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ORIGINAL ARTICLE

The Relationship Between Disease Severity and CRP/Prealbumin Ratio in Individuals Diagnosed with Obstructive Sleep Apnea Syndrome

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ÖZET

Giriş: Obstrüktif Uyku Apne Sendromu (OUAS) yaygın bir uyku hastalığıdır. Yüksek CRP düzeylerinin şiddetli OUAS durumunda yükseldiği saptanmıştır. CRP/Prealbümin (CRP/PAB) oranı ölüm riski ve kötü sonuçlar açısından yeni bir indekstir. CRP/PAB oranı ile OUAS şiddetini kıyaslanması amaçlanmıştır. **Materyal ve Metod:** Kesitsel bu çalışmada OUAS tanılı 99 hasta (ortalama yaş: 54.34±10.3) AHI kriterine dayalı olarak OUAS şiddeti durumuna göre hafif (n: 28 [28.3%]), orta (n:23 [23.2%]) ve şiddetli (n:48 [48.5%]) 3 sınıfa ayrılmıştır. **Bulgular:** Ortalama CRP/PAB oranı gruplar arasında benzer saptandı (hafif: 0.03± 0.03; orta: 0.02 ± 0.02, şiddetli: 0.03 ± 0.04, p=0.759). Demografik ve bazal özellikler gruplar arasında benzer saptandı. CRP/PAB oranı ile yaş, BMI, şeker, nötrofil, platelet ve monocit değerleri ile pozitif yönde ve Hgb, MCH, MCHC değerleri ile negatif yönde zayıf korelasyon saptandı (p<0.05). Tüm grupların değerlendirilmesinde regresyon analizi CRP/PAB oranı ile uyku süresi, apne ve hipopne indeksleri arasında zayıf ama anlamlı pozitif ilişki saptandı. Ayrıca uyku etkinliği ile zayıf ama anlamlı negatif ilişki saptandı (tümü için p<0.05). **Sonuç:** Her ne kadar CRP/PAB oranı ile OUAS şiddeti arasında anlamlı bağlantı saptanmasa da CRP/PAB oranı ile BMI, monosit sayısı arasında pozitif ama zayıf bir korelasyon ve apne ve hipopne indeksleri ile düşük düzeyde ilişki saptandı bu CRP/PAB oranının OUAS'daki inflamasyonun anlamlı bir belirteci olabileceğini ifade eder.
Anahtar kelimeler: CRP, CRP/Prealbumin, İnflamasyon, OUAS, Prealbumin

ABSTRACT

Introduction: Obstructive sleep apnea syndrome (OSAS) is a common sleep disorder. Higher CRP levels has been found to rise in severe OSAS. The CRP/Prealbumin (CRP/PAB) ratio is a new index of risk of death and poor outcomes. We aimed to compare the CRP/PAB ratio with the severity of OSAS. **Material and Methods:** In this cross-sectional study, 99 patients with OSAS (mean age=54.34±10.3) were classified into three categories based on severity of OSAS into mild (n: 28 [28.3%]), moderate (n:23 [23.2%]), and severe (n:48 [48.5%]) based on AHI criteria. **Results:** The mean CRP/PAB ratios were similar among the groups (mild: 0.03± 0.03; moderate=0.02 ± 0.02; severe=0.03 ± 0.04; p=0.759). The demographic and baseline features were similar between the groups. The CRP/PAB ratio had a weak positive correlation with the age, BMI, glucose, neutrophil, platelet and monocyte values and a weak negative correlation with the Hgb, MCH and MCHC values (p<0.05). Considering all groups in the regression analysis, it was showed that low levels of positive and significant relationship between the CRP/PAB and sleep duration and the apnea and hypopnea indices. It was also showed low-level of negative and significant relationship with sleep efficiency (p<0.05 for all). **Conclusion:** Although, there was no significant between the CRP/PAB ratio and the severity of OSAS, it was showed that low-level positive correlation between CRP/PAB ratio and BMI, monocyte count and low-level relationship with the apnea and hypopnea indices and it may indirectly mean that CRP/PAB ratio may be a significant marker of inflammation in OSAS.
Keywords: CRP, CRP/Prealbumin, Inflammation, OSAS, Prealbumin

