priori t-test student analysis, 10 out of 14 of the variables showed a significant *P*-value. For the hemogram: RBC, HGB, HCT and MCV show a *P*-value < 0.001, WBC also show significance with $P = 0.001$ and creatinine with $P = 0.017$. HCT levels are higher in the case of EE (t (114) = 49.31, $P < 0.001$), for women normal range are between (36.1% - 44.3%). In the same way, the mean HGB in EE exceeds the limit level of normal ranges (12.1 - 15.1 g/dL) showing (t (114) = 16.33, $P < 0.001$). Both are related with the higher amount of RBC present in EE.
For MCV, WBC, and creatinine, although *P*-value shows significance in EE, the values are within normal limits. Regarding the variables of vital signs: diastolic pressure, respiratory rate and temperature showed significance, however, they are in normal ranges. In the case of $SatO_2$, it shows levels that tend towards hypoxemia ($< 90\%$) with values of (t (109) = 89.99, $P = 0.011$), however, it must be related with HA.

Variable	EE			No EE			*P*-value
	n	Mean	SD	n	Mean	SD	
Hemogram:							
RBC (10^12 cells/uL)	29	6.47	0.58	244	5.34	0.48	**<0.001**
HCT (%)	29	53.91	9.62	244	47.06	4.74	**0.001**
HGB (g/dL)	29	17.63	2.07	244	15.85	1.62	**0.004**
MCV (fL)	29	82.91	10.34	241	87.86	5.88	**0.017**
MCHC (g/dL)	29	32.44	2.21	240	31.84	2.09	0.148
PLT (10^9/ L)	29	249.97	124.35	244	268.78	76.29	0.431
WBC (10^9/L)	29	9.83	4.02	242	7.52	3.17	**0.005**
Creatinine (mg/dL)	18	1.04	0.26	191	1.01	0.28	0.765
Health signs:							
Systolic pressure (mm Hg)	22	105.45	17.98	216	113.26	18.30	0.057
Diastolic pressure (mm Hg)	22	70.45	12.96	215	73.09	11.81	0.325
Heartbeat (beats/min)	29	94.79	25.46	242	81.47	21.29	**0.002**
Breathing frequency (breaths/min)	25	25.72	8.15	222	22.47	7.18	0.036
O_2 saturation (%)	28	89.93	5.59	236	92.21	4.44	**<0.001**
Temperature (C)	29	36.97	0.94	235	36.75	1.16	0.310

Significant *P*-values are in bold letter

Table 3.3: Contingency tables of contrast between vital variables and blood variables in the EE cohort compared to the No EE cohort in the men group.

Table 3.3 shows the significance in the case of the vital and blood variables for men. A priori t-test student analysis, 7 out of 14 of the variables showed a significant *P*-value. For the hemogram: RBC, HCT, HGB, MCV, and WBC show significance. HCT levels are higher in the case of EE (t (29) = 53.91, $P = 0.001$) for men normal range are between (40.7% - 50.3%). In the same way the mean HGB in EE exceeds the limit level of normal ranges (13.8 - 17.2 g/dL) showing (t (29) = 17.63, $P = 0.004$)). Both are related with the higher amount of RBC present in EE.
For MCV, WBC, although *P*-value shows significance in EE, the values are within normal limits. Regarding the vital signs variables, the heart rate shows significance, however, they are in normal ranges. In the case of $SatO_2$, it shows levels that tend to hypoxemia ($< 90\%$) with values of (t (28) = 89.93, $P = 0.011$), however, it must be related with HA, specially because mean value is nearby to a normal range.

3.1.3 Analysis of EE risk factors

Tables 3.3 and 3.4 show relationship between the occurrence of EE and the possible demographic risk variables in women and men respectively. The Cramer V analysis (φc) is the intercorrelation of two discrete variables based in chi-square value (Sheskin, 2011) φc values is between 0 - 1 tending to 1 show more association between the variables. In the case of women (group altitude: ($\varphi c = 0.243$, $P < 0.001$)); (age: ($\varphi c = 0.198$, $P < 0.001$)); for men (group altitude: ($\varphi c = 0.301$, $P = 0.001$)); (age: ($\varphi c = 0.272$, $P < 0.001$)) show more relation compared to BMI.

Tables 3.5 and 3.6 show the significant association between EE and the blood variables, in the case of women (HCT: ($\varphi c = 0.469$, $P < 0.001$)); (HGB: ($\varphi c = 0.507$, $P < 0.001$)); (MCV: ($\varphi c = 0.132$, $P = 0.019$); (PLT: ($\varphi c = 0.141$, $P < 0.05$)); (WBC: ($\varphi c = 0.200$, $P < 0.001$)); (Creatinine: ($\varphi c = 0.182$, $P < 0.01$)). For men group (HCT: ($\varphi c = 0.380$, $P < 0.001$)); (HGB: ($\varphi c = 0.392$, $P < 0.001$)); (PLT: ($\varphi c = 0.296$, $P < 0.001$)); (WBC: ($\varphi c = 0.245$, $P < 0.001$)). Tables 3.7 and 3.8 obtain the relationship between EE and vital variables, in the case of women (DP: ($\varphi c = 0.165$, $P < 0.01$)); (BF: ($\varphi c = 0.147$, $P < 0.005$)). In men (SP: ($\varphi c = 0.241$, $P < 0.005$)); (DP: ($\varphi c = 0.240$, $P < 0.005$)); ($SatO_2$: ($\varphi c = 0.263$, $P < 0.001$)). Some of the values that present with significance do not show relevance, despite their relationship with EE, the values that present are within the normal ranges for people in specific age and gender groups.

In tables 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, in the same way, the values of odds ratios (OR) are observed, for each table OR value will have more significance depending on the case. Regarding demographic variables, living with HA is more associated with having EE in men than in women. In both sexes, there is a higher prevalence of EE in the 15 - 24 year age group (OR = 2.884, between 1.365 and 6.093 with $P = 0.006$, in women) and (OR = 5.885, between 1.317 and 26.297 with $P = 0.020$, in men), concerning the other age groups.

The analyzes in tables 3.5 and 3.6 with the blood variables, for women group, show high HCT (OR = 0.142, between 0.032 and 0.636 with $P = 0.011$); high HGB (OR = 0.176, between 0.039 and 0.807 with $P = 0.025$); normal MCV (OR = 2.580, between 1.287 and 5.171 with $P = 0.008$); high PLT (OR = 5.375 between 1.417 and 20.260 with $P = 0.013$); high WBC (OR = 0.378, between 0.150 and 0.952 with $P = 0.039$). For men, high HCT (OR = 0.210, between 0.046 and 0.995 with $P = 0.043$); normal HGB (OR = 9.889, between 1.595 and 61.320 with $P = 0.014$); normal PLT (OR = 11.450, between 3.379 and 38.798 with $P < 0.001$).

