Sleep and Breathing (2025) 29:181
https://doi.org/10.1007/s11325-025-03330-2

SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

Impact of obstructive sleep apnea on hematocrit levels and erythrocytosis – a clinical study

Patrícia Guerra[1] · Daniel Alfaiate[1,2] · Nuno Pinto[3,4] · Telmo Pereira[5] · Alexandre Pereira[2]

Received: 10 January 2025 / Revised: 26 March 2025 / Accepted: 11 April 2025 / Published online: 9 May 2025

Abstract

Objective Assess differences between hematocrit levels in a population with and without obstructive sleep apnea (OSA) and determine if these differences correlate with disease severity and/or with levels of hypoxemia.

Material and methods Data was collected from patients who underwent level I polysomnography (PSG) in the sleep laboratory at Hospital Rainha Santa Isabel, Torres Novas, Portugal, between January 2018 and December 2022. The patients' medical data was analyzed and sociodemographic (gender, body mass index (BMI) and age), polysomnographic (Apnea and Hypopnea Index (AHI), mean SpO2, minimum SpO2, Oxygen Desaturation Index (ODI), T90 and T85) and laboratory data (hematocrit (HCT), hemoglobin (HGB) and erythrocyte count) were collected. Statistical analysis included one-way ANOVA with Tukey's HSD for pairwise comparisons, Pearson's correlation for associations between polysomnographic and hematological parameters, and multivariate regression to identify independent factors.

Results HCT levels were found to be higher in the moderate OSA group, particularly compared to the no OSA group ($42.34 \pm 4.09\%$ vs $40.28 \pm 2.75\%$), with significant differences between groups ($p = 0.032$). Although HCT levels were shown to be higher in the OSA group, the mean values remained within normal range, so no patient manifested erythrocytosis.

Conclusion Our results suggest that moderate OSA is associated with increased HCT levels but does not seem to cause secondary erythrocytosis. Future research should further evaluate the hypoxic burden of OSA, as increased HCT may raise the risk of cardiovascular complications.

Keywords Obstructive sleep apnea · Erythrocytosis · Hematocrit and hypoxemia

Introduction

Obstructive Sleep Apnea (OSA) involves repeated partial (hypopnea) or complete (apnea) obstruction of the upper airway during sleep, causing transient airflow restriction [1]. These periodic events lead to sympathetic stimulation, intermittent hypoxemia, hypercapnia, hypoxia-reoxygenation phenomenon, endothelial dysfunction, oxidative stress, increased insulin resistance and sleep fragmentation [2, 3].

It's estimated that 936 million adults aged 30–69 years have mild to severe OSA globally [4]. In Portugal, research has shown a low prevalence of OSA (0.89%) in the population aged 25 years and older, which may indicate underdiagnosis of this condition [5].

Hypoxemia strongly stimulates erythropoietin (EPO) production and release, triggering erythropoiesis, which increases erythrocyte production, hemoglobin, hematocrit, and circulating red blood cells. EPO regulates red blood cell mass, while sustained hypoxia activates the transcription

All authors have seen and approved the current manuscript.

✉ Patrícia Guerra
ticha_guerra@hotmail.com

1 Present Address: Médio Tejo Local Health Unit, Rua António Gonçalves Curado nº30, Vila Nova Barquinha, 2260 - 390 Torres Novas, Portugal

2 Polytechnic University of Castelo Branco, Castelo Branco, Portugal

3 Faculty of Health Sciences, University of Beira Interior, Covilhã, Portugal

4 CICS-Health Sciences Research Center, University of Beira Interior, Covilhã, Portugal

5 Polytechnic Institute of Coimbra, Coimbra, Portugal

factor HIF- 1, inducing genes that enhance EPO expression [6–8]. This overstimulation can lead to erythrocytosis (polycythemia), which may be primary, due to a myeloproliferative disorder, or secondary, as a response to hypoxemia [9, 10]. It is known that two hours of continuous or four hours of intermittent hypoxemia increase erythropoietin by 50% [11]. The molecular response to intermittent hypoxemia remains unclear. Repeated hypoxemia in OSA, followed by reoxygenation, likely induces cellular stress due to mitochondrial dysfunction, triggering factors that promote erythropoietin production [12].

