Plasma Plasminogen Activator Inhibitor Type I Level As Early Predictor For Development Of Cardiovascular Complications In Adults With Obstructive Sleep Apnea

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ABSTRACT

Objectives: The present study tried to investigate the plasma levels of endothelial damage parameters and fibrinolysis-inhibiting enzyme plasminogen activator inhibitor type-1 (PAL-1) as possible risk factors related to obstructive sleep apnea syndrome (OSAS)-induced cardiovascular complication and as a trial to define an appropriate screening parameter for early detection of OSAS adult patients at risk of cardiovascular complications.

Patients & Methods: The study included 60 patients allocated into four groups (n = 15): OSA patients with and without ischemic heart disease (IHD) and OSA patients with hypertension (HT) and patients with IHD but without OSA and 15 healthy volunteers (control group). All patients underwent complete otorhinolaryngologic examination and evaluation of daytime sleepiness using the Epworth Sleepiness Scale (ESS); an ESS Score >10 was used to confirm the presence of OSAS. Blood pressure (BP) was estimated to calculate the mean arterial BP (MAP); then Pulse oximetry was performed for determination of the frequency of desaturation episodes and the lowest SaO2%. All patients and controls gave fasting blood samples for ELISA estimation of plasma levels of von Willebrand factor (vWF), soluble tissue factor (sTF), PAI-1 and d-dimer.

Results: Mean ESS score was significantly higher in patients with complicated OSAS compared to those had OSAS only. Patients with OSAS+IHD had significantly higher frequency of desaturation episodes compared to those with OSAS+HT or OSAS only, but the lowest SaO2 saturation was non-significantly different between OSAS patients. Mean plasma levels of studied parameters were significantly higher in patients compared to control levels. Mean plasma levels of PAI-1 and vWF were significantly higher in patients with complicated OSAS compared to those with uncomplicated OSAS or IHD that showed non-significant difference. Plasma levels of d-Dimer in OSAS+IHD patients were significantly higher compared to the other patients' groups with non-significant difference between these groups. Plasma sTF levels were significantly higher in patients with complicated versus those with uncomplicated OSAS with significantly higher levels in patients with OSAS+IHD compared to those with OSAS+HT. There was a positive significant correlation between plasma levels of PAI-1 and vWF estimated in OSAS patients and the severity of OSAS manifested as ESS scores and number of desaturation episodes. However, all estimated parameters showed a negative correlation with the lowest SaO2 saturation recorded in OSAS patients, such correlation was significant with PAI-1 and vWF levels but was non-significant with d-Dimer and sTF levels. There was a positive significant correlation between the presence of OSAS-induced cardiovascular complications and estimated levels of the four parameters. Regression analysis defined plasma PAI-1 and vWF levels as the most significant predictors for occurrence of complications. These results were confirmed using ROC curve analysis that defined plasma PAI-1 as a highly specific predictor for occurrence of cardiovascular complications (AUC=0.857) followed by plasma vWF (AUC=0.839).

Conclusion: In conclusion, OSAS in adults could be considered as one of cardiovascular risk factors attributed to associated antifibrinolytic activity and estimation of PAI-1 could be used as a specific predictor for the probability of developing such complications in OSAS patients.
INTRODUCTION

Stroke is the second leading cause of death worldwide and the leading cause of long-term disability. Strategies for stroke prevention, including the control of hypertension, treatment of atrial fibrillation, and smoking cessation, have reduced the disease burden, but stroke still remains an important public health challenge. (1)

Obstructive sleep apnea is a common chronic respiratory disorder that occurs in approximately 4% of men and 2% of woman >30 years old. Increase in the ratio with age may depend on the role of OSA on the complications of the disease, (2) OSA is well-defined syndrome that includes one or two of the following symptoms: severe snoring, nocturnal respiratory arrest, repeated nocturnal awakening, non-recuperative sleep, diurnal fatigue, and altered concentration. These clinical findings are related to the extent of hypoxemia and hypercapnia that develop as a result of disordered breathing. (3)

Despite, being a treatable form of disordered breathing, OSA associated with vascular risk factors and with substantial cardiovascular morbidity and mortality, (4) Several studies have shown a prevalence of the syndrome among patients with stroke that exceeds 60% as compared with 4% in the middle-aged adult population. (5)