For tables 3.7 and 3.8, the results with OR show a relationship of EE with the vital variables, for women group with high PD (OR = 0.318, between 0.109 and 0.922 with $P = 0.035$); high BF (OR = 0.507, between 0.321 and 0.799 with $P = 0.003$); For men group, normal SP (OR = 5.074, between 1.987 and 12.959 with $P = 0.001$); normal DP (OR = 4.974, between 1.974 and 12.708 with $P = 0.001$); $SatO_2$ (OR = 5.179, between 2.297 and 11.676 with P <0.001).

When considering OR significance obtained, the tables show how likely is a group

results limited have greater weight in terms of suffering EE. These values may lack a strong correlation because the measures are on average for a healthy person, as in case of normal systolic and diastolic pressure in men with EE. In high WBC for women case, the consequence would be more linked to the fact that the main diagnosis for these patients in the consultation area was urinary tract infection, for which their count of WBC is higher than normal, however, the average (Table 3.2) is not diagnosed as leukocytosis (WBC counts $>$ 11 * 10ˆ9/L). The same explanation applies for platelet level (Table 3.2) does not reach the count to be diagnosed as thrombocytosis (PLT counts $>$ 450 * 10ˆ9/L).

Variable	EE	No EE	Women OR (95% CI) (*P*-value)	Cramer´s V (*P*-value)	EE	No EE	Men OR (95% CI) (*P*-value)	Cramer´s V (*P*-value)
Group altitude No. (%)								
High-altitude	108 (94.7)	241 (71.3)	7.245 (3.081 – 17.039)	**0.243**	27 (93.1)	108 (44.3)	17.000 (3.954 – 73.082)	**0.301**
Medium-altitude	6 (5.3)	97 (28.7)	(<0.001)	**(<0.001)**	2 (6.9)	136 (55.7)	(<0.001)	**(<0.001)**
Age (years) No. (%)								
1-14 years	26 (22.8)	55 (16.3)	1.204 (0.472 – 2.217) (0.953)		6 (20.7)	32 (13.1)	1.231 (0.267 - 5.675) (0.790)	
15-24 years	25 (21.9)	149 (44.1)	2.884 (1.365 – 6.093) (0.006)	**0.198**	6 (20.7)	153 (62.7)	5.885 (1.317-26.297) (0.020)	**0.272**
25-65 years	48 (42.1)	103 (30.5)	1.038 (0.513 – 2.102) (0.917)	**(0.001)**	14 (48.3)	46 (18.9)	0.758 (0.189 – 3.046) (0.696)	**(<0.001)**
>65 years	15 (13.2)	31 (9.2)	1 (baseline) (0.001)		3 (10.3)	13 (5.3)	1 (baseline) (0.001)	
BMI No. (%)								
Underweight	20 (19.0)	52 (16.3)	1 (baseline) (0.791)		5 (19.2)	31 (13.2)	1 (baseline) (0.462)	
Normal weight	46 (43.8)	148 (46.3)	1.237 (0.671 – 2.284) (0.496)	0.033 (0.790)	10 (38.5)	75 (32.1)	1.210 (0.382 – 3.829) (0.746)	0.078 (0.465)
Overweight	39 (37.1)	120 (37.5)	1.183 (0.631 – 2.221) (0.600)		11 (42.3)	128 (54.7)	1.877 (0.608 – 5.796) (0.274)	

Significant *P*-values are in bold letter

Table 3.4: Cross-tabulation, OR and *P*-values of demographic characteristics for patients in EE cohort against No EE cohort in women and men groups.

Variable	Categories	EE		No EE		OR (95% CI) (*P*-value)	Cramer's V (*P*-value)
		n	%	n	%		
HGB	Low	2	1.8	12	3.6	1 (baseline) (<0.001)	
	Normal	9	7.9	217	64.2	4.019 (0.781 - 20.690) (0.096)	**0.507 (<0.001)**
	High	103	90.4	109	32.2	0.176 (0.039 - 0.807) (0.025)	
HCT	Low	2	1.8	15	4.4	1 (baseline) (<0.001)	
	Normal	17	14.9	222	65.7	1.741 (0.367 - 8.250) (0.485)	**0.469 (<0.001)**
	High	95	83.3	101	29.9	0.142 (0.032 - 0.636) (0.011)	
MCV	Low	16	14.0	20	5.9	1 (baseline) (0.028)	
	Normal	98	86.0	316	93.8	2.580 (1.287 - 5.171) (0.008)	**0.132 (0.019)**
	High	0	0.0	1	0.3		
MCHC	Low	32	28.1	115	34.1	1 (baseline) (0.028)	
	Normal	78	68.4	204	60.5	0.728 (0.455 - 1.165) (0.186)	0.073 (0.302)
	High	4	3.5	18	5.3	1.252 (0.396 - 3.963) (0.702)	
PLT	Low	9	8.0	7	2.1	1 (baseline) (0.021)	
	Normal	97	86.6	300	90.4	3.976 (1.443 - 10.960) (0.008)	**0.141 (0.012)**
	High	6	5.4	25	7.5	5.375 (1.417 - 20.260) (0.013)	
WBC	Low	7	6.1	26	7.8	1 (baseline) (<0.001)	
	Normal	65	57.0	250	74.6	1.036 (0.430 - 2.492) (0.938)	**0.200 (<0.001)**
	High	42	36.8	59	17.6	0.378 (0.150 - 0.952) (0.039)	
Creatinine	Low	0	0.0	10	4.4	1 (baseline) (0.045)	
	Normal	51	81.0	200	88.1	(0.999)	**0.182 (0.008)**
	High	12	19.0	17	7.5	(0.999)	

Significant *P*-values are in bold letter

Table 3.5: Cross-tabulation, OR and *P*-values of blood characteristics of the patients in the EE cohort against No EE cohort in women group.

OR and Cramer's V test (*P*-value). Units: HGB in g/dL; HCT in %; MCV in fL; MCHC g/dL; platelets in (10^9 units/L); WBC in (10^9 units/L); creatinine in mg/dL. Significant *P*-values are in bold letter.

