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Hemostatic alterations in patients with obstructive sleep apnea: an observational study

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ABSTRACT

Background: Obstructive sleep apnoea (OSA) is characterized by repetitive partial or complete collapse of the upper airway during sleep, which results in disruptions of normal sleep architecture. It is associated with cardiopulmonary consequences like hypertension, myocardial infarction and stroke. Although the pathogenesis of this association remains unclear, an alteration in coagulability is suspected as a linkage. Hence, the present study aims at the reliability of Bleeding time, platelet count, PT, aPTT and INR to assess the effect on OSA patients' cardiovascular system.
Methods: This is an observational study done on 32 individuals diagnosed with OSA after level I polysomnography from time period of January 01, 2018 to December 31, 2018. The blood coagulation parameters studied for each individual were platelet count, bleeding time (BT), activated partial thromboplastin time (aPTT) and prothrombin time (PT/INR).
Results: Out of a total 32 subjects, 17 (53.13%) were male and 15 (46.87%) were female. There is a significant difference in mean prothrombin time ($p=0.022$). Kruskal-Wallis test showed a significant difference in the median of the PT/INR ($p=0.01$) and AHI ($p<0.001$) for different categories of OSA. Prothrombin time is the only factor which is affecting the OSA.
Conclusions: Patients with severe OSA may have elevated coagulability levels, particularly in the length of prothrombin time. The potential for anticoagulant and antiplatelet medications to reduce mortality in patients with OSA merits exploration, particularly for patients who are unwilling or unable to achieve full control of OSA with currently available treatment options.

Keywords: Obstructive sleep apnea, Coagulation profile, Prothrombin time

INTRODUCTION

The lay term for obstructive breathing during sleep, snoring, is one of the most prevalent of obnoxious human habits. It is almost exclusively found in humans, as opposed to the rest of the animal kingdom.

"Wild animals do not snore", wrote Immelmann, the German naturalist.[1] "They either sleep in the ventral position or on the side so that the lower jaw is always somehow sustained, thus preventing its falling back." But when humankind's primate ancestors developed the alternative of sleeping on their backs, they become snorers. However, bulldogs snore terribly, and they often require surgical resection of the soft palate and uvula to keep them from strangling while asleep.[2]

Obstructive sleep apnoea (OSA) is characterized by repetitive partial or complete collapse of the upper airway during sleep, which results in disruptions of normal sleep

architecture and usually associated with arterial desaturations.[3] It is the most common cause of daytime sleepiness due to fragmented sleep at night and affects about 24% of middle-aged men and 9% of women in the United States.[4] OSA is characterized by complete breath-holds (apnoeas) and partial breath-holds (hypopnoeas). Breathing ceases for more than 10 s during frequent episodes of obstruction of the upper airway (especially the pharynx) due to reduction in muscle tone. The apnoea causes brief arousals from sleep in order to re-establish upper airway tone. An individual with OSA typically begins to snore soon after falling asleep. The snoring gets progressively louder until it interrupted by an episode of apnoea, which is then followed by a loud snort and gasp, as the individual tries to breathe. OSA is not associated with a reduction in total sleep time, but individuals with OSA experience a much greater time in stage 1 NREM sleep (from an average of 10% of total sleep to 30–50%) and a marked reduction in slow-wave sleep (stages 3 and 4 NREM sleep). The pathophysiology of OSA includes both a reduction in neuromuscular tone at the onset of sleep and a change in the central respiratory drive.

If these respiratory events occur more than five times per hour of sleep and are associated with symptoms, most commonly witnessed snoring, sleep deprivation, excessive daytime fatigue, insomnia and pauses in breathing or choking during sleep, impaired alertness, loss of concentration or memory the term obstructive sleep apnoea/hypopnea syndrome (OSAHS) is applied.[5]

Apnea was defined as a decrease in airflow by 90% or more that lasts for at least 10 seconds and hypopnea was defined as a decrease in airflow by 30% or more associated with a reduction in oxygen saturation of 4% or more for at least 10 seconds. The apnea index was defined as the number of apnea episodes per hour of sleep, and AHI was defined as the number of apnea and hypopnea episodes per hour.