Enhanced blood coagulability plays a paramount role in the initiation and progression of atherosclerosis and clinical manifestation of coronary artery disease. (6) Previous work has suggested that different aspects of disrupted sleep as OSA contribute to a prothrombotic state in populations with increased coronary risk. (7) As compared to patients with no OSA, those with OSA have higher plasma levels of several procoagulant molecules such as fibrinogen, activated clotting factor V, FXIIa, and thrombin/antithrombin III complexes, (6) Platelet activity and the fibrinolysis-inhibiting enzymes have also been reported as higher in sleep apnea patients. (9)

An increased plasma level of von Willebrand factor (vWF) and of soluble tissue factor (sTF) both indicates endothelial damage. vWF exerts its procoagulant function by mediating platelet adhesion to subendothelial structures and by stabilizing FVIII in plasma. The binding of circulating sTF to FVIIa initiates blood coagulation. (10) The hypercoagulability marker d-dimer is generated on degradation of fibrin by plasmin and reflects activation of the entire coagulation and fibrinolysis cascades. (11) PAI-1 inhibits fibrinolytic activity by virtue of inactivating circulating tissue-type plasminogen activator in a tissue-type plasminogen activator/PAI-1 complex, (12)

In view of the strong associations between OSA and cardiovascular morbidity and mortality, and between blood coagulability and cardiovascular morbidity and mortality, the present study tried to investigate the plasma levels of endothelial damage parameters and fibrinolysis-inhibiting enzyme PAI-1 as possible risk factors related to OSAS-induced cardiovascular complication and as a trial to define an appropriate screening parameter for early detection of OSAS adult patients at risk of cardiovascular complications.

PATIENTS & METHODS

The present study was conducted at Otorhinolaryngology and Cardiology departments in conjunction with Medical Biochemistry department, Faculty of Medicine, Benha University. The study included 60 patients allocated into four groups (n=15) OSA patients with and without ischemic heart disease (IHD) and OSA patients with hypertension (HT) and patients with IHD but without OSA and 15 healthy volunteers of cross-matched age and sex (control group). All patients underwent determination of demographic data including age, sex, weight, height and BMI was computed as the ratio of body weight in kilograms divided by the square of height in meters. (kg/m²) and ideal BMI was defined as BMI≤25, (13)

All patients underwent complete otorhinolaryngologic examination and sleep-history data taking included self-reported habitual snoring, which was defined as loud snoring occurring "frequently" or "constantly" and a validated measure of daytime sleepiness using the Epworth Sleepiness Scale (ESS) using
the following scale to choose the most appropriate number for each situation: 0= would never doze, 1= slight chance of dozing, 2= moderate chance of dozing & 3= high chance of dozing. Inquired situations included watching TV, sitting inactive in a public place, e.g. a theatre or meeting, as a passenger in a car for an hour without a break, lying down to rest in the afternoon when circumstances permit, sitting and talking to someone, sitting quickly after a lunch and/or in a car while stopping for a few minutes in the traffic, then the sum of numbers was calculated. (14). An ESS Score >10 was used to confirm the presence of excessive daytime sleepiness and the higher the score, the greater the severity of OSA. (15).

Then patients were referred to and admitted at Cardiology department for cardiac assessment and measurement of systolic and diastolic blood pressures and the average BP based on three seated resting measurements was used to calculate the mean arterial BP (MAP) which equals the diastolic BP plus one-third of the difference between systolic and diastolic BP. (16).

Pulse oximetry was performed using either a Nellcor (Pleasanton, CA) N-200 (mode 2, fast averaging) or N-3000 oximeter. The impact of OSAS on peripheral blood oxygenation (desaturation episodes) was evaluated as the number of drops of SaO2 to <90%, <85% and <80% throughout sleep period as following: severe OSA (score=3) if the drop of SaO2 to <90%, <85% and <80% was recorded >3 times for each saturation throughout sleep period; moderate OSA (score=2) if the drop of SaO2 to <90% and <85% was recorded >3 times for each saturation but the drop to <80% was recorded once or twice throughout sleep period and mild OSA (score=1) if the drop of SaO2 to <90% was recorded >3 times but the drop to <85% was recorded once or twice and no drop to 80% was recorded throughout sleep period and lowest SaO2% were also determined. (17).