Variable	Categories	EE		No EE		OR (95% CI) (*P*-value)	Cramer's V (*P*-value)
		n	%	n	%		
HGB	Low	2	6.9	25	10.2	1 (baseline) (<0.001)	
	Normal	3	10.3	156	63.9	4.160 (0.662 - 26.150) (0.129)	**0.380 (<0.001)**
	High	24	82.8	63	25.8	0.210 (0.046 - 0.995) (0.043)	
HCT	Low	2	6.9	9	3.7	1 (baseline) (<0.001)	
	Normal	4	13.8	178	73.0	9.889 (1.595 - 61.320) (0.014)	**0.392 (<0.001)**
	High	23	79.3	57	23.4	0.551 (0.110 - 2.747) (0.467)	
MCV	Low	5	17.2	20	8.3	2.302 (0.792 - 6.689)	0.096
	Normal	24	82.8	221	91.7	(0.116)	(0.116)
MCHC	Low	12	41.4	133	55.4	1 (baseline) (0.354)	
	Normal	16	55.2	99	41.3	0.558 (0.253 - 1.233) (0.149)	0.089 (0.346)
	High	1	3.4	8	3.3	0.722 (0.083 - 6.266) (0.767)	
PLT	Low	6	20.7	6	2.5	1 (baseline) (<0.001)	
	Normal	20	69.0	229	93.9	11.450 (3.379 - 38.798) (<0.001)	**0.296 (<0.001)**
	High	3	10.3	9	3.7	3.000 (0.533 - 16.897) (0.213)	
WBC	Low	2	6.9	20	8.3	1 (baseline) (0.001)	
	Normal	16	55.2	196	81.0	1.225 (0.263 - 5.716) (0.796)	**0.245 (<0.001)**
	High	11	37.9	26	10.7	0.236 (0.047 - 1.189) (0.080)	
Creatinine	Low	1	5.6	11	5.8	1 (baseline) (0.998)	
	Normal	16	88.9	170	89.0	0.996 (0.117 - 73.969) (0.974)	0.005 (0.998)
	High	1	5.6	10	5.2	0.909 (0.050 - 16.540) (0.949)	

Significant *P*-values are in bold letter

Table 3.6: Cross-tabulation, OR and *P*-values of blood characteristics of the patients in the EE cohort against No EE cohort in men group.

OR and Cramer's V test (*P*-value). Units: HGB in g/dL; HCT in %; MCV in fL; MCHC g/dL; platelets in (10^9 units/L); WBC in (10^9 units/L); creatinine in mg/dL. Significant *P*-values are in bold letter.

Variable	Categories	EE		No EE		OR (95% CI) (*P*-value)	Cramer's V (*P*-value)
		n	%	n	%		
SP	Low	45	47.9	128	43.2	1 (baseline) (0.408)	
	Normal	45	47.9	234	54.4	1.258 (0.783 - 2.020) (0.343)	0.068 (0.402)
	High	4	4.3	7	2.4	0.615 (0.172 - 2.201) (0.455)	
DP	Low	49	52.7	135	45.5	1 (baseline) (0.008)	
	Normal	36	38.7	155	52.2	1.563 (0.959 - 2.546) (0.073)	**0.165 (0.005)**
	High	8	8.6	7	2.4	0.318 (0.109 - 0.922) (0.035)	
HR	Low	5	4.4	24	7.2	1 (baseline) (0.541)	
	Normal	89	78.8	262	78.2	0.613 (0.227 - 1.656) (0.335)	0.053 (0.535)
	High	19	16.8	49	14.6	0.537 (0.179 - 1.613) (0.268)	
BF	Normal	45	44.6	184	61.3	0.507 (0.321 - 0.799)	**0.147**
	High	56	55.4	116	38.7	(0.003)	**(0.003)**
$SatO_2$	Low	38	34.9	90	28.0	1.380 (0.868 - 2.192)	0.066
	Normal	71	65.1	232	72.0	(0.172)	(0.172)
T. axillary	Low	0	0.0	2	0.6	1 (baseline) (0.018)	
	Normal	70	64.2	249	77.6	(0.999)	**0.144 (0.012)**
	High	39	35.8	70	21.8	(0.999)	

Significant *P*-values are in bold letter

Table 3.7: Cross-tabulation, OR and *P*-values of blood characteristics of the patients in the EE cohort against No EE cohort in women group.

OR and Cramer's V test (*P*-value). Units: systolic and diastolic pressures in mm Hg; axillary temperature in °C; heart rhythm in beats per minute and breathing frequency in cycles per minute and oxygen saturation in %. Significant *P*-values are in bold letter.

Variable	Categories	EE		No EE		OR (95% CI) (*P*-value)	Cramer's V (*P*-value)
		n	%	n	%		
SP	Low	13	59.1	49	22.7	1 (baseline) (0.003)	
	Normal	8	36.4	153	70.8	5.074 (1.987 - 12.959) (0.001)	**0.241 (0.001)**
	High	1	4.5	14	6.5	3.714 (0.446 - 30.910) (0.225)	
DP	Low	13	59.1	49	22.8	1 (baseline) (0.003)	
	Normal	8	36.4	150	69.8	4.974 (1.974 - 12.708) (0.001)	**0.240 (0.001)**
	High	1	4.5	16	7.4	4.245 (0.514 - 35.041) (0.179)	
HR	Low	0	0.0	21	8.7	1 (baseline) (0.772)	
	Normal	25	86.2	200	826	(0.998)	0.110 (0.193)
	High	4	13.8	21	8.7	(0.998)	
BF	Normal	11	44.0	136	61.5	0.419 (0.213 - 1.132)	0.108
	High	14	56.0	85	38.5	(0.090)	(0.090)
$SatO_2$	Low	15	53.6	43	18.2	5.179 (2.297 - 11.676)	**0.263**
	Normal	13	46.4	193	81.8	(<0.001)	**(<0.001)**
T. axillary	Low	0	0.0	2	0.9	1 (baseline) (0.200)	
	Normal	19	65.5	187	79.6	(0.999)	0.117 (0.165)
	High	10	34.5	46	19.6	(0.999)	

Significant *P*-values are in bold letter

Table 3.8: Cross-tabulation, OR and *P*-values of blood characteristics of the patients in the EE cohort against No EE cohort in men group.

OR and Cramer's V test (*P*-value). Units: systolic and diastolic pressures in mm Hg; axillary temperature in °C; heart rhythm in beats per minute and breathing frequency in cycles per minute and oxygen saturation in %. Significant *P*-values are in bold letter.

3.1.4 Multivariate binary logistic regression model for EE risk factors

MBLR is a type of analysis that provides information about categorical variables. Shows a prediction model of suffering EE. It was carried out on the variables with significance in the Cramer´s V test and whose data correspond to at least 80% of the patients. The analysis performed in demographic variables for women (Table 3.9) and men (Table 3.10) shows values with statistical significance for the prediction model correspond to the following equation.