The link between OSA and erythrocytosis remains debated. Studies suggest a significant association between HCT and erythropoietin levels in OSA patients. Meta-analyses by Zhang et al. and Wu et al. confirmed elevated erythropoietin (EPO) and HCT levels in OSA, particularly in severe cases [13, 14]. Winnicki et al. further showed that increased EPO levels in severe OSA returned to baseline after 4–5 h of effective Continuous Positive Airway Pressure (CPAP) treatment [15]. In Portugal there are very few studies carried out on this subject. Feliciano et al. reported a significant association between hematological parameters and OSA severity. They also found significant decreases in Hb and HCT after six months of therapy with positive airway pressure (PAP), particularly in mild and severe OSA cases [16].

Nevertheless, other studies have found no significant relationship between OSA and erythrocytosis. Choi et al. reported no association between OSA and polycythemia [17]. Solmaz et al. found no significant differences in HCT and HGB levels between OSA and non-OSA patients [18]. Similarly, Nguyen et al. concluded that OSA severity does not correlate with increased HCT levels and is unlikely to cause erythrocytosis [10].

Given the inconsistent findings in the literature and the unclear role of hypoxemia severity versus OSA severity in hematological changes, this study aims to evaluate HCT levels in patients with and without OSA and investigate their correlation with both disease severity and hypoxemia.

Methods

Study design

This was a retrospective, observational study in which data was collected from Rainha Santa Isabel Hospital's sleep laboratory, Torres Novas, Portugal. Patients who underwent level I polysomnography (PSG) between January 2018 and December 2022 were included for analysis.

Data collection

Patients'medical records were analyzed and biographical data (gender, body mass index (BMI) and age), polysomnographic data data (Apnea and Hypopnea Index (AHI), mean SaO2, minimum SaO2, Oxygen Desaturation Index (ODI), T90, T85) and laboratory data (hematocrit, hemoglobin and erythrocyte count) were collected. Patients under the age of 18, with chronic obstructive pulmonary disease (COPD) and/or asthma, CPAP treatment or ear, nose and throat (ENT) surgery, hematological diseases, diabetes, iron supplementation, testosterone supplementation, kidney or liver disease, cancer, anemia, leukemia, chronic alcoholism, smoking, neuromuscular disease, acute infections, pregnancy or polycythemia vera were excluded from the study.

Polysomnography protocol

The level I PSG included monitoring the electroencephalogram, electrooculogram, electromyogram, electrocardiogram, oronasal flow, snoring, thoraco-abdominal movements, arterial oxygen saturation, body position and video recording. The poly-somnography and analysis software used included Embla N7000® and Alice 6® for signal acquisition, as well as Remlogic® and Sleepware G3®. PSG monitoring and subsequent analysis of polysomnographic data were based on the guidelines of the American Academy of Sleep Society (AASM) V 2.5 and performed by highly experienced professionals[17]. Respiratory events were classified as apneas (episodes of oronasal flow cessation of more than 90%, for at least 10 s) and hypopneas (episodes of oronasal flow cessation of more than 30%, for at least 10 s and accompanied by a drop in arterial saturation of 3% or more or in the presence of as-sociated micro-awakenings). The AHI was calculated taking into account the number of apneas and hypopneas per hour, with an AHI of less than 4.9/h reflecting the absence of OSA, an AHI of between 5/h and 14.9/h reflecting mild OSA (if associated with symptoms), an AHI of between 15/h and 29.9/h reflecting moderate OSA and an AHI of 30/h or more reflecting severe OSA [18].

Laboratory testing

Laboratory tests considered valid were those carried out up to 3 months before or up to 3 months after the date of the PSG and prior to any OSA treatment. Erythrocytosis was defined as HGB levels greater than 17.6 g/dL in women and 17.8 g/dL in men and/or HCT levels greater than 52% in women and greater than 55% in men [19]. HCT, HGB and erythrocyte count were measured using automated

hematology ana-lyzer (XN- 1000 series) performed at the clinical laboratory of the Hospital Rainha Santa Isabel, Torres Novas, Portugal.

Ethical considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Centro Hospitalar do Médio Tejo ethics committee number 154421) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Statistical analysis

Patients with complete medical reports, containing all the relevant information required for the study, were included for analysis, and respective data was compiled in a database in SPSS, version 25.

Descriptive statistics were provided for all demographic, clinical and laboratory variables by calculating absolute and relative frequencies (categorical variables) and mean value, standard deviation (SD) or 95% confidence interval (continuous variables).