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INTRODUCTION

Background and Rationale

Obstructive sleep apnea syndrome (OSAS) is a common sleep disorder which is characterized by intermittent hypoxia, sleep fragmentation and increased systemic inflammation. (1) Increased serum levels of C-reactive protein reflect systemic inflammation and its role in the severity of OSAS is still debatable. Some authors reported the higher levels of CRP in the severe OSAS however some did fail to show this connection. (2) Serum prealbumin (PAB) is a negative acute-phase protein which is increased in various situations such as severe renal failure; corticosteroid use and obesity. A recent meta-analysis showed the higher PAB levels is associated with lower of all-cause mortality in hemodialysis (HD) patients. Cardiovascular mortality has also been shown to be inversely associated with PAB levels. (3-4) The high-sensitive (hs)-CRP/PAB ratio has been introduced as a new index of inflammation which has been proposed to better reflect the patient's inflammatory status than either hs-CRP or PAB levels. In a recent study which was included 659 patients with acute coronary syndrome (ACS), the ratios of total major adverse cardiac events (MACE), re-infarction and heart failure were higher in the highest hs-CRP/PAB ratio group as compared to the lower group ($p<0.001$, respectively). (5) Another prospective study was enrolled 240 patients in medical intensive care unit showed that hospital mortality was significantly increased in patients with CRP/PAB ratio> 0.24. (6) In contrast to these studies, the predictive value of the CRP/PAB ratio in OSAS patients has not been investigated before. So, we aimed to determine the importance of CRP/PAB ratio as it related to OSAS severity and with the other variables of sleep apnea indices.

MATERIAL AND METHODS

Study Design and Setting

This study is a cross-sectional study. Patients with diagnosis OSAS were included in this study. Patients were separated into 3 groups according to level of the apnea-hypopnea index (AHI). The design of study was drawn as comparing of results among these groups so mild OSAS disease group or group -1 was accepted as control, so we didn't add any other control group from healthy individuals. The study was approved by the Ethics Committee of Kırşehir Ahi Evran University, School of Medicine with the Decision No:2020-20/10 with date of February/11/2020. It was performed in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all the patients. Physical examinations and demographic data were collected from all patients.

Participants and Polysomnography (PSG)

Patient selection: Patients with the symptoms of relating to OSAS like severe snoring, daytime sleepiness, sleeping interrupts

with were examined in Clinic of Sleep Disorder in our facility. After carefully done routine physical examinations including blood pressure, and laboratory examinations all individuals were subjected to overnight PSG testing for diagnosis of OSAS. Standard full overnight PSG (Alice® 4, Philips Respironics, Murrysville, PA, USA) attended by an experienced technician were performed to all patients. Only patients with new diagnosis of OSAS were included in this study. We excluded the patients with a long term-diagnosis of diabetes mellitus (DM), central type sleep apnea, neurological diseases such as the history of cerebrovascular disease and recent head trauma, along with those who had cardiovascular diseases, including heart failure, acute coronary syndrome, history of idiopathic pulmonary hypertension, rheumatologic disease or autoimmune diseases, chronic obstructive pulmonary disease (COPD), currently smoking and on PAP therapy for any of other chest diseases. All of sleep records were manually scored, according to standardized criteria by a single observer who was blind to the study. Apnea was defined as a 90% of reduction in airflow for at least 10 seconds. Hypopnea was defined as a 30% reduction in airflow for at least 10 sec in combination with oxyhemoglobin desaturation of at least 3% or an arousal registered by the electroencephalogram. AHI was calculated as the average number of apneas and hypopneas per hour of the PSG-recorded sleep time. OSAS was defined as AHI ≥5/h accompanied by related symptoms. OSAS was graded as mild (AHI: 5-14.9/hour), moderate (AHI: 15-29.9/hour) and severe (AHI ≥30/hour). (7)

Biomarker Detection

Venous blood samples were collected from the patients following fasting for at least 8 hours. On the obtained serum, routine biochemical parameters including triglycerides (TG), total cholesterol (T-Chol), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), plasma glucose (Glu), hemogram, urea, creatinine as well as CRP and prealbumin were studied. All parameters including prealbumin and CRP were studied using a Cobas 501 (Roche Diagnostics, Germany) autoanalyzer. Although hs-CRP was more sensitive than CRP but many of the facility still use standard CRP and standard CRP is simple to be studied in rural area also we still use standard CRP in our facility so as researcher authors we decided to examinate standard CRP/PAB ratio in OSAS patients.