For women group:

Table 3.9: Multivariate logistic regression analysis of risk factors for patients in EE cohort in women.

Variable	B	S.E.	Wald	Df	p.	Exp(B)	95% C.I. for Exp (B)
Constant	-1.013	0.518	3.042	1	0.081	0.363	
Group altitude	1.739	0.489	12.672	1	0.000	5.694	2.185 - 14.837
Age			1.260	3	0.739		
Age (1)	-0.019	0.395	0.002	1	0.962	0.981	0.452 - 2.129
Age (2)	0.333	0.409	0.662	1	0.416	1.395	0.626 - 3.110
Age (3)	0.030	0.360	0.007	1	0.933	1.031	0.5090- 2.087

B, Regression coefficient; S.E., Standard error; Wald, Test de Wald; df, degrees of freedom; CI, confidence interval; Age (1) = 1-14 years, Age (2) = 15-24 years, and Age (3) = 25-65 years; Group altitude = High altitude.

Table 3.9: Multivariate logistic regression analysis of risk factors for patients in EE cohort in women.

$$\hat{y}_a = -0.635 + (1.956) * Group\,altitude - (0.458)* Age_{1-14years} + (0.109) * Age_{15-24years} + (0.009) * Age_{25-64years}$$

$\hat{y}_a$ = predict logit score for EE

For men group:

Variable	B	S.E.	Wald	Df	p.	Exp(B)	95% C.I. for Exp (B)
Constant	-1.134	1.087	1.089	1	0.297	0.322	
Group altitude	2.600	0.878	8.718	1	0.003	13.466	2.411 - 75.210
Age			1.268	3	0.737		
Age (1)	0.179	0.780	0.052	1	0.819	1.196	0.259 - 5.519
Age (2)	0.167	0.834	0.040	1	0.841	1.182	0.230 - 6.064
Age (3)	-0.338	0.710	0.226	1	0.635	0.714	0.177 - 2.872

B, Regression coefficient; S.E., Standard error; Wald, Test de Wald; df, degrees of freedom; CI, confidence interval; Age (1) = 1-14 years, Age (2) = 15-24 years, and Age (3) = 25-65 years; Group altitude = High altitude.

Table 3.10: Multivariate logistic regression analysis of risk factors for patients in EE cohort in men.

$$\hat{y}_b = -1.134 + (2.600) * Group\,altitude + (0.179)* Age_{1-14years} + (0.167) * Age_{15-24years} + (0.338) * Age_{25-64years}$$

$\hat{y}_b$ = predict logit score for EE

In both cases, height has a positive association with the probability of developing EE, with higher the height, the greater the risk of having EE, in the case of women (OR: 5.694; 95% CI: 2.185 - 14.837, $P < 0.001$), for men group (OR: 13.466; 95% CI: 2.411 - 75.210, $P = 0.003$)

3.1.5 Logistic Regression for blood and vital variables

For LR model the results (appendix 4.1 and 4.2) show not clear enough information to completely understand the risk factors of having EE. For this reason blood and vital values where analyzed in separated groups, to achieve a better comprehension and get a broad analysis of the variables.

3.1.6 Multivariate linear regression model for blood variables in EE

The MLR uses both quantitative and qualitative variables to fit linear models, in this case, the independent variables of blood are taken with the dependent variable of EE and obtain a model in the form of the following equation:

For women group:

Variable	B	S.E.	Beta	t	p.	95% C.I. for Exp (B)
Constant	1.449	0.291		4.986	<0.001	0.877 - 2.022
HCT	-0.080	0.007	-1.035	-12.117	<0.001	(-0.093) - (-0.067)
MCV	0.029	0.003	0.528	9.182	<0.001	0.023 - 0.036
HGB	0.087	0.017	0.432	5.183	<0.001	0.054 - 0.121

B, Regression coefficient; S.E., Standard error; Beta, Standard coefficient; CI, confidence interval; MLR of hemodynamic analysis of EE with only significant variables: Hematocrit (HCT) (%); Medium Corpuscular Volume (MCV) (fL); Hemoglobin (HGB) (g/dL).

Table 3.11: Multivariate linear regression analysis of risk factors in blood variables for patients in EE cohort for women group.

$$EE = 1.449 - (0.080) * HCT + (0.029) * MCV + (0.087) * HGB \tag{3.1}$$

Overall success rate of the model 68.8%

For men group:

Variable	B	S.E.	Beta	t	p.	95% C.I. for Exp (B)
Constant	2.080	0.382		5.450	<0.001	1.327 - 2.832
HCT	-0.067	0.009	-1.184	-7.213	<0.001	(-0.086) - (-0.049)
MCV	0.025	0.003	0.459	7.890	<0.001	0.019 - 0.031
HGB	0.106	0.028	0.611	3.762	<0.001	0.051 - 0.162
MCHC	-0.027	0.008	-0.194	-3.378	0.001	(-0.042) - (-0.011)

B, Regression coefficient; S.E., Standard error; Beta, Standard coefficient; CI, confidence interval; MLR of hemodynamic analysis of EE with only significant variables: Hematocrit (HCT) (%); Medium Corpuscular Volume (MCV) (fL); Hemoglobin (HGB) (g/dL).

Table 3.12: Multivariate linear regression analysis of risk factors in blood variables for patients in EE cohort for men group.

$$EE = 2.080 - (0.067) * HCT + (0.025) * MCV + (0.106) * HGB - (0.027) * MCHC \quad (3.2)$$

Overall success rate of the model 65.2%

The models gives the following nomenclature EE (1) and No EE (2), so the result of the equations is rounded to the nearest whole number.

Example 1: A women person with 40.56 HCT; 78 of MCV and 17 of HGB, which group is this patient in?

Using (3.1) equation:

$$EE = 1.449 - (0.080) * 49.65 + (0.029) * 78 + (0.087) * 17$$

$$EE = 1.21 \approx 1$$

Solution: Patient is in EE group

Example 2: A men patient with 42.95 HCT; 82 of MCV; 15.60 of HGB and 36.30 of MCHC, which group are you in?

Using (3.2) eqution:

$$EE = 2.080 - (0.067) * 42.95 + (0.025) * 82 + (0.106) * 15.60 - (0.027) * 36.30$$

$$EE = 1.92 \approx 2$$

Solution: Patient is in No EE group

3.1.7 Multivariate linear regression model for health variables in EE

The model is obtained from the following equations.