One-way Analysis of Variance (ANOVA) was used to evaluate characteristics among OSA severity groups, followed by Tukey's Honest Significant Difference (HSD) test to identify specific differences between pairs of groups. Pearson's correlation coefficient was employed to assess relationships between polysomnographic variables (AHI, ODI, SpO2, T90, T85) and hematological parameters (HCT, HGB, erythrocyte count). To identify independent factors associated with HCT, HGB, and erythrocyte count, multivariate linear regression models were constructed using the backward method. Variables considered in these models included age, gender, BMI, AHI, ODI, mean and minimum SpO2, T90, and T85. Statistical significance was defined with p-values less than 0.05 and p-values between 0.05 and 0.10 were considered marginally significant.

Results

A total of 200 patients were included in this retrospective study. The general characteristics of all patients are depicted in Table 1.

The sample was divided in four groups defined by OSA severity, and the characteristics of all patients are summarized in Table 2.

When analyzing the data, we realized that the patients with moderate OSA were the oldest, with significant differences between groups ($p < 0.001$). The no OSA group had the largest number of females (82%) and the severe OSA group had the highest BMI. Relatively to hematological parameters, we found the highest value of HCT in the moderate OSA group, with significant differences between groups ($p = 0.032$). There were no significant differences between groups ($p = 0.189$) concerning to hemoglobin values. The number of erythrocytes between groups had a marginally significant statistical difference ($p = 0.095$).

Regarding Table 3, we verified that there was a weak positive correlation, showing that as the AHI, the ODI and the T90 increases, there is a slight increase in HCT levels. On the other hand, we found a weak negative correlation between the mean SpO2 and HCT, showing that as the mean SpO2 increases there's a slight decrease in HCT levels.

No correlation was found between HGB and the polysomnographic variables. Relatively to the number of erythrocytes, in Table 4 we saw a weak positive correlation with the ODI, showing that as the ODI increases, there is a slight increase in number of erythrocytes. However, mean SpO2 and the number of erythrocytes had a weak negative correlation ($r = -0.188$) showing that as the mean SpO2 increases there's a slight decrease in the number of erythrocytes (Table 4). We verified a weak negative correlation between age and HGB ($r = -0.172$) and with the number of erythrocytes ($r = -0.190$), with a significance level of 0.015 and 0.007 respectively. Revealing that as age increases there

Table 1 General sample characterization

		n (%)	
Gender	Female	106 (53%)	-
	Male	94 (47%)	-
		Mean ± SD	Range
Age (years)		56.89 ± 13.98	18–88
BMI (Kg/m^2)		29.60 ± 4.98	18.10–46.90
AHI (events/h)		20.45 ± 19.33	0.1–102.2
ODI (events/h)		17.32 ± 18.09	0.1–101.10
Mean SpO2 (%)		94.02 ± 2.06	88–98
Minimum SpO2 (%)		84.16 ± 6.59	60–96
T90 (%)		5.72 ± 12.39	0–66.8
T85 (%)		0.96 ± 2.99	0–26.70
Hematocrit (%)		41.43 ± 3.79	31.20–51.70
Hemoglobin (g/Dl)		13.96 ± 1.44	9.7–18
Erythrocytes (10^12/L)		4.69 ± 0.43	3.43–5.80

The data are presented as mean ± SD. Categorical variables are presented as numbers and percentages

SD standard deviation, *%* percentage, *BMI* body mass index, *AHI* apnea hypopnea index, *ODI* oxygen desaturation index, *SpO2* peripheral arterial oxygen saturation, *T90%* of time with SpO2 < 90%, *T85%* of time with SpO2 < 85%

Table 2 - Demographic characterization, Polysomnographic data and Hematological parameters of all patients divided by OSA severity