Obstructive sleep apnea is a common event, occurring to a significant degree (≥5 per hour of sleep) in 4-9% of the population.[6] Severe disease (>20 apneas/hour) is associated with excess mortality[7,8] and presents with complaints related to excessive day time sleepiness, disturbed sleep, and heavy snoring.

There is evidence that sleep apnea is associated with the development of a chronic illness with cardiopulmonary and neuropsychological symptoms and signs. There is a spectrum of disease. At the present time, indications for treatment are clear for those with the severe disease, with multiple apnoea, and accompanied by disturbing excessive sleepiness or signs of hypoxic stress. There is a larger population with lesser degrees of symptoms and apnoeic activity who may be at risk for disease progression or who may benefit from treatment in regard to automobile accidents, cognitive deficits, hypertension, and stroke. Cellular and organ system events result in what is termed mild, moderate, or severe disease and its potential complications.

Cardiopulmonary consequences of severe obstructive apneas include pulmonary hypertension, corpulmonale, and cardiorespiratory failure (hypoxemia and hypercapnia).[9] Epidemiologically, sleep apnea and snoring are both associated with hypertension, stroke and myocardial infarction.[10] Although the pathogenesis of this association remains unclear, an alteration in coagulability is suspected as a linkage. Hence, the present study is carried out to assess the association of coagulative profile with obstructive sleep apnea. This study aims at the reliability of Bleeding time, Clotting time, platelet count, PT, aPTT and INR to assess the effect on obstructive sleep apnea patients' cardiovascular system.

METHODS

This is an observational study done on 32 individuals diagnosed with obstructive sleep apnoea after level I polysomnography from time period of January 01, 2018 to December 31, 2018 who had attended the outpatient clinic of KLE's Dr. Prabhakar Kore Hospital, Belagavi. Patients who were already on CPAP therapy or LTOT were excluded from the study. Patient details along with thorough history and clinical examination was done. The blood coagulation analysis was performed in the hospital laboratory using standard methods. The parameters studied were platelet count, bleeding time (BT), activated partial thromboplastin time (aPTT) and prothrombin time (PT/INR). This study was approved by the institutional ethical committee. The patients provided written informed consent, no financial compensation was provided.

Statistical analysis

Data analysis was performed using R i386 3.5.1 and microsoft excel. The continuous variables were summarized in mean±SD form, and categorical variables represented in frequency tables. The comparisons were done using ANOVA for mean and Kruskal Wallis test for the median. Fisher exact test is used to study the association between categorical variables and ordinal logistic regression is used to study the different factors affecting the diagnosis of obstructive sleep apnoea (OSA). The p-value less than 0.05 is considered as statistically significant.

Platelet count was done with automated instruments to achieve reasonably accurate platelet estimates were based on the Wallace Coulter method of orifice impedance. Bleeding time calculated by Duke's method and activated partial thromboplastin time (aPTT) and prothrombin time (PT/INR) were calculated with automated machine.

RESULTS

Out of a total 32 subjects, 17 (53.13%) were male and 15 (46.87%) were female. The sex distribution is depicted in Figure 1. Considering the age-wise distribution of cases, more number of patients were found in the age group of 50-60 years (12) and patients from 60-70 years (6). There

were 4 patients each in the age group of 30-40 years, 40-50 years and 70- 80 years while patients below the 30 years group and above 80 years group was only 1 each. Mean age group was found to be 56.44±13.82 years. This age-wise distribution is depicted in Figure 2.

Among the total male subjects, majority 7 (41%) had severe OSA while among female subjects, 3 (20%) had a severe problem of OSA (Figure 3). Among the 32 subjects of age group 56.44±13.82 years, the majority (37%) were of the age group 50-60 years followed by 60-70 years and 70-80 years (Figure 4).