For the women group:

Variable	B	S.E.	Beta	t	p.	95% C.I. for Exp (B)
Constant	1.324	0.341		3.878	<0.001	0.652 - 1.995
DP	-0.006	0.002	-0.161	-2.959	0.003	(-0.010) - (-0.002)
SatO₂	0.009	0.004	0.142	2.612	0.009	0.002 - 0.016

B, Regression coefficient; S.E., Standard error; Beta, Standard coefficient; CI, confidence interval; MLR of health signs analysis of EE with only significant variables: Diastolic pressure (DP) (mm Hg); Oxygen saturation ($SatO_2$) (%).

Table 3.13: Multivariate linear regression analysis of risk factors for patients in EE cohort for women group.

$$EE = 1.324 - (0.006) * DP + (0.009) * SatO_2 \tag{3.3}$$

Overall success rate of the model 4.2%

For the men group:

Variable	B	S.E.	Beta	t	p.	95% C.I. for Exp (B)
Constant	2.159	0.103		21.044	<0.001	1.956 - 2.361
HB	-0.003	0.001	-0.169	-2.499	0.013	(-0.006) - (0.001)

B, Regression coefficient; S.E., Standard error; Beta, Standard coefficient; CI, confidence interval; MLR of health signs analysis of EE with only significant variables: Heartbeat (HB) (pulse per minute).

Table 3.14: Multivariate linear regression analysis of risk factors for patients in EE cohort for men group.

Predicted logit of EE model

$$EE = 2.159 - (0.003) * HB \tag{3.4}$$

Overall success rate of the model 2.8%

In vital variables, EE and Non-EE results show significance depending on sex, however, since the constant B in the MLR is within normal ranges, it has little weight. For this reason, vital variables do not have a enough correlation with the risk of suffering EE. Specially according with low percentage of overall success rate in both models.

3.2 Discussion

Several studies around the world search risk factors for suffering from EE, especially in HA, where the mountain population has developed protection against various cardiac pathologies. (Faeh et al., 2009; Hurtado, 1960; Marticorena et al., 1969; Mortimer et al., 2004; Negi et al., 2012), however, in part of the population, there is a poor adaptation to the height, which reduces tolerance to hypoxic environments, leading to EE and CMS (León-Velarde et al., 2005; Monge, 1943; Talbott and Dill, 1936). According to the results (Tables 3.1, 3.4), HA has great significance with EE, this conjecture can be evidenced in studies carried out in Peru, with populations with similar ancestry to the Ecuadorian, which show between 15% - 20% of the men population has CMS, its main characteristic being viscous blood related to EE (Monge et al., 1992; Leon-Velarde et al., 1994; Frayser et al., 1975; Singh et al., 1990).

For the set of data analyzed in the present study, relationship between women and men who have EE is 3:1, showing novel results since most studies report EE results with a higher prevalence in men and relates the levels of serum testosterone to increased red blood cell production (Beall et al., 1992; Coviello et al., 2008; García Hjarles, 1989; Gonzales et al., 2009, 2012; Gonzales and Chaupis, 2015; Jiang et al., 2014; León-Velarde et al., 2001; Penaloza and Arias-Stella, 2007; Monge et al., 1992; Wu et al., 2007; Xing et al., 2008), on the other hand, some studies report a higher incidence of EE in women (León-Velarde et al., 1997; Negi et al., 2012), and it is age-related since there is an increase in red blood cells in postmenopausal women, also the results may be affected due to unequal number of patients studied, with a greater number of women.

Regarding blood variables, a higher correlation was obtained with EE, resulting in values above the limit of the range in the case of HCT (Table 3.2 and 3.3). The categorical analysis (Table 3.5 and 3.6) showed significance for high levels of HCT and occupies a place in the risk variables. This results are in accordance with those carried out in several studies, high values of HCT go together with the increase in blood viscosity, EE, and CMS (Basu et al., 2007; Bigham, 2016; Frappell et al., 2007; Frisancho, 2013; Hanley et al., 2009; Lozano and C., 1965; Monge, 1943; Monge et al., 1965; Naeije, 2010; Piedras et al., 1995; Sime et al., 1975). Similarly, HGB results have a similar behavior to HCT, establishing it as a risk variable, according to other studies (Beall, 2006; Frappell et al., 2007; Gonzales et al., 2009, 2012; Heinicke et al., 2006; León-Velarde et al., 2005; Miserocchi and Bartesaghi, 2011; Monge et al., 1992; Moore et al., 2007; Naeije, 2010; Spicuzza et al., 2004; Villafuerte et al., 2004; Wilson et al., 2009; Wu et al., 2005). MCV results show that for women and men, mean MCV is lower for people with EE compared to No EE (Table 3.2 and 3.3), this results infer that the increase in RBC and HCT, have as a consequence a MCV decrease, RBC amount increase in hypoxic conditions, would lead to decreasing the volume of erythrocytes, there are few previous studies of people living at high altitudes related to MCV, usually relate with people who ascend for short periods of time (Hematy et al., 2014; Zhong et al., 2015), in these cases the tendency for the subjects is to increase the MCV. MCHC in table 3.12 shows the significance and is present in the equation. This result appears in men group, so it may be related to difference in hemoglobin results compared to women group (Figure 3.5).

Although in the final equation did not show enough weight to count as a risk variable, WBC count showed significance (Table 3.2 and 3.3). No previous studies have been found that relate people with EE and with a high number of WBC. One of the possible explanations is that blood tests in this study were taken in people with different pathologies as comorbidities, such as urinary tract infection or gastroenteritis. Another possible explanation is an unknown mechanism that produces WBC increase, like RBC and HCT in people who have EE. However, there is a relationship between the amount of WBC and the rapid rise to HA, but these studies were carried out in short periods (Beidleman et al., 2006; Rimoldi et al., 2012).

For vital variables, there was a difference between parameters that gave significance to each gender, for women there was an increase in the mean on SP and DP, in men there was a decrease in the same parameters. A study carried out in Peru indicates that when hemoglobin levels increase, there is an increase in SP and DP values (Gonzales et al., 2013) as well as others (Penaloza et al., 2008). Regarding HB and BF for both genders, there was an increase in the number/minute, for BF it does not match the theory, especially in CMS where this disease produces a progressive loss of respiratory rate (León-Velarde et al., 2005; Monge et al., 1992). For this variable, a possible explanation for the low oxygen saturation is that people suffer from sleep apnea common in EE (Burgess et al., 2004; Erba et al., 2004; Franke et al., 2013; Kryger et al., 1978; Richalet et al., 2005; Spicuzza et al., 2004; Nussbaumer-Ochsner et al., 2012). The HB increase may be related to the decrease in $SatO_2$, in both cases less than 90%, this may be a sign of lung disease for EE (Villegas-Martínez et al., 2020).