		No OSA ($n=50$)	Mild OSA ($n=50$)	Moderate OSA ($n=50$)	Severe OSA ($n=50$)	p-*value Anova*
Age (years)		48.46 ± 13.60	55.14 ± 13.11	62 ± 10.87	61.96 ± 13.78	< 0.001[a,b,c,d,e]
BMI (Kg/m^2)		28.01 ± 5.16	28.51 ± 4.65	30.40 ± 4.49	31.46 ± 4.94	0.001[c,e]
Gender	Female	41(82%)	27(54%)	19(38%)	19(38%)	< 0.001
	Male	9(18%)	23(46%)	31(62%)	31(62%)	
AHI (events/h)		2.21 ± 1.48	9.53 ± 2.77	22.13 ± 4.41	47.92 ± 15.96	< 0.001[a–f]
ODI (events/h)		1.84 ± 1.95	7.37 ± 3.79	18.02 ± 6.13	42.02 ± 17.47	< 0.001[a–f]
Mean SpO2 (%)		95.51 ± 1.34	94.62 ± 1.60	93.44 ± 1.96	92.50 ± 1.93	< 0.001[b,c,d,ef]
Minimum SpO2 (%)		89.20 ± 4.62	85.58 ± 4.82	82.64 ± 5.57	79.22 ± 6.77	< 0.001[a–f]
T90 (%)		0.47 ± 1.37	2.03 ± 6.71	7.53 ± 13.64	12.86 ± 17.11	< 0.001[b,c,e]
T85 (%)		0.12 ± 0.59	0.13 ± 0.43	0.64 ± 1.19	2.94 ± 5.38	< 0.001[c,e,f]
Hematocrit (%)		40.28 ± 2.75	41.13 ± 3.48	42.34 ± 4.09	41.95 ± 4.41	0.032[b]
Hemoglobin (g/Dl)		13.61 ± 1.02	13.99 ± 1.36	14.23 ± 1.48	14.01 ± 1.77	0.189
Erythrocytes (10^12/L)		4.58 ± 0.38	4.66 ± 0.37	4.78 ± 0.44	4.75 ± 0.51	0.095

The data are presented as mean ± SD. Categorical variables are presented as numbers and percentages

SD standard deviation, *N* number of individuals, % percentage, *BMI* body mass index, *AHI* apnea hypopnea index, *ODI* oxygen desaturation index, *SpO2* peripheral arterial oxygen saturation, *T90%* of time with SpO2 < 90%, *T85%* of time with SpO2 < 85%

[a] *p*-value < 0.05 between No OSA and Mild OSA

[b] *p*-value < 0.05 between No OSA and Moderate OSA

[c] *p*-value < 0.05 between No OSA and Severe OSA

[d] *p*-value < 0.05 between Mild OSA and Moderate OSA

[e] *p*-value < 0.05 between Mild OSA and Severe OSA

[f] *p*-value < 0.05 between Moderate OSA and Severe OSA

Table 3 Univariate Pearson's correlations between hematocrit and polysomnographic variables

Variables	R	P
Age (years)	**− 0.130**	**0.067**
AHI (events/h)	0.152	0.031
ODI (events/h)	0.151	0.033
Mean SpO2 (%)	− 0.208	0.003
Minimum SpO2 (%)	− 0.080	0.262
T90 (%)	0.181	0.011
T85 (%)	0.043	0.550

AHI apnea hypopnea index, *ODI* oxygen desaturation index, *SpO2* peripheral arterial oxygen saturation, *T90%* of time with SpO2 < 90%, *T85%* of time with SpO2 < 85%

Table 4 Univariate Pearson's correlations between the number of erythrocytes and polysomnographic variables

Variables	R	P
Age (years)	**− 0.190**	**0.007**
AHI (events/h)	0.122	0.084
ODI (events/h)	0.139	0.049
Mean SpO2 (%)	− 0.188	0.008
Minimum SpO2 (%)	− 0.129	0.068
T90 (%)	0.134	0.059
T85 (%)	0.072	0.313

AHI apnea hypopnea index, *ODI* oxygen desaturation index, *SpO2* peripheral arterial oxygen saturation, *T90%* of time with SpO2 < 90%, *T85%* of time with SpO2 < 85%

is a slight decrease in the HGB levels and in the number of erythrocytes.

Linear multivariate regression models, using the backward method, were constructed to evaluate the association between OSA, hypoxemia, and other factors with HCT (Table 5). Lower nocturnal SpO2 and T85 were associated with higher hematocrit after controlling for age and gender. In contrast, SpO2 min.; AHI; ODI; T90 and BMI were excluded and were not associated with HCT in the assessed models. Analyzing the SpO2, for each unit increase in average SpO2, HCT decreases by 0.568 units, with other variables constant and for each unit increase in T85, HCT decreases by 0.201 units, holding other variables steady. This regression analysis demonstrates that age and average SpO2 have a significant negative relationship with HCT, while male gender has a significant positive relationship. The variable T85 also shows a significant negative impact on HCT, but with a smaller effect size.