From the Fischer test, there was no significant association observed between age group and diagnosis of OSA (p=0.1957).

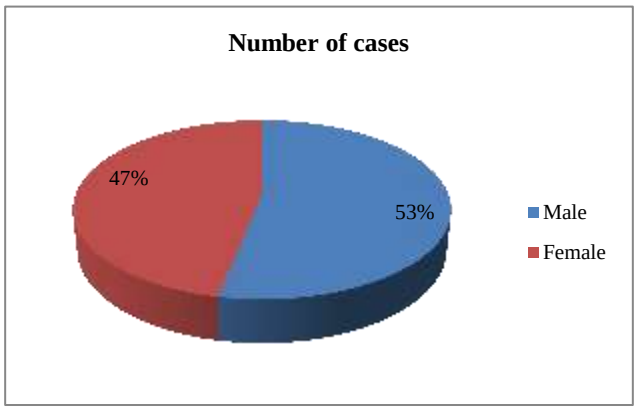


Figure 1: Sex ratio.

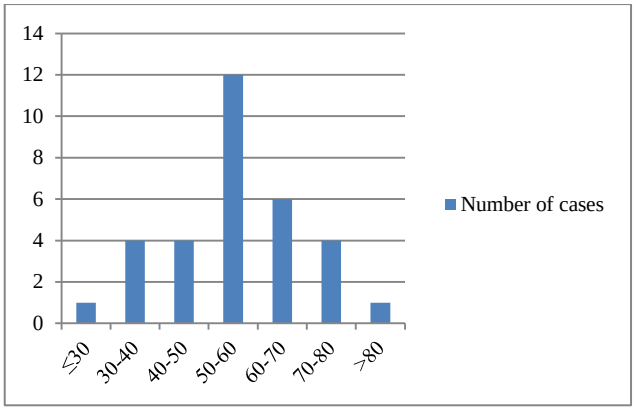


Figure 2: Age-wise distribution.

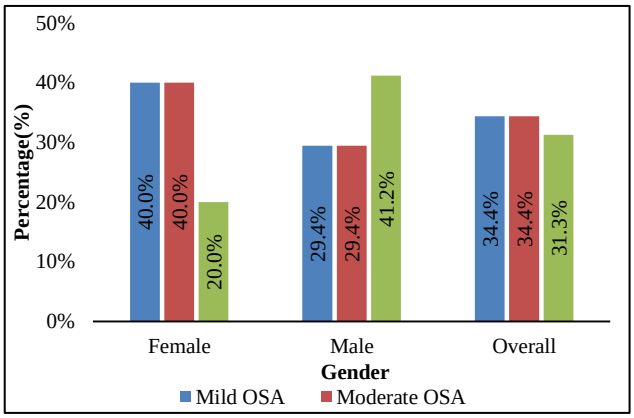


Figure 3: Distribution of obstructive sleep apnea (OSA) by gender.