Reproducibility

To calculate the intra-observer and inter-observer coefficients of variation for measurements of PSG recordings and CRP/PAB ratio results, 20 randomly selected patients in the severe group were assessed by repeating the measurements under the same baseline conditions. To test the interobserver variability, we performed the measurements offline from video recordings by a second observer. The intra-observer and inter-observer coefficients of variation for the PSG and CRP/PAB measurements were found to be <5% and insignificant.

Statistical Analysis

The continuous variables are presented as mean ± standard deviation (SD) or median (inter-quartile range). The categorical variables are presented as frequency (percentage). The data were checked for normality using Kolmogorov-Smirnov test. ANOVA and Kruskal-Wallis tests were used to examine the differences between the continuous variables when appropriate. Tukey's HSD test was used as the post-Hoc analysis. Pearson chi-squared test or Spearman's test was used to determine the potential correlation between the CRP/PAB ratio and other variables. Multiple, stepwise, linear regression analysis was also performed to identify which variables best explained the variance in the CRP/PAB ratio. The statistical analyses were performed using SPSS for Windows (version 18.0, SPSS Inc., Chicago, IL, USA). All analyses were two-tailed, and a p-value of <0.05 was considered statistically significant.

RESULTS

Baseline and demographic characteristics (Tables-1,2,3,4): Ninety-nine consecutive patients with OSAS (69 male patients [69.7%] and 30 female patients [30.3%], mean age=54.34±10.3) were included in study. 28 (28.3%) patients were included in the mild OSAS group (group-1), 23 (23.2%) patients were included in the moderate OSAS group (group-2), and 48 (48.5%) were included in the severe group (group-3). All demographic and baseline characteristics of study patients were demonstrated in Tables-1-3. The mean CRP/PAB ratio was found in group-1 as 0.03± 0.03, in group-2 as 0.02 ± 0.02 and in group-3 as 0.03 ± 0.04, and there was no significant difference among the groups (p=0.759). The groups did not show a significant difference in terms of their mean PAB levels and many of the laboratory results (p>0.05). There was significant difference among the groups for mean monocyte counts (p=0.033). Based on the PSG results, the groups differed significantly in terms of their mean AHI scores and many of the results of PGS reports (p<0.001, in table 2-3).

Table 1: Baseline characteristics of all study patients

Variables	Groups (Group-1, 2, 3)	n = 99 (total)	Mean & Std. Deviation	Total Mean & std. Deviation (minimum and maximum) / Count (% within total AHI)	p
Patients number (% within AHI)	1	28(28.3%)		99 (100%)	
	2	23(23.2%)			
	3	48(48.5%)			
Male	1	20 (71.4%)			