Because of this disease occurs when people live in hypoxic HA environments, the main and most recommended treatment is the displacement of the patient to sea level environment (Cui et al., 2013; Kryger et al., 1978; Monge et al., 1965; Rivera-Ch et al., 2007), however, this is not convenient socially and economically for people who have been living at HA for many years, a quick method treatment and specific for remote places is phlebotomy, alone or with isovolemic hemodilution, as a treatment for symptoms (Cruz et al., 1979; Julian et al., 2013; Klein, 1983; León-Velarde et al., 2005; Manier et al., 1988; Richalet et al., 2008; Sharma et al., 2017; Villafuerte, 2015; Vyas et al., 2015; Winslow et al., 1985; Wu, 1979; Wu et al., 2005; Zubieta-Calleja, 2004). Regarding pharmacological treatment, several approaches have been presented, among them: medroxyprogesterone, enalapril, and almitrine (Kryger et al., 1978; Pelouch et al., 1997; Plata et al., 2002; Vargas et al., 1996; Villena et al., 1985), the most studied is acetazolamide because it reduces erythropoiesis, (Eckardt et al., 1989; Hackett et al., 1987; Miller et al., 1973; Pichon et al., 2012; Richalet et al., 2005; Rivera-Ch et al., 2008; Sutton et al., 1979), there have even been experiments in rats with methazolamide in which they show encouraging results, however, studies are still lacking, dosing in human patients (Zhang et al., 2017).

The main limitation of this study was the lack of clinical information of the patients, for the elaboration of a predictive model with variables that generate greater significance, also, for a correct development of the study. Information is necessary on a third group of the cohort with residence at sea level (0 - 1000 m.a.s.l.), to obtain more reliable refer-

ence parameters according to the Ecuadorian population. Despite the lack of information regarding EE in Ecuador, the study has its consistencies and differences with the disease behavior presented in other reports about Andean countries, which shows the relevance of the evolutionary-genetic variable in adaptation process of populations (Beall et al., 2002; Beall, 2006; Gonzales and Chaupis, 2015; Xing et al., 2008; Zhou et al., 2013).

Chapter 4

Conclusions and recommendations

4.1 Conclusion

In summary, the risk factors associated with EE were the altitude of residence and sex in demographic variables, for the blood variables were HGB, HCT, and MCV. Residing at HA was more relevant when developing EE, being a woman, despite the results in previous studies, was shown to have a higher prevalence compared to being a man. Although age was not significant, it was found that the largest number of patients with EE were adults. High levels of HGB and HCT showed great relevance in the development of this disease.

HA diseases are a public health problem to which authorities have not given enough attention. Even though several cities with large populations live in HA and had diseases such as: CMS, acute mountain sickness, EE, high altitude pulmonary edema among others, affect the well-being and health of people and are fatal in some cases. The patient´s profile for having a higher risk of developing EE is: a woman between 25-65 years of age living with HA, (Highlanders), with high levels of HGB and HCT. For people prone to EE, it is advisable to closely monitor the results of their tests, especially blood tests, other signs such as: sleep apnea, cyanosis, headaches, paresthesia. Due to the close relationship between EE and CMS, it is recommended that patients undergo preventive studies in heart and lungs looking for abnormalities or malfunction caused by high viscosity in the blood.

4.2 Recommendations

Finally, the following research paths are proposed:

1. Because EE is a problem in the production of RBC in the blood, the recommendation is to carry out more in-depth studies in the investigation of alterations in erythropoietin and erythrogenesis.

2. Due to the unique characteristics of the Ecuadorian population, without forgetting its close genetic relationship with the population of the same region. It is necessary to conduct a study with genetic markers such as SENP-1 and HIF-1.

3. This study can serve as a basis for the development of future studies on HA diseases for the Ecuadorian population and eventually can elaborate protocols and treatments in the country's health system.

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Appendices

.1 Appendix 1

Appendix A: Two-variable clustered bar-chart of demographic variables

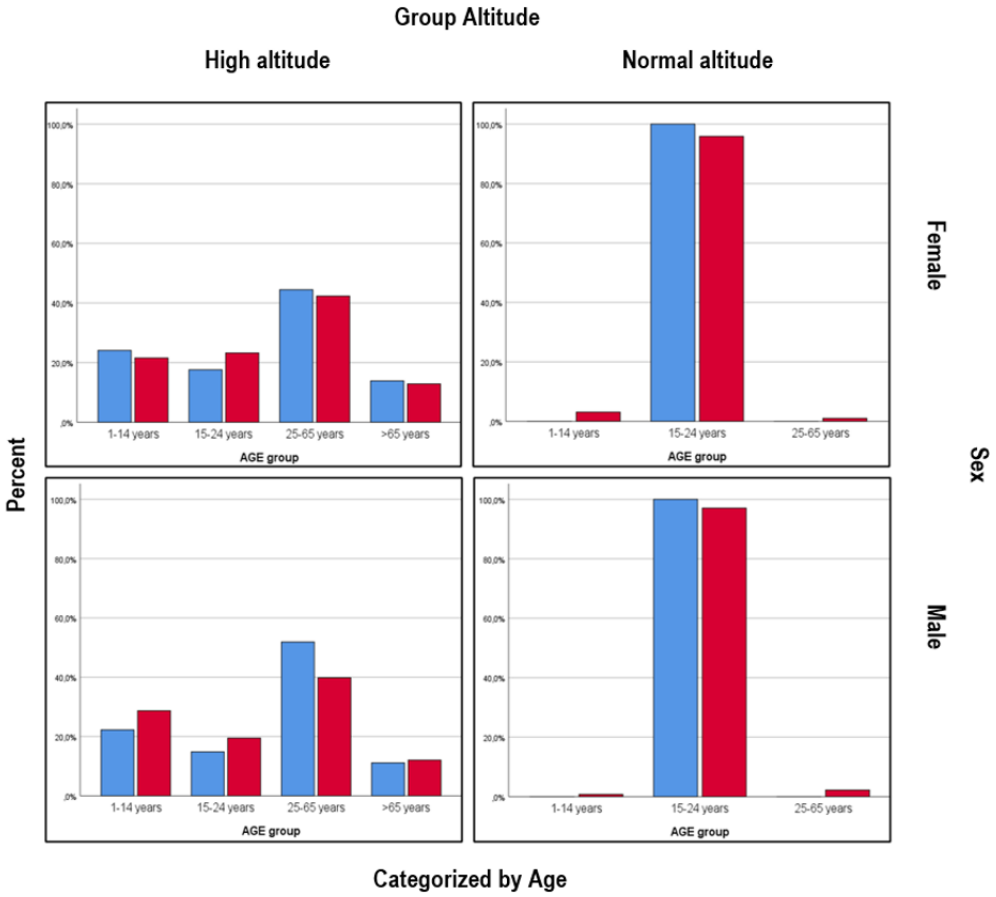

Figure 1: Bar-chart of two variables (Group altitude vs Sex), in distribution for EE diagnosis (EE in blue; No EE in red) across age segments. The group age of 25 - 65 years gets the higher prevalence of EE, for both sex the tendency has a normal distribution.