In Table 6 we have the multivariable regression with HGB. Lower nocturnal SpO2 and T85 were associated with

higher HGB after controlling for age and gender. In contrast, SpO2 min.; AHI; ODI; T90 and BMI were excluded and were not associated with HGB in the assessed models. Analyzing the SpO2, for each unit increase in average SpO2, HGB decreases by 0.161 units, with other variables constant and for each unit increase in T85, HGB decreases by 0.078 units, holding other variables steady. This regression analysis demonstrates that age and average SpO2 have a significant negative relationship with hemoglobin, while male gender has a significant positive relationship. The variable T85 also shows a significant negative impact on HGB, but with a smaller effect size.

The multivariable regression with the number of erythrocytes is written in Table 7. Lower nocturnal SpO2 was associated with higher number of erythrocytes after controlling for age and gender. In contrast, SpO2 min.; AHI; ODI; T90, T85 and BMI were excluded and were not associated with the number of erythrocytes in the assessed models. Analyzing the SpO2, for each unit increase in average SpO2, the number of erythrocytes decreases by 0.050 units, with other variables constant. This regression analysis demonstrates that age and average SpO2 have a significant negative relationship with the number of erythrocytes, while male gender has a significant positive relationship.

Discussion

OSA is considered a potential cause of secondary erythrocytosis, but evidence showing an association between OSA and erythrocytosis or elevated HCT values remains inconsistent. Increased HCT levels in OSA are thought to arise in response to intermittent episodes of hypoxemia, which stimulate circulating erythropoiesis-inducing factors. In this study, we observed that the highest value of HCT was found in the moderate OSA group, with significant differences between groups, particularly between the no OSA and moderate OSA groups. Despite this, HCT values remained within the normal range, and no cases of erythrocytosis were identified. This finding is consistent with several studies (Cummins et al., Li et al., Rha et al.) reporting higher HCT

Table 5 Multivariable regression with dependent variable hematocrit

Variable	B	*SE*	95,0% CI *LL*	95,0% CI *UL*	B	*p*
(Constant)	93.995	14.190	66.009	121.981		< 0.001
Gender (m)	3.590	0.455	2.693	4.486	0.474	< 0.001
Age	− 0.075	0.018	− 0.110	− 0.040	− 0.276	< 0.001
Mean SpO2 (%)	− 0.568	0.144	− 0.852	− 0.284	− 0.309	< 0.001
T85 (%)	− 0.201	0.089	− 0.378	− 0.025	− 0.159	0.026

SpO2 peripheral arterial oxygen saturation, *T85%* of time with SpO2 < 85%

Table 6 Multivariable regression with dependent variable hemoglobin

Variable	B	*SE*	95,0% CI *LL*	95,0% CI *UL*	B	*P*
(Constant)	28.699	5.317	18.213	39.185		< 0.001
Gender (m)	1.481	0.170	1.145	1.816	0.514	< 0.001
Age	− 0.030	0.007	− 0.043	− 0.017	− 0.289	< 0.001
Mean SpO2 (%)	− 0.161	0.054	− 0.268	− 0.055	− 0.231	0.003
T85 (%)	− 0.078	0.034	− 0.144	− 0.012	− 0.163	0.021

SpO2 peripheral arterial oxygen saturation, *T85%* of time with SpO2 < 85%

Table 7 Multivariable regression with dependent variable number of erythrocytes

Variable	B	*SE*	95,0% CI *LL*	95,0% CI *UL*	b	*P*
(Constant)	9.518	1.440	6.678	12.359		< 0.001
Gender (m)	0.326	0.055	0.218	0.433	0.376	< 0.001
Age	− 0.010	0.002	− 0.014	− 0.006	− 0.316	< 0.001
Mean SpO2 (%)	− 0.050	0.015	− 0.079	− 0.022	− 0.240	0.001

SpO2 peripheral arterial oxygen saturation

values in OSA patients but a low prevalence of erythrocytosis, ranging from 0.3% to 8% [7, 13, 14, 18–20].