Count	2	17 (73.9%)		69	0.844
(% within AHI group)	3	32 (66.7%)		(69.7%)	¥
Female	1	8 (28.6%)			
Count	2	6 (26.1%)		30 (30.3%)	0.844
(% within AHI group)	3	16 (53.3%)			¥
DM	1	4 (14.3%)			
Count	2	8 (34.8%)		26	0.211¥
(% within AHI group)	3	14 (29.2%)		(26.3%)	
Age	1	28	53.68 ± 9.42		
Mean & Std.	2	23	54.61 ± 10.10	54.34±10.3	0.924
Deviation	3	48	54.60 ± 11.16	(32-80)	*
BMI	1	27	32.63 ± 6.8		
Mean & Std.	2	23	34.32 ± 6.62	33.56 ± 5.9 (23-55.4)	0.456
Deviation	3	48	33.73 ± 5.14		**
Prealbumin(mg/dL)	1	28	23.39 ± 4.33		
Mean & Std.	2	23	22.17 ± 4.56	22.80 ± 4.4 (6-33)	0.410
Deviation	3	48	22.77 ± 4.52		**
CRP-PREALBUMIN	1	28	0.03± 0.03		
RATIO Mean & Std.	2	23	0.02 ± 0.02	0.027 ± 0.035 (0.002-0.247)	0.759
Deviation	3	48	0.03 ± 0.04		**
A-H Ratio Index	1	28	7.87 ± 4.02		
Mean & Std.	2	23	22.31 ± 4.01	32.71 ± 24.1	<0.001
Deviation	3	48	52.19 ± 19.83	(0.5-103.3)	**
HAB1C	1	27	6.07 ± 0.88		
Mean & Std.	2	21	6.62 ± 1.21	6.3 ± 1.02 (5.1-10.7)	0.098
Deviation	3	46	6.40 ± 1.00		**
Glucose (mg/dL)	1	28	97.39 ± 18.69		
Mean & Std.	2	23	116.78 ± 34.01	111.59 ± 41.07 (67-319)	0.106
Deviation	3	48	117.51 ± 51.25		**
CRP	1	28	0.56 ± 0.57		
(mg/dL)	2	23	0.46 ± 0.44	0.58 ± 0.7 (0.03-4.4)	0.707
	3	48	0.66 ± 0.86		**
T-CHOL	1	28	196.64 ± 44.52	186.8 ± 44.1	
(mg/dL)	2	22	173.18 ± 50.44	(95-307)	0.175
	3	44	187.41 ± 39.63		*
LDL	1	28	117.25 ± 41.51		
(mg/dL)	2	22	98.77 ± 43.38	110.1 ± 39.6 (36-222)	0.256
	3	42	111.33 ± 35.92		*
HDL	1	28	44.29 ± 10.61		
(mg/dL)	2	22	39.77 ± 9.53	46.5 ± 30.9 (20-70)	0.198
	3	44	40.16 ± 10.73		*
Triglycerides	1	28	194.89 ± 99.48	195.1 ± 118.3 (50-643)	0.734
(mg/dL)	2	21	185.05 ± 128.36		**

	3	40	200.73 ± 127.33	

* One-Way Analysis of Variance; ** Kruskal-Wallis One-Way Analysis of Variance on Ranks; ¥ Chi-Squared Tests. AHI: Apnea-Hypopnea Index, DM: Diabetes Mellitus, BMI: Body Mass Index.

Table 2: Baseline characteristics to be continued

Variables	Groups	n = 99 (total)	Mean & Std. Deviation	Total Mean & std. Deviation (minimum and maximum)	p
Apnea Number	1	28	9.50 ± 12.26	55.9 ± 89.7 (0-437)	<0.001 **
	2	23	19.70 ± 14.99		
	3	48	100.48 ± 112.44		
Hypopnea Number	1	28	23.96 ± 19.98	118.36 ± 91.9 (0-492)	<0.001 **
	2	23	102.22 ± 28.61		
	3	48	181.17 ± 86.87		
Apnea+ Hypopnea Total Number (A+H Total Number)	1	28	33.46 ± 20.59	174.3 ± 144.6 (1-628)	<0.001 **
	2	23	121.91 ± 31.54		
	3	48	281.65 ± 134.12		
Central Apnea Number	1	28	2.96 ± 4.14	10.09 ± 18.7 (0-122)	<0.001 **
	2	23	6.26 ± 6.96		
	3	48	16.08 ± 25.01		
Obst. Apnea Number	1	28	5.00 ± 8.99	36.6 ± 65.4 (0-363)	<0.001 **
	2	23	9.52 ± 8.12		
	3	48	68.06 ± 82.96		
Mixed Central and Obst Apnea Number	1	28	1.86 ± 3.03	9.3 ±19.4 (0-149)	<0.001 **
	2	23	3.9 ± 4.17		
	3	48	16.33 ± 26.05		
NONREM-ratio	1	28	94.59 ± 7.63	93.7 ± 11.4 (0-100)	0.321 **
	2	22	92.41 ± 6.70		
	3	48	93.82 ± 14.62		
Stage-1-ratio (%)	1	28	21.51 ± 14.49	15.6 ± 12.8 (0.3-52.9)	0.021 **
	2	23	14.32 ± 11.18		
	3	48	12.97 ± 11.67		
Sleep Duration (minutes)	1	28	243.50 ± 70.72	300.4 ± 79.9 (109.5-471.4)	<0.001 *
	2	23	321.90 ± 80.41		
	3	48	323.45 ± 68.66		
Stage-2-ratio (%)	1	28	52.79 ± 13.34	54.09 ± 14.9 (12.5-89.9)	0.448*
	2	23	51.67 ± 16.86		
	3	48	56.03 ± 14.89		
Stage-3-ratio (%)	1	28	20.31 ± 16.15	25.0 ± 19.4 (0-84.8)	0.434 **
	2	23	26.77 ± 21.20		