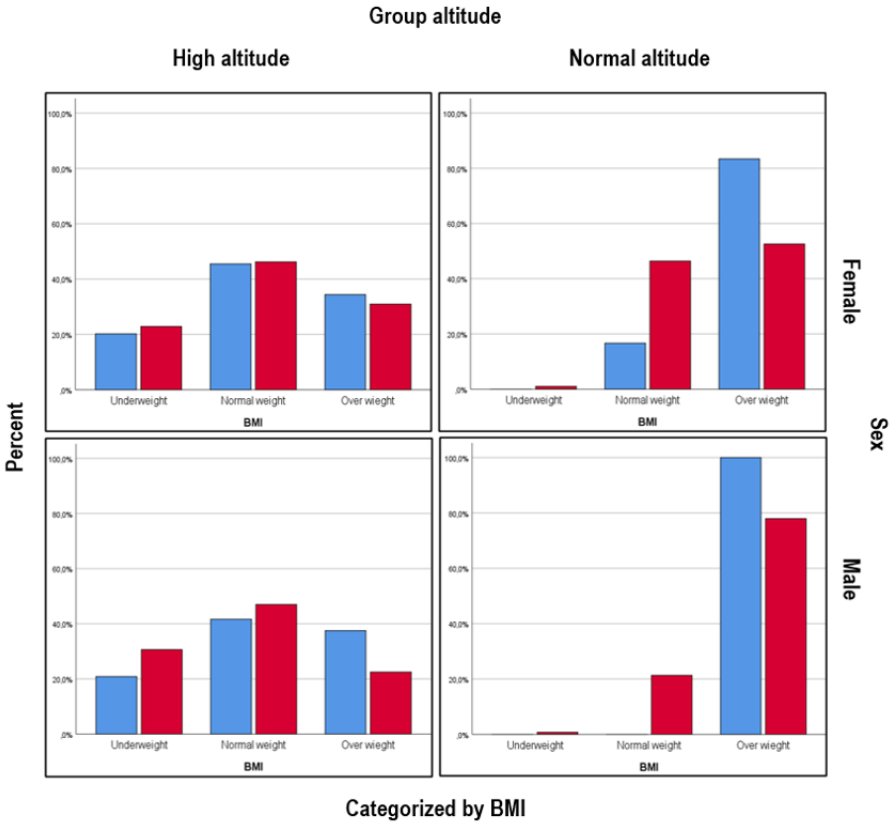

Figure 2: Bar-chart of two variables (Group altitude vs Sex), in distribution for EE diagnosis (EE in blue; No EE in red) across BMI segments. For both sex, prevalence as weight increase with age for NA, in the other side, for HA the tendency has a normal distribution. For HA there is no a relation between increasing of weight and risk of EE.

.2 Appendix 2

Appendix B: Two-variable clustered bar-chart of blood variables

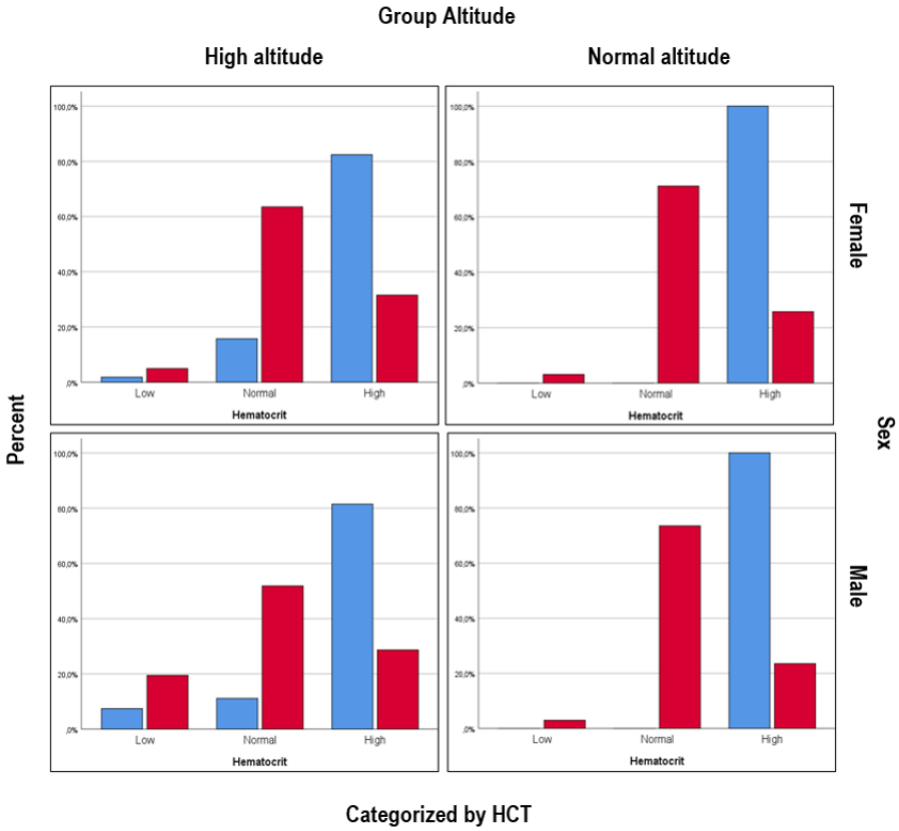

Figure 3: Bar-chart of two variables (Group altitude vs Sex), in distribution for EE diagnosis (EE in blue; No EE in red) across HCT segments. For both sex and group altitude the risk of having increase with HCT (high) percentage.