Patients with BMI>30, resting BP >180/110 mmHg, congestive heart failure; symptomatic obstructive pulmonary, coronary, and cerebrovascular disease; history of life-threatening arrhythmias; cardiomyopathy; history of psychosis; narcolepsy; or previous surgery for treatment of OSA were excluded off the study.

Blood Sampling:
All patients and controls gave fasting blood samples while resting; plasma was collected into 10-ml plastic tubes containing 3.8% sodium citrate (ratio 9:1) as an anticoagulant and samples were centrifuged at 3000 rpm for 10 minutes, then, undiluted plasma was immediately frozen and was stored at -80°C till be assayed.

Investigations:
1. Estimation of plasma vWF antigen level using the AssayMax vWF ELISA kit designed for detection of human vWF. (18).
2. Estimation of plasma sTF antigen level using the AssayMax human tissue factor (TF) ELISA kit designed for detection of human TF. (19).
3. Estimation of plasma PAI-1 antigen level using the DiaPharma Tissue-Plasminogen Activator Inhibitor Type I Activity (PAI-1) ELISA kit. (20).
4. Estimation of plasma d-Dimer level using the DiaPharma Tissue-Plasminogen Activator Inhibitor Type I Activity (PAI-1) ELISA kit. (21).

Statistical Analysis:
Obtained data were presented as mean±SD, ranges, numbers and ratios. Results were analyzed using Wilcoxon Ranked Z-test and Chi-square test. Possible relationships were investigated using Pearson linear regression. Data were analyzed using Regression multivariate analysis (Stepwise Method) to define the specific predictors for occurrence of cardiovascular complications in OSAS patients and were confirmed using the receiver operating characteristic (ROC) curve analysis judged by the area under the curve (AUC). Statistical analysis was conducted using the SPSS (Version 10, 2002) for Windows statistical package. p-value < 0.05 was considered statistically significant.

RESULTS
The study included 60 patients with mean age of 43 ± 7.3; range: 29-56 years; there were 45 males and 15 females with M:F ratio of 3:1. Mean body weight was 77.4 ± 8.9; range: 62-92 kg and mean height was 165.7 ± 6.5; range: 145-
173 cm with a mean BMI of 28.1 ± 2.4; range: 21.2-31.6 kg/m². There was a non-significant difference between studied groups as regards inter-group difference or as compared to control group, (Table 1). Mean MAP was significantly higher in patients with IHD, (Z = 2.230, p = 0.026) and in patients with complicated OSAS, (Z = 3.411 & 3.412, p = 0.001, respectively) compared to control group and in patients with complicated OSAS, (Z = 3.408, p = 0.001) compared to those with OSAS only and in patients with OSAS+HT (Z = 3.191, p = 0.001) compared to those with OSAS+IHD, (Table 1, Fig. 1).

Table (1): Mean (±SD) of demographic data of patients enrolled in the studied groups.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>IHD</th>
<th>OSAS</th>
<th>OSAS+HT</th>
<th>OSAS+IHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39.9 ± 9.1</td>
<td>44.5 ± 7.3</td>
<td>41.5 ± 6</td>
<td>43 ± 7.9</td>
<td>42.9 ± 8.4</td>
</tr>
<tr>
<td>Sex, M:F</td>
<td>11 : 4</td>
<td>10 : 5</td>
<td>12 : 3</td>
<td>11 : 4</td>
<td>12 : 3</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>76.9 ± 7.8</td>
<td>77.1 ± 8.7</td>
<td>76.3 ± 9.6</td>
<td>77.9 ± 8.6</td>
<td>78.1 ± 9.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.1 ± 4.2</td>
<td>168.1 ± 3.3</td>
<td>164.6 ± 7.4</td>
<td>164.8 ± 6.9</td>
<td>165.3 ± 7.4</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>27.5 ± 1.8</td>
<td>27.3 ± 3.2</td>
<td>28.1 ± 2</td>
<td>28.6 ± 1.5</td>
<td>28.3 ± 2.6</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>94.2 ± 4.2</td>
<td>97.4 ± 4.5</td>
<td>95.7 ± 4.6</td>
<td>117.5 ± 5.6</td>
<td>107.9 ± 4.2</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD; ranges are in parenthesis. BMI = Weight (Kg)/Height (meter)².