	3	48	26.93 ± 20.35		
REM-ratio (%)	1	28	5.40 ± 7.61	5.1 ± 6.2 (0-23.4)	0.292 **
	2	23	7.25 ± 6.70		
	3	48	4.06 ± 4.77		
NONREM-AHI	1	28	7.34 ± 3.89	37.4 ± 69.2 (0.4-680.5)	<0.001 **
	2	23	22.02 ± 6.00		
	3	48	49.74 ± 19.62		
REM-AHI	1	28	2.90 ± 6.07	21.1 ± 27.4 (0-120)	<0.001 **
	2	23	23.76 ± 23.92		
	3	48	30.63 ± 31.36		
Apnea-index	1	28	2.09 ± 2.39	10.2 ± 14.8 (0-62.3)	<0.001 **
	2	23	3.87 ± 2.98		
	3	48	18.01 ± 18.17		
Hypopnea-index	1	28	5.78 ± 4.19	22.4 ± 15.5 (0-73.3)	<0.001 **
	2	23	19.49 ± 4.87		
	3	48	33.65 ± 13.67		
Left-Side-AHI	1	28	8.29 ± 16.50	28.9 ± 28.5 (0-112.5)	<0.001 **
	2	22	15.35 ± 10.22		
	3	48	47.25 ± 28.29		
Sleep Efficiency (%)	1	28	60.02 ± 18.66	80.04 ± 75.4 (25.7-80.4)	<0.001 *
	2	23	78.25 ± 13.08		
	3	48	77.52 ± 13.84		

* One-Way Analysis of Variance; ** Kruskal-Wallis One-Way Analysis of Variance on Ranks. AHI: Apnea-Hypopnea Index.

Table 3: Baseline characteristics and Post-Hoc analysis

Variables	**Groups**	**n = 99 (total)**	**Mean & Std. Deviation**	**Total Mean & std. Deviation (minimum and maximum)**	**p**	**Variables**	**Groups 1 vs. 2** p^{μ}	**Groups 1 vs. 3** p^{μ}	**Groups 2 vs. 3** p^{μ}
						Post-Hoc tests-multiple comparisons: Tukey's HSD Test.			
Supine-AHI	1	28	15.88 ± 19.69	41.9 ± 28.5 (0-123)	<0.001 **	Monocyte	0.035	Ns.	Ns.
	2	23	38.56 ± 21.28			Sleep duration	0.001	0.001	Ns.
	3	48	58.76 ± 23.81			Sleep efficiency	0.001	0.001	Ns.
Right-Side-AHI	1	28	2.89 ± 4.15	24.9 ± 27.1 (0-99)	<0.001 **	Apnea number	Ns.	0.001	0.001

	2	23	17.00 ± 12.66			Hypopnea number	0.001	0.001	0.003
	3	48	41.62 ± 29.02			A-H total number	0.001	0.001	0.001
Left-Side-Sleep time (minutes)	1	28	79.94 ± 60.47	97.6 ± 67.1 (0-263)	0.131 *	Central apnea number	0.001	Ns.	Ns.
	2	21	118.86 ± 78.69			Obst. apnea number	Ns.	0.001	0.027
	3	46	98.83 ± 63.76			Stage-1	Ns.	0.018	Ns.
Left-Side Deep-Sleep time (minutes)	1	28	17.75 ± 27.11	25.1 ± 31.0 (0-164)	0.148 **	NON-REM-AHI	0.002	0.001	0.001
	2	21	33.77 ± 40.42			REM-AHI	0.010	0.001	Ns.
	3	46	25.81 ± 27.96			Apnea-Index	Ns.	0.001	0.001
Supine-Sleep time (minutes)	1	28	111.44 ± 84.08	115.7 ± 90.2 (0-375)	0.253 **	Hypopnea-Index	0.001	0.001	0.002
	2	23	89.72 ± 74.55			Left-Side-AHI	Ns.	0.001	0.001
	3	48	130.66 ± 98.70			Supine-AHI	0.003	0.001	0.021
Supine-Deep-Sleep time (minutes)	1	28	27.51 ± 45.99	27.9 ± 42.3 (0-205)	0.559 **	Right-Side-AHI	0.005	0.001	0.008
	2	23	20.94 ± 37.97						
	3	48	31.64 ± 42.51						