Several studies support our findings. Cummins et al. reported significant differences in HCT and HGB across OSA severity levels, with higher HCT in severe OSA compared to no OSA [19]. Li et al. found that RBC count, HGB, and HCT increased with OSA severity [20], while Rha et al., in a meta-analysis, reported significantly higher HCT values in OSA patients compared to controls [7]. Notably, the highest HCT levels were typically observed in moderate or severe OSA groups, likely due to greater episodes of hypoxemia stimulating erythropoiesis. In contrast, milder OSA does not provide sufficient hypoxemic stimulus to significantly raise HCT levels. Studies by Choi et al. and Fan et al. also found higher HCT in severe OSA patients compared to non-apneic or mild-to-moderate OSA groups [3, 17].

Our study did not identify significant differences in HGB values between OSA groups ($p = 0.189$). This aligns with previous research suggesting that hypoxemia in OSA increases HCT and RBC count but does not sufficiently stimulate an increase in HGB levels. A possible explanation lies in the multifactorial nature of anemia, which becomes more prevalent with age [21]. Given the mean age of our cohort was 57 years, age-related anemia ("anemia of aging") may have influenced our results.

We found that patients with higher AHI, ODI, and T90 had higher HCT levels. HCT was also raised in patients with lower mean SpO2. These findings are consistent with Cummins et al., who reported positive correlations between AHI, HGB, HCT, and RBC count, and negative correlations between average SpO2 and these hematological parameters [19]. Similarly, Choi et al. showed that AHI, mean SpO2, and T90 were highly correlated with HCT [17]. However, Li et al. identified average SpO2, rather than AHI, as an independent predictor of polycythemia [20]. In contrast, our results did not show a correlation between HGB and the polysomnographic variables.

Incorporating age adjustment, we used linear multivariable regression models, which revealed that age and average SpO2 had significant negative associations with all hematological parameters evaluated (HCT, RBC, and HGB). T85 had a negative impact on HCT and HGB but with a smaller effect size. These findings highlight the stronger influence of sustained hypoxemia (as indicated by T85) compared to intermittent hypoxemia (e.g., AHI and ODI) on hematological variables. It should also be noted that AHI was not significantly associated with any hematological parameter in our adjusted models.

Although we observed increased HCT levels in OSA groups, the average values remained within normal ranges, and no patients exhibited erythrocytosis. This low prevalence aligns with studies suggesting that OSA-induced erythrocytosis depends on the intensity, frequency, and duration of intermittent hypoxia [7, 10, 17–20]. Ryan et al. showed that intermittent hypoxia and reoxygenation selectively activate inflammatory pathways rather than hypoxia-dependent transcriptional pathways required for erythropoiesis [22]. Sustained hypoxemia, however, does activate these pathways, as shown in studies like Yuan et al. and Nagel et al. [23, 24]. Our sample, with an average SpO2 of 94%, and 93% in the severe OSA group, likely did not experience sufficient hypoxemic burden to stimulate EPO production. Furthermore, Wojan et al. demonstrated that short protocols of intermittent hypoxia (e.g., five cycles) are insufficient to trigger a rise in EPO levels, requiring longer or more severe desaturation episodes [25].

Another explanation for the absence of erythrocytosis is the well-documented role of inflammation in suppressing erythropoiesis. OSA patients often exhibit elevated inflammatory markers, which induce hepcidin production, restricting iron availability and suppressing erythropoiesis [26]. Song et al. reported modest erythropoietic stimulation in OSA, which normalized after CPAP therapy, with no accompanying increase in HGB [27]. These findings reinforce the suppressive role of inflammation in erythropoiesis in OSA patients.

This study provides valuable insights into the relationship between OSA, hypoxemia, and hematological parameters by analyzing a well-defined sample of 200 patients diagnosed through full overnight polysomnography, the gold standard for OSA assessment. The use of strict inclusion and exclusion criteria reduces confounding factors. Also, this study evaluates key hypoxemia indicators (mean SpO2, T85, and T90), helping to clarify whether intermittent hypoxemia is a sufficient stimulus for sustained erythropoiesis. The inclusion of multivariable regression analysis further enhances the robustness of the results by identifying independent predictors of hematocrit, hemoglobin, and erythrocyte count while adjusting for confounders such as age, gender, and BMI. Otherwise, some limitations may be considered. The study is retrospective, implying that data was collected from existing records. This can lead to selection bias and limitations in the quality and consistency of available data (failure to record in the clinical diary). Uncontrolled confounding factors, including individual variations in lifestyle, diet, and other undiagnosed health problems, may influence results. The use of SpO2 averages and minimum values may not fully capture the complexity of intermittent hypoxemia associated with OSA, potentially underestimating its influence on hematological variables.