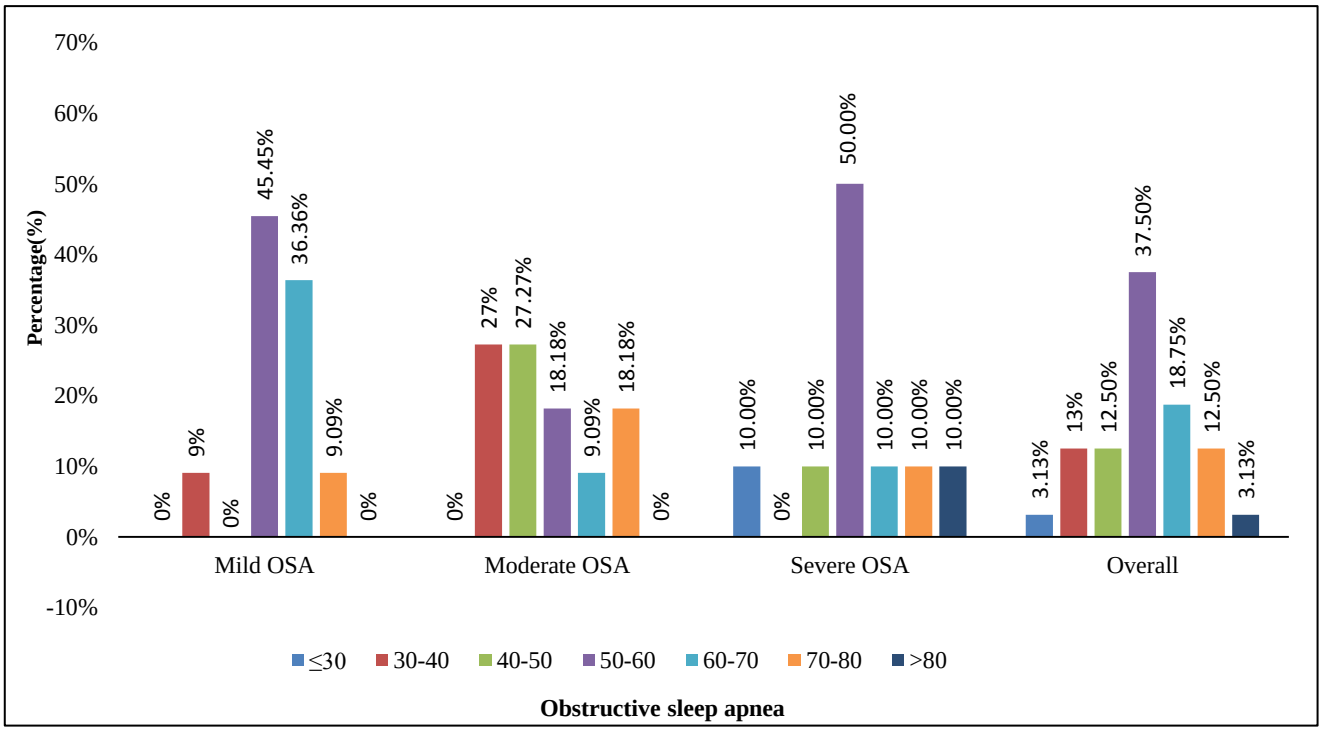