* One-Way Analysis of Variance; ** Kruskal-Wallis One-Way Analysis of Variance on Ranks; µ Post-Hoc tests-Multiple comparisons: Tukey's HSD Test; Ns.: Not Significant. AHI: Apnea-Hypopnea Index.

However, some of the results of PSG reports were not found to be different among groups ($p<0.05$ in table 2-3). Post-Hoc analysis (Table-3): There was a significant difference between group-1, group-2 and group-3 in regard of their some of the PSG results ($p<0.05$ for all). The post-hoc analysis were shown separately in table-4. Correlation analysis (Table-4): In the assessments of all groups, it was determined that the CRP/PAB ratio was weakly and positively correlated with the age, BMI, Glu, neutrophil, platelet and monocyte values, while it was weakly and negatively correlated with the Hgb, MCH and MCHC values ($p<0.05$). In group-1 analysis: the CRP/PAB ratio had a moderate, positive and significant correlation with BMI and a moderate, negative and

significant correlation with MCV and MCH ($p<0.05$). In group-2 analysis: CRP/PAB ratio was moderately, positively and significantly correlated with age and monocyte counts ($p<0.05$). In group-3 analysis: CRP/PAB ratio was a moderate, positive and significant correlated with BMI and weak, negative and significant relationship with Hgb and supine sleep duration time ($p<0.05$). Regression analysis on all groups: Based on the analysis on all groups, the CRP/PAB had a weak, positive and significant relationship to sleep duration, apnea index and hypopnea index. It also had a weak, negative and significant relationship to sleep efficiency ($p<0.05$ for all). Regression analysis for separate groups (Table-5): In group-1, CRP/PAB ratio had a weak, positive and significant relationship with the apnea and hypopnea indices and a weak, negative and significant relationship with the number of apneas and Non-REM-Stage-1 ratio ($p<0.05$ for all). In group-2, CRP/PAB ratio had a weak, positive and significant relationship with the number of central apneas, number of obstructive apneas, number of mixed apneas, hypopnea index and supine-AHI ratio, as well as a weak, negative and significant relationship with sleep duration, apnea index and left-side deep sleep duration ($p<0.05$ for all). In group-3, CRP/PAB ratio had a weak, positive and significant relationship with the apnea and hypopnea indices.

Tablo 4. Correlation analysis on all groups and separately for each group

Spearman's Correlation Variables	CRP/PREALBUMIN All groups		CRP-PREALBUMIN Group-1		CRP-PREALBUMIN Group-2		CRP-PREALBUMIN Group-3	
	n=99		n=28		n=23		n=48	
	r	p*	r	p*	r	p*	r	p*
AHI Ratio Index	0.03	Ns.		Ns.		Ns.		Ns.
Age	0.199	0.048		Ns.	0.633	0.001		Ns.
BMI	0.419	<0.0001	0.479	0.011		Ns.	0.404	0.005
HBA1C	0.202	0.051		Ns.		Ns.		Ns.
Glu	0.217	0.032		Ns.		Ns.		Ns.
Hgb	-0.272	0.007		Ns.		Ns.	-0.363	0.012
Neutrophil	0.214	0.034		Ns.		Ns.		Ns.
Platelet	0.210	0.038		Ns.		Ns.		Ns.
Monocyte	0.235	0.020		Ns.	0.499	0.015		Ns.
MCH	-0.224	0.026	-0.572	0.001		Ns.		Ns.
MCV	-0.089	Ns.	-0.408	0.031		Ns.		Ns.
MCHC	-0.285	0.004		Ns.		Ns.		Ns.
Sleep Duration	-0.036	Ns.		Ns.		Ns.		Ns.
Sleep Efficiency	-0.044	Ns.		Ns.		Ns.		Ns.
Apnea Number	0.054	Ns.		Ns.		Ns.		Ns.
Hypopnea Number	0.035	Ns.		Ns.		Ns.		Ns.