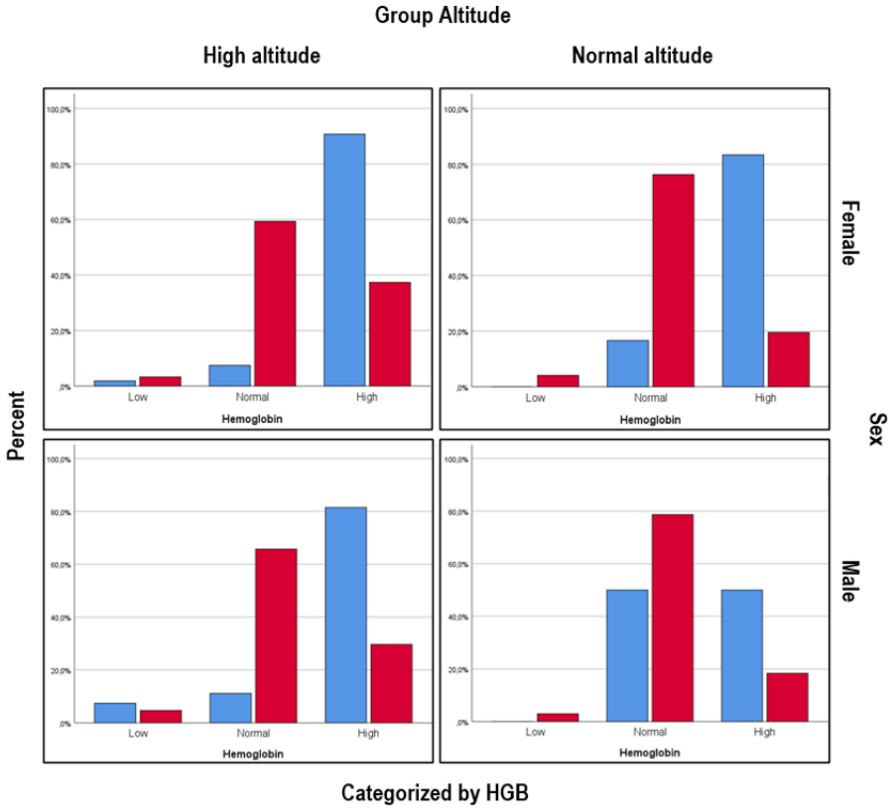

Figure 4: Bar-chart of two variables (Group altitude vs Sex), in distribution for EE diagnosis (EE in blue; No EE in red) across HGB segments. For group altitude the risk of EE increase with HGB (high). In sex group the tendency in women increase in relation EE – HGB (high) for HA and NA. In men the number maintained similar in NA despite the HGB and increase in HA.

.3 Appendix 3

Appendix c: Two-variable clustered bar-chart of health variables

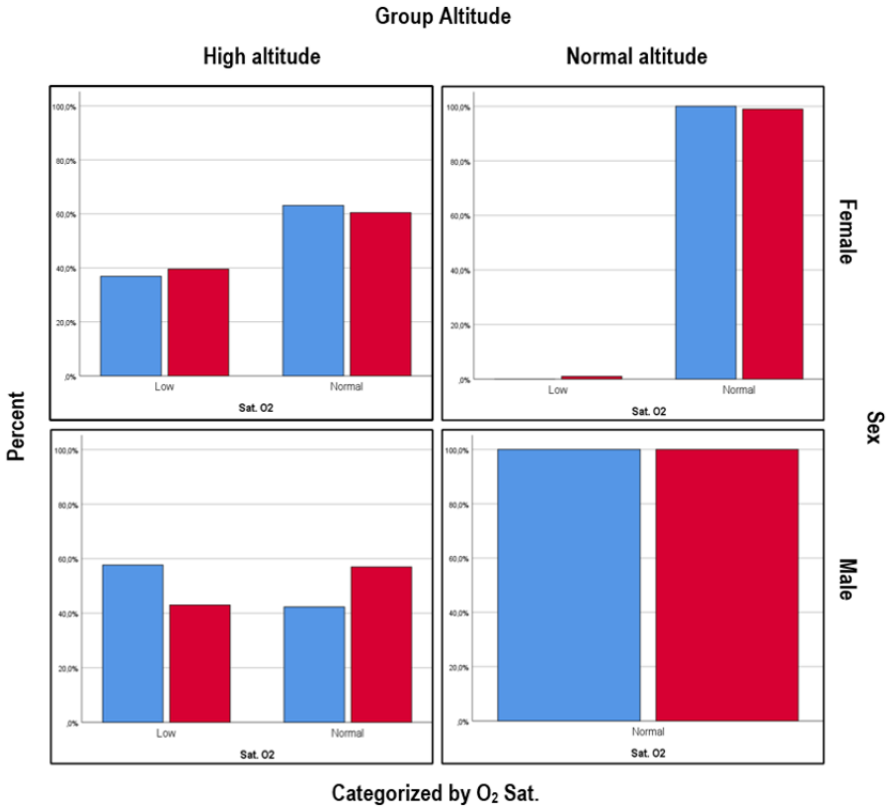

Figure 5: Bar-chart of two variables (Group altitude vs Sex), in distribution for EE diagnosis (EE in blue; No EE in red) across $SatO_2$ segments. Difference between group altitude are very clear, NA has almost all cases studied in the normal saturation, HA group show similar percentages for EE risk. Women group shows more cases of EE patients with normal saturation, in other side, men group shows more cases in low saturation.

.4 Appendix 4

.4.1 Appendix d: Logistic regression model for women´s vital and blood variables

Variable	B	S.E.	Wald	Df.	Sig.	Exp(B)	95% C.I. for Exp(B)
Constant	-10.042	7.528	1.780	1	0.182	0.000	
HCT	-2.138	0.428	24.940	1	<0.001	0.118	0.051 - 0.273
HGB	2.650	0.618	18.367	1	<0.001	14.418	4.212 - 47.525
MCV	0.829	0.183	20.482	1	<0.001	2.291	1.600 - 3.281
Creatinine	-3.212	1.659	3.747	1	0.053	0.040	0.002 - .1041

B, Regression coefficient; S.E., Standard error; Beta, Standard coefficient; CI, confidence interval; LR of EE with significant variables: Hematocrit (HCT) (%); Hemoglobin (HGB) (g/dL) Medium Corpuscular Volume (MCV) (fL); Creatinine (mg/dL).

Table 1: Logistic regression model of women vital and blood variables where only blood variables appears in the model due to significance.

.4.2 Appendix e: Logistic regression model for men´s vital and blood variables

Variable	B	S.E.	Wald	Df.	Sig.	Exp(B)	95% C.I. for Exp(B)
Constant	-12.025	5.334	5.083	1	0.024	0.000	
MCV	0.164	0.061	7.100	1	0.008	1.178	1.044 - 1.329

B, Regression coefficient; S.E., Standard error; Beta, Standard coefficient; CI, confidence interval; LR of EE with significant variables: Medium Corpuscular Volume (MCV) (fL).

Table 2: Logistic regression model of men vital and blood variables where only blood variables appears in the model due to significance.