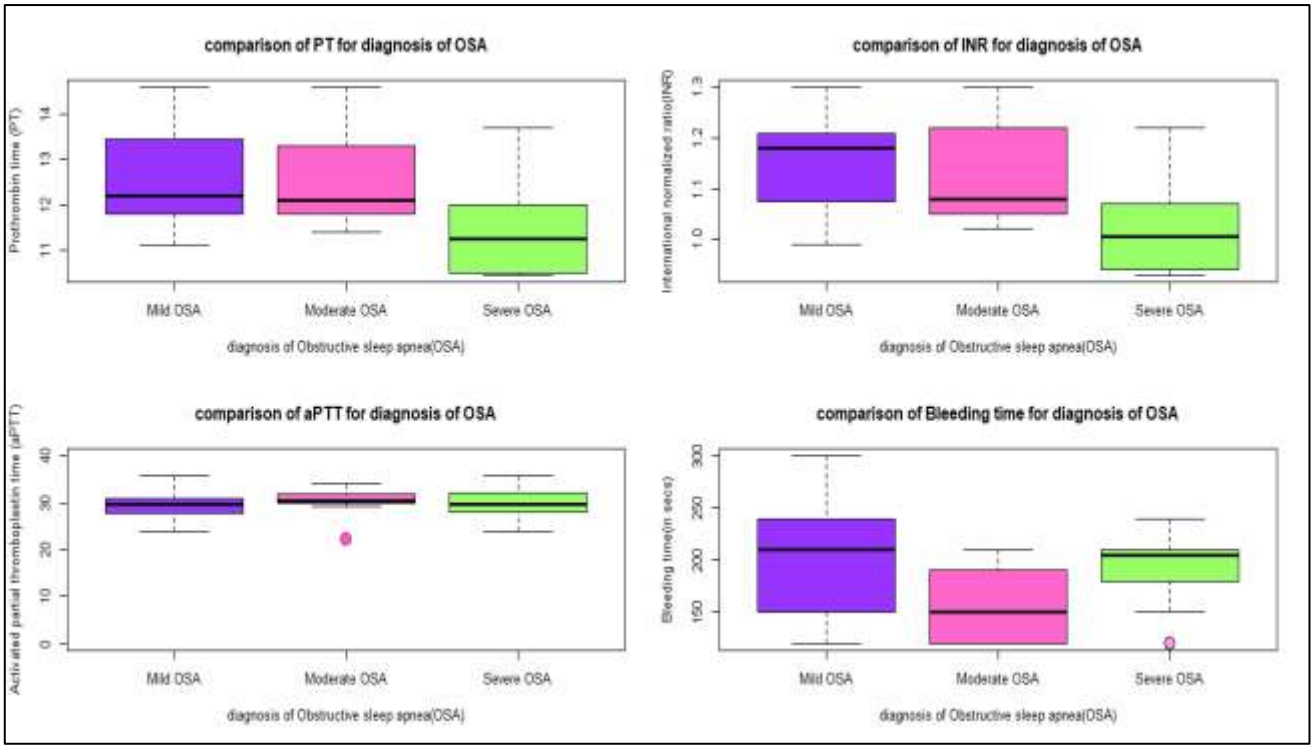