In conclusion, while our study found that OSA, particularly in moderate cases, is associated with increased HCT, these values remain within normal ranges, and OSA does not typically cause secondary erythrocytosis. Our findings suggest that clinicians may consider evaluating OSA in patients with higher or borderline HCT levels, particularly

when other causes of elevated HCT have been ruled out. Identifying underlying sleep-disordered breathing in these patients could contribute to better management of potential cardiovascular risks associated with both OSA and increased HCT.

Future research should focus on quantifying OSA-specific hypoxic burden, which considers the frequency, depth, and duration of respiratory event-related desaturation, and correlating it with hematological variables to elucidate these mechanisms further.

Abbreviations *AHI*: Apnea and Hypopnea Index; *ANOVA*: One-way Analysis of Variance; *BMI*: Body mass index; *COPD*: Chronic obstructive pulmonary disease; *CPAP*: Continuous positive airway pressure; *ENT*: Ear, nose and throat surgery; *EPO*: Erythropoietin; *HB*: Hypoxic burden; *HCT*: Hematocrit; *HGB*: Hemoglobin; *HSD*: Tukey's Honest Significant Difference; *IHR*: Intermittent hypoxia and reoxygenation; *ODI*: Oxygen desaturation index; *OSA*: Obstructive sleep apnea; *PSG*: Polysomnography; *RBC*: Red Blood Cell; *SD*: Standard deviation; *SH*: Sustained hypoxia

Acknowledgements The researchers would like to thank very deeply Rainha Santa Isabel Hospital sleep technologists for performing and scoring the sleep studies that took part in this article. We also want to thank Rainha Santa Isabel Hospital for ethical approval.

Authors contributions Patrícia Guerra: Manuscript preparation; data collection; review of manuscript.

Daniel Alfaiate: Data collection; literature search; review of manuscript.

Nuno Pinto: Analysis of data; review of manuscript.

Telmo Pereira: Study design; review of manuscript.

Alexandre Pereira: Study design; analysis of data; review of manuscript.

Funding No funding was received for this research.

This manuscript is not a clinical trial.

Data availability This manuscript has no associated data.

Declarations

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers'bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