Apnea+ Hypopnea Total Number	0.015	Ns.	Ns.	Ns.	Ns.
Central Apnea Number	-0.100	Ns.	Ns.	Ns.	Ns.
Obst. Apnea Number	0.075	Ns.	Ns.	Ns.	Ns.
Mixed Apnea Number	0.050	Ns.	Ns.	Ns.	Ns.
NON-REM-Ratio	-0.032	Ns.	Ns.	Ns.	Ns.
Stage-1-Ratio	-0.029	Ns.	Ns.	Ns.	Ns.
Stage-2-Ratio	-0.100	Ns.	Ns.	Ns.	Ns.
Stage-3 Ratio	0.078	Ns.	Ns.	Ns.	Ns.
REM-Ratio	0.065	Ns.	Ns.	Ns.	Ns.
NON-REM-AHI	0.001	Ns.	Ns.	Ns.	Ns.
REM-AHİ	-0.069	Ns.	Ns.	Ns.	Ns.
Apnea Index	0.044	Ns.	Ns.	Ns.	Ns.
Hypopnea Index	0.032	Ns.	Ns.	Ns.	Ns.
Left-Side-AHI	0.097	Ns.	Ns.	Ns.	Ns.
Supine-AHI	-0.011	Ns.	Ns.	Ns.	Ns.
Right-Side-AHI	-0.027	Ns.	Ns.	Ns.	Ns.
Left-Side-Sleep time	0.061	Ns.	Ns.	Ns.	Ns.
Left-Side-Deep-Sleep time	0.148	Ns.	Ns.	Ns.	Ns.
Supine-Sleep time	-0.122	Ns.	Ns.	Ns.	-0.389	0.006
Supine-Deep-Sleep time	-0.078	Ns.	Ns.	Ns.	Ns.

* Spearman's Correlation Analysis, AHI: Apnea-Hypopnea Index, DM: Diabetes Mellitus, BMI: Body Mass Index, Hgb: Hemoglobin, RBC: Red Blood Cell, WBC: White Blood Cell, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW: red cell distribution width, Glu: Glucose.

Table 5: Results of separate regression analyses for groups 1, 2 and 3

Model	**Group- 1**	**Unstandardized Coefficients**		**Standardized Coefficients**	**t**	**Sig.**	**95,0% Confidence Interval for B**	
		B	**Std. Error**	**Beta**				
	(Constant)	0.014	0.023		0.620	0.541	-0.034	0.062
	Apnea Number	-0.012	0.005	-0.038	-2.284	0.032	-0.024	-0.001
	Stage-1-Ratio	-0.002	0.001	-0.007	-2.502	0.020	-0.003	0.000
	Apnea Index	1.060	0.028	0.631	38.354	0.000	1.003	1.117
13	**Hypopnea Index**	1.002	0.002	1.047	423.178	0.000	0.998	1.007
	Apnea Index	1.060	0.028	0.631	38.354	0.000	1.003	1.117
	Hypopnea Index	1.002	0.002	1.047	423.178	0.000	0.998	1.007
	Group- 2				**t**	**Sig.**	**95,0% CI for B**	

		B	Std. Error	Beta				
8	(Constant)	11.065	2.239		4.943	0.000	6.187	15.942
	Sleep Duration	-0.030	0.007	-0.532	-4.530	0.001	-0.045	-0.016
	Central Apnea Number	0.471	0.103	0.622	4.578	0.001	0.247	0.695
	Obst. Apnea Number	0.622	0.078	1.104	7.943	0.000	0.451	0.793
	Mixed . Apnea Number	1.071	0.081	1.051	13.266	0.000	0.895	1.247
	Apnea Index	-2.846	0.308	-1.987	-9.249	0.000	-3.516	-2.176
	Hypopnea Index	0.866	0.061	1.017	14.151	0.000	0.732	0.999
	Supine-AHI	0.070	0.014	0.372	4.841	0.000	0.038	0.101
	Left-Side-Deep-Sleep time	-0.021	0.008	-0.207	-2.619	0.022	-0.039	-0.004
	Group-3				**t**	**Sig.**	**95,0% CI for B**	
		B	**Std. Error**	**Beta**				
14	(Constant)	3.797	1.719		2.209	0.033	0.331	7.263
	Apnea Index	0.965	0.031	0.899	31.231	0.000	0.903	1.028
	Hypopnea Index	0.923	0.041	0.645	22.412	0.000	0.840	1.006