Figure 4: Distribution of OSA by age (years) group.



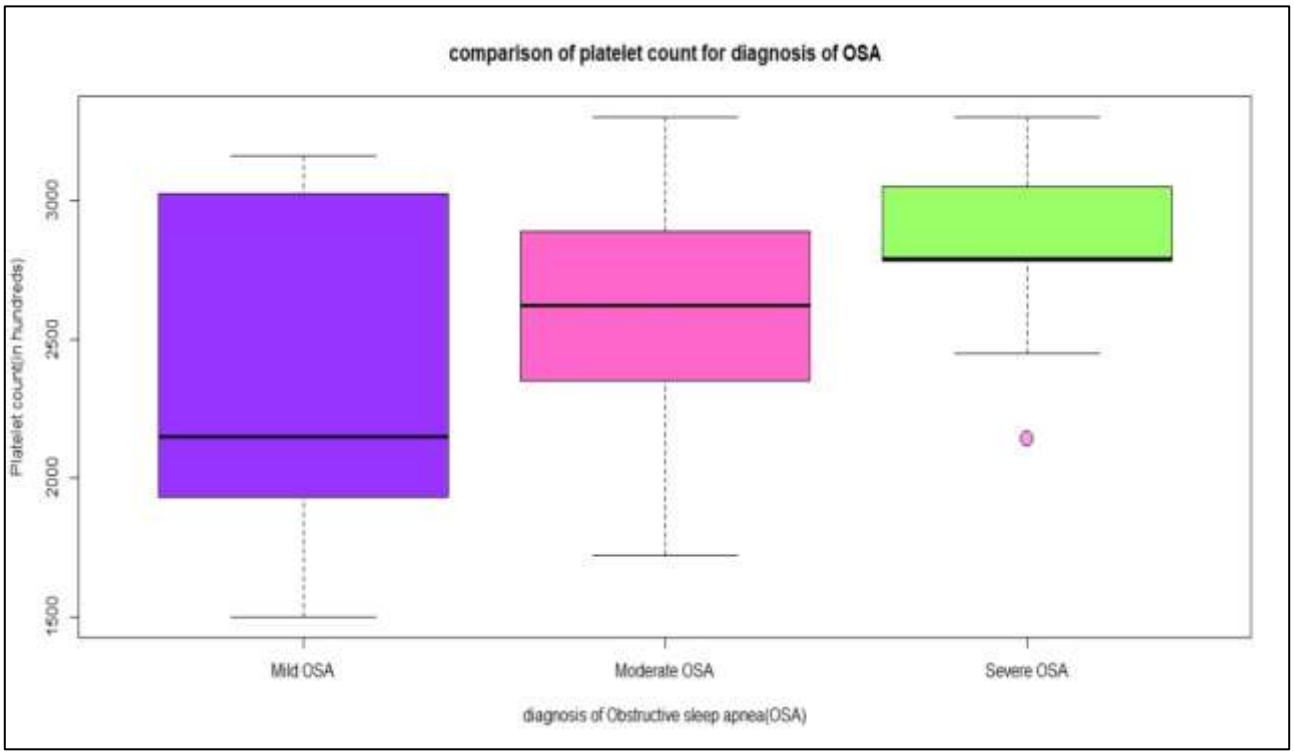


Figure 5: Comparison of different factors with the diagnosis of obstructive sleep apnea (OSA).

While there is a significant difference in mean prothrombin time (p=0.022). Kruskal-Wallis test showed a significant difference in the median of the PT/INR (p=0.01) and AHI (p<0.001) for different categories of OSA (Figure 5). There is a significant difference in the median value of the apnea-hypopnea index and mean value of prothrombin time and international normalized ratio for different levels of obstructive sleep apnea. There is a significant negative correlation between the apnea-hypopnea index and prothrombin time and international normalized ratio. Prothrombin time is the only factor which is affecting the obstructive sleep apnea (Table 1).

Table 1: Summary statistics of all factors.

Factors		OSA diagnosis			Overall	P value[1]	Odds ratio	P value[2]
		Mild OSA	Moderate OSA	Severe OSA				
Number of cases n (%)		11 (34.38)	11 (34.38)	10 (31.25)	100	-	-	-
Gender	**Female**	6 (40)	6 (40)	3 (20)	15 (46.87)	0.4974	5.47	0.0697
	Male	5 (29.41)	5 (29.41)	7 (41.18)	17 (53.13)			
Age (years)		59.27± 10.82	53.55± 14.9	56.5± 16.15	56.44± 13.82	0.6382	1.0730	0.0536
Prothrombin time (secs)	**Mean±sd**	12.64± 1.1	12.61± 1.07	11.41± 1.07	12.24± 1.19	0.02246*	0.3598	<0.001*
	Median (Range)	12.2 (11.1-14.6)	12.1 (11.4-14.6)	11.25 (10.45-13.70)	12.05 (10.45-14.60)			
International normalized ratio	Mean±sd	1.15± 0.1	1.12± 0.1	1.02± 0.09	1.1± 0.11	0.0116*	-	-
	Median (Range)	1.18 (0.99-1.30)	1.08 (1.02-1.30)	1.01 (0.93-1.22)	1.075 (0.93-1.30)			
aPTT	Mean±sd	29.49± 3.23	29.62± 3.93	30.02± 3.39	29.7± 3.43	0.9389	0.9963	0.9746
	Median (Range)	29.80 (23.9-35.7)	30.40 (22.1-34.1)	29.63 (23.9-35.7)	30.40 (22.1-35.7)			
Platelet counts (in hundreds)	Mean±sd	2381.82± 648.07	2622.73± 447.04	2828± 341.36	2604.0± 517.3	0.3517	1.0017	0.3075
	Median (Range)	2150 (1500-3160)	2620 (1720-3300)	2790 (2140-3300)	2780 (1500-3300)			
Bleeding time (secs)	Mean±sd	204.55± 66.84	156.36± 38.02	193± 34.66	184.38± 51.99	0.06636	0.5149	0.0885
	Median (Range)	210 (120-300)	150 (120-210)	205 (120-240)	210 (120-300)			