References

1. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP (2010) Pathophysiology of sleep apnea. Physiol Rev 90(1):47–112. https://doi.org/10.1152/physrev.00043.2008
2. Eckert DJ, Malhotra A (2008) Pathophysiology of adult obstructive sleep apnea. Proc Am Thorac Soc 5(2):144–153. https://doi.org/10.1513/pats.200707-114MG
3. Fan Z, Lu X, Long H, Li T, Zhang Y (2019) The association of hemocyte profile and obstructive sleep apnea. J Clin Lab Anal 33(2) https://doi.org/10.1002/jcla.22680
4. Benjafield AV et al (2019) Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med 7(8):687–698. https://doi.org/10.1016/S2213-2600(19)30198-5
5. Rodrigues AP, Pinto P, Nunes B, Bárbara C (2017) Obstructive sleep apnea: epidemiology and Portuguese patients profile. Revista Portuguesa de Pneumologia (English Edition) 23(2):57–61. https://doi.org/10.1016/j.rppnen.2017.01.002
6. Ciftci TU, Kokturk O, Demirtas S, Gülbahar Ö, Bukan N (2011) Consequences of hypoxia-reoxygenation phenomena in patients with obstructive sleep apnea syndrome. Ann Saudi Med 31(1):14–18. https://doi.org/10.4103/0256-4947.75772
7. Rha M, Jeong Y, Kim J, Kim C, Yoon J, Cho H (2022) Is obstructive sleep apnea associated with erythrocytosis? A systematic review and meta-analysis. Laryngoscope Investig Otolaryngol 7(2):627–635. https://doi.org/10.1002/lio2.751
8. Haider MZ, Anwer F (2004) Secondary Polycythemia. StatPearls Publishing
9. Jelkmann W (2011) Regulation of erythropoietin production. J Physiol 589(6):1251–1258. https://doi.org/10.1113/jphysiol.2010.195057
10. Nguyen CD, Holty J-EC (2017) Does untreated obstructive sleep apnea cause secondary erythrocytosis? Respir Med 130:27–34. https://doi.org/10.1016/j.rmed.2017.07.003
11. Knaupp W, Khilnani S, Sherwood J, Scharf S, Steinberg H (1992) Erythropoietin response to acute normobaric hypoxia in humans. J Appl Physiol 73(3):837–840. https://doi.org/10.1152/jappl.1992.73.3.837
12. Li C, Jackson RM (2002) Reactive species mechanisms of cellular hypoxia-reoxygenation injury. Am J Physiol Cell Physiol 282(2):C227–C241. https://doi.org/10.1152/ajpcell.00112.2001
13. Zhang X-B, Zeng Y-M, Zeng H-Q, Zhang H-P, Wang H-L (2017) Erythropoietin levels in patients with sleep apnea: a meta-analysis. Eur Arch Otorhinolaryngol 274(6):2505–2512. https://doi.org/10.1007/s00405-017-4483-1
14. Wu M, Zhou L, Zhu D, Lai T, Chen Z, Shen H (2018) Hematological indices as simple, inexpensive and practical severity markers of obstructive sleep apnea syndrome: a meta-analysis. J Thorac Dis 10(12):6509–6521. https://doi.org/10.21037/jtd.2018.10.105
15. Winnicki M et al (2004) Erythropoietin and obstructive sleep apnea. Am J Hypertens 17(9):783–786. https://doi.org/10.1016/j.amjhyper.2004.04.011
16. Feliciano A et al (2017) Hematological evaluation in males with obstructive sleep apnea before and after positive airway pressure. Revista Portuguesa de Pneumologia (English Edition) 23(2):71–78. https://doi.org/10.1016/j.rppnen.2016.12.001
17. Choi JB et al (2006) Does obstructive sleep apnea increase hematocrit? Sleep Breathing 10(3):155–160. https://doi.org/10.1007/s11325-006-0064-z
18. Solmaz S, Duksal F, Ganidağlı S (2015) Is obstructive sleep apnoea syndrome really one of the causes of secondary polycythaemia? Hematology 20(2):108–111. https://doi.org/10.1179/1607845414Y.0000000170
19. Cummins E et al (2022) Can the complete blood count be used as a reliable screening tool for obstructive sleep apnea? Sleep Breathing 26(2):613–620. https://doi.org/10.1007/s11325-021-02383-3
20. Li N, Li HP, Wang P, Yan YR, Li SQ, Li QY (2019) Nocturnal mean oxygen saturation is associated with secondary polycythemia in young adults with obstructive sleep apnea, especially in men. Nat Sci Sleep 11:377–386. https://doi.org/10.2147/NSS.S226143
21. Maggio M et al (2015) The role of the multiple hormonal dysregulation in the onset of 'Anemia of Aging': Focus on Testosterone,

IGF-1, and Thyroid Hormones. Int J Endocrinol 2015:1–22. https://doi.org/10.1155/2015/292574
22. Ryan S, Taylor CT, McNicholas WT (2005) Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. Circulation 112(17):2660–2667. https://doi.org/10.1161/CIRCULATIONAHA.105.556746
23. Yuan G, Nanduri J, Bhasker CR, Semenza GL, Prabhakar NR (2005) Ca2+/Calmodulin kinase-dependent activation of hypoxia inducible factor 1 transcriptional activity in cells subjected to intermittent hypoxia. J Biol Chem 280(6):4321–4328. https://doi.org/10.1074/jbc.M407706200
24. Nagel MJ, Jarrard CP, Lalande S (2020) Effect of a single session of intermittent hypoxia on erythropoietin and oxygen-carrying capacity. Int J Environ Res Public Health 17(19):7257. https://doi.org/10.3390/ijerph17197257
25. Wojan F, Stray-Gundersen S, Nagel MJ, Lalande S (2021) Short exposure to intermittent hypoxia increases erythropoietin levels in healthy individuals. J Appl Physiol 130(6):1955–1960. https://doi.org/10.1152/japplphysiol.00941.2020
26. Song J et al (2018) Pathophysiology of Obstructive Sleep Apnea (OSA) - blood cells' reactive oxygen species and inflammation prevent polycythemia. Blood 132(Supplement 1):1028–1028. https://doi.org/10.1182/blood-2018-99-116658
27. Song J et al (2023) Increased blood reactive oxygen species and hepcidin in obstructive sleep apnea precludes expected erythrocytosis. Am J Hematol 98(8):1265–1276. https://doi.org/10.1002/ajh.26992