Mean recorded ESS score was 12.9 ± 1.8; 10-17 irrespective of presence of associated medical problems. Mean ESS score was significantly higher in patients with OSAS+HT, (Z=1.98, p = 0.048) and in those with OSAS+IHD, (Z=2.969, p = 0.003) compared to those had OSAS only with a non-significant, (Z = 0.984, p > 0.05) difference between patients with complicated OSAS, (Fig. 2). Patients had OSAS+IHD had significantly higher, (Z = 2.487, p = 0.013 & z = 2.929, p = 0.003, respectively) frequency of desaturation episodes with a mean score of 20.4 ± 12.2, range: 6 - 42 compared to those with OSAS+HT (14.6 ± 6.7, range: 6-26) or those with uncomplicated OSAS (12.1 ± 5; range : 6-23) with a non-significant difference, (Z = 1.794, p > 0.05) between the latter groups, (Fig. 3). On contrary, the lowest SaO₂ saturation was non-significantly (p < 0.05) different between the complicated and uncomplicated OSAS.

Table (2): Mean (± SD) plasma levels of estimated parameters in the studied groups.

<table>
<thead>
<tr>
<th>PAI-1 (ng/ml)</th>
<th>vWF (mL/ml)</th>
<th>D-Dimer (ng/ml)</th>
<th>sTF (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD Z</td>
<td>p Mean±SD Z</td>
<td>p Mean±SD Z</td>
<td>p Mean±SD Z</td>
</tr>
<tr>
<td>Control</td>
<td>173±0.65</td>
<td>22.6±8.6</td>
<td>101±3.86</td>
</tr>
<tr>
<td>IHD</td>
<td>48.3±13.4</td>
<td>3.408 p&lt;0.001</td>
<td>97.4±24.8</td>
</tr>
<tr>
<td>OSAS</td>
<td>38.7±12.1</td>
<td>3.408 p&lt;0.001</td>
<td>121.3±28.8</td>
</tr>
<tr>
<td>OSAS+HT</td>
<td>57.2±16.3</td>
<td>3.408 p&lt;0.001</td>
<td>143.8±30</td>
</tr>
<tr>
<td>OSAS+IHD</td>
<td>72.1±21.7</td>
<td>3.408 p&lt;0.001</td>
<td>195±31.7</td>
</tr>
<tr>
<td></td>
<td>1.534 p&lt;0.05</td>
<td>3.295 p&lt;0.001</td>
<td>3.295 p&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD p₁: significance versus control group  p₂: significance versus IHD group. p₃ = significance versus OSAS+HT group  p₄ = significance versus OSAS+IHD group.
Mean estimated plasma levels of studied parameters were significantly \((p_1 = 0.001)\) higher in patients compared to control levels. Mean estimated plasma levels of PAI-1 were significantly higher in patients with OSAS+HT and OSAS+IHD but non-significantly lower in patients with uncomplicated OSAS compared to those with IHD, \((p_2 = 0.003, 0.001 & >0.05,\) respectively). Moreover, estimated plasma levels of PAI-1 were significantly higher in patients with OSAS+HT and OSAS+IHD compared to patients with uncomplicated OSAS, \((p_3 = 0.001 & 0.002,\) respectively) with non-significantly higher levels \((p_4 > 0.05)\) in patients with OSAS+IHD, (Fig. 4).

Similarly, mean estimated plasma levels of vWF were significantly higher in patients with OSAS+HT and OSAS+IHD but non-significantly higher in patients with uncomplicated OSAS compared to those with IHD, \((p_5 = 0.003, 0.001 & >0.05,\) respectively) and were significantly higher in patients with OSAS+HT and OSAS+IHD compared to patients with uncomplicated OSAS, \((p_6 = 0.048 & 0.002,\) respectively) with significantly higher levels \((p_7 = 0.001)\) in patients with OSAS+IHD compared to those with OSAS+HT, (Fig. 5).