DISCUSSION

Many clinical studies have suggested that OSA is an independent risk factor for cardiovascular diseases like hypertension, coronary artery disease, stroke, heart failure etc. OSA has also shown association with impaired neurocognitive function, diminished attention span and concentration, memory disorders and psychomotor functioning.[11]

OSA is a risk factor for stroke independently of sex, body mass index (BMI), diabetes, and hypertension, at least in men. Cardiovascular association may, in addition to road traffic and work-related accidents, contribute to the increased morbidity and mortality associated with OSA, and the reduction in mortality seen in uncontrolled treatment studies using continuous positive airway pressure (CPAP).

OSA has gathered attention in causation of development of hypertension, insulin resistance and hyperlipidaemia, as well as various cardio-pulmonary diseases and cerebro-vascular accidents.[12]

Platelet aggregability increases in patients with OSA, it may be secondary to elevated nocturnal levels of catecholamines. Abolition of OSA by CPAP therapy reduces platelet aggregation in association with reduction in nocturnal levels of catecholamines. Increase in haematocrit, fibrinogen and blood viscosity predisposes to clot formation and atherosclerosis in patients with OSA.

According to the study carried out by Tufik et al they have concluded that 4 percent of men and 2 percent of women aged more than 50 years suffer from symptomatic OSA , that is about 1 of every 5 adults and that 1 of every 15 adults have moderate OSA. The prevalence rate in females increases from 3% for the third decade of life to 36% in the seventh decade. In men the prevalence for the third decade is 4% and increases to 50% during the seventh decade.[13] However it should be borne in mind

that OSA is often asymptomatic and can constitute a bulk as high as 20–30% in the middle-aged population.[14]

Hong et al[15] conducted in their retrospective cohort study that significant correlations were found between the apnoea- hypopnoea index and the PT seconds and PT INR in case of moderate and severe OSA patients whereas in mild OSA there was no significant difference. This result is consistent with the result of our study.

Two studies found a positive association between AHI and 9 pm platelet activation,[16] and between RDI and fibrinogen.[17] So in one of these studies,[17] fibrinogen also showed an inverse association with both Sao2min and average Sao2min. Multiple linear regression analyses showed independent associations between AHI and platelet activity,[16] epinephrine and platelet activity,[18] and average Sao2min and fibrinogen.[17] These significant associations may suggest that pro-coagulant changes are related to OSA.

The work of Chin et al.[18] confirmed increased levels of fibrinogen and haematocrit in OSA in the morning, suggesting increased blood viscosity. The level of D-dimer, a plasmin-derived degradation product of cross-linked fibrin, is a direct measure of activated coagulation and has been used as a measure of hypercoagulability.

In our study, PT was shortened, but aPTT did not show any difference in patients with moderate to severe OSA. Because the PT, aPTT, and BT levels indicate the actual time of coagulation in certain circumstances, the difference in PT level is clinically significant even though data are within the reference range. In addition, PT is an important factor, as it reflects the function of the extrinsic and common coagulation pathways.

It is known that chronic inflammatory responses are often associated with the activation of coagulation. One of the primary proposed mechanisms of hypercoagulability in inflammatory conditions is tissue factor–mediated thrombin production, which is induced by pro-inflammatory cytokines. Because tissue factor also initiate the extrinsic coagulation pathway, inflammatory response can be an etiologic factor for PT shortening that occurs when the extrinsic coagulation pathway is activated.[15] Therefore, in our study, shortening of the PT in patients with OSA may be due to the underlying chronic inflammatory processes of OSA.

CONCLUSION

Patients with severe OSA may have elevated coagulation profile, particularly elevated prothrombin time. The potential for anticoagulant and antiplatelet medications as a treatment modality merits exploration given the high degree of cardiovascular morbidity and mortality associated with OSA.

In conclusion, the association between OSA and coagulative factors is independent of other risk factors, including hypertension and diabetes.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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