DISCUSSION

OSAS has been known to be related to development of endothelial dysfunctions (ED), and eventually, atherosclerotic and cardiovascular consequences. CRP is an inflammatory protein which has been used as a potential diagnostic tool and risk factor for atherosclerosis. It is believed that the mechanisms of OSAS-induced elevation in CRP include repeated hypoxic events, sleep deprivation and inflammatory processes. In a cross-sectional study, CRP levels were found to be significantly different only between the mild and severe OSAS groups (p=0.009) but not different between the other groups (p>0.05 for all). (2) Along with this in another recent meta-analysis showed higher levels of CRP in OSAS

to be positively influenced by the severity of OSAS. However, in another recent study, CRP levels were reported to be increased in OSAS patients with ongoing acute cardiovascular or ischemic stroke events ($p<0.05$). So, CRP could be a part of the pathophysiological pathway linking OSAS to stroke and CVD. (8-11) Interestingly, in contrast to these facts, several authors have failed to demonstrate a relationship between CRP levels and OSAS. (12) So, considering these reports, CRP levels in OSAS are still debatable, and we found that CRP levels were similar among all OSAS groups in our study.

Studies have reported the correlation between PAB levels and patient recovery and nutritional status. Serum PAB is associated with inflammation and known as a negative acute phase protein that is related to conditions such as stroke, heart failure. (13) In a retrospective cohort study, PAB was found to have a negative linear relationship with the risk of all-cause death in COVID-19 patients [odds ratio (OR), 20.09; 95% confidence interval (CI), 3.62-111.64; $p=0.0006$]. (14) In our study, no significant relationship was identified between severity of OSAS and PAB levels.

As a new index, the CRP/PAB ratio has been evaluated before as an inexpensive and useful marker in many diseases like acute kidney injury (AKI) and multiorgan dysfunctions. Xie et al. reported that the CRP/PAB ratio was independently associated with mortality in AKI patients, where CRP/PAB ratio levels higher indicated particularly higher mortality rates. In the same prospective cohort study (n=155 patients), CRP/PAB ratio was found to be significantly higher in non-survivors in comparison to survivors ($p<0.001$) and the CRP/PAB ratio remained a significant and independent predictor of mortality in multivariate analysis ($p=0.027$). (15) In another prospective study (n = 70), the CRP/PAB ratio was determined to have a correlation with a diagnosis of sepsis and multiorgan dysfunction. (16) So, the CRP/PAB ratio has been found to be a newly index of predictor of mortality and multiorgan dysfunction, however it has not been examined in OSAS patients previously. The CRP/PAB ratio was not discovered to be connected to the severity of OSAS or increased AHI in our study ($p=0.759$). But CRP/PAB ratio was positively linked to the apnea and hypopnea indices. On the other hand, there was a positive correlation between CRP/PAB ratio and monocyte count, which is an inflammatory marker, indirectly means that CRP/PAB ratio may be a significant marker of inflammation in OSAS.

Our study had several limiting factors. One of the limited factors, the fact that the cardiovascular risks of the patients, their relevant past diseases and other conditions like stroke or renal and that would affect the CRP/PAB ratio were not examined in our study may have influenced the results. Also, there was no data about PAP therapy on CRP/PAB ratio levels.

Our study investigated the CRP/PAB ratio in OSAS patients as a new risk index that has not been researched much in the literature, and thus, it is the first study that has worked on this particular topic. Perhaps, a novel risk index may be defined in OSAS patients by conducting

an in-depth analysis of this topic in the future with studies that have a broader scope.

CONCLUSION

Our study could not show a significant relationship between the CRP/PAB ratio and the severity of OSAS. However, the CRP/PAB ratio had a weak, positive and significant relationship to sleep duration, apnea index and hypopnea index.

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