On contrary, mean plasma levels of d-Dimer estimated in patients with OSAS+IHD were significantly higher compared to the other patients' groups, \((p_8 = 0.001, p_9 = 0.002 & p_10 = 0.001,\) respectively) with non-significant difference between these groups, (Fig. 6). Mean plasma levels of sTF were non-significantly higher in OSAS+IHD, \((p_11 > 0.05)\), but were significantly higher in those with uncomplicated OSAS and OSAS+HT compared to those with IHD without OSAS, \((p_12 = 0.001 & 0.020,\) respectively). However, sTF levels were significantly higher in patients with complicated versus those with uncomplicated OSAS, \((p_13 = 0.011 & 0.003,\) respectively) with significantly higher \((p_14 = 0.003)\) levels in patients with OSAS+IHD compared to those with OSAS+HT, (Fig. 7).

There was a positive significant correlation between plasma levels of PAI-1 and vWF estimated in OSAS patients and the severity of OSAS manifested as ESS scores, (Fig. 8) and number of desaturation episodes, (Fig. 9), while such correlation was positive non-significant with estimated levels of d-Dimer and sTF. However, all estimated parameters showed a negative correlation with the lowest \(\text{SaO}_2\) saturation recorded in OSAS patients, such correlation was significant with PAI-1 and vWF levels, (Fig. 10) but was non-significant with d-Dimer and sTF levels. There was a positive significant correlation between the presence of OSAS-induced cardiovascular complications and estimated levels of the four parameters, (Table 3, Fig. 11).

Using regression analysis (Stepwise method) to identify the predictors of occurrence of OSAS-induced cardiovascular complications defined plasma PAI-1, \((\beta = 9.246, p = 0.002)\) and vWF, \((\beta = 4.015, p = 0.007)\) levels as the most significant predictors for occurrence of complications. These results were confirmed using ROC curve analysis, (Fig. 12) that defined plasma PAI-1 as a highly specific predictor for occurrence of cardiovascular complications \((\text{AUC} = 0.857)\) followed by plasma vWF \((\text{AUC} = 0.839)\).

| Table (3) : Correlation coefficient "r" between ESS score, number of desaturation episodes and lowest \(\text{SaO}_2\) and the presence of cardiovascular complications and plasma PAI-1, vWF, d-Dimer and sTF estimated levels in OSAS groups. |
|-----------------|-------|-------|-------|-------|-------|-------|
|                 | Plasma PAI-1 | Plasma vWF | plasma d-Dimer | plasma sTF |
|                 | "r"  | p    | "r"  | p    | "r"  | p    |
| ESS score       | 0.316 | <0.034 | 0.466 | <0.001 | 0.235 | >0.05 | 0.106 | >0.05 |
| Number of desaturation episodes | 0.407 | 0.005 | 0.294 | 0.05 | 0.271 | >0.05 | 0.121 | >0.05 |
| Lowest \(\text{SaO}_2\) (%) | -0.312 | <0.037 | -0.309 | 0.039 | -0.251 | >0.05 | -0.188 | >0.05 |
| Presence of cardiovascular complications | 0.569 | <0.001 | 0.534 | <0.001 | 0.483 | =0.001 | 0.460 | <0.001 |

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Fig. (1): Mean \( \pm \text{SD} \) of MAP recorded in studied patients compared to control levels

Fig. (2): Mean \( \pm \text{SD} \) of ESS score recorded in OSAS patients
Figure (3): Mean (±SD) of frequency of desaturation episodes recorded in OSAS patients.

Figure (4): Mean (±SD) of PAI-1 levels estimated in studied patients compared to control levels.
Fig. (5): Mean (±SD) of vWF levels estimated in studied patients compared to control levels.

Fig. (6): Mean (±SD) of d-Dimer levels estimated in studied patients compared to control levels.
Fig. (7): Mean (±SD) of sTF levels estimated in studied patients compared to control levels.

Fig. (8): Correlation between OSAS severity manifested as ESS score and estimated levels of PAI-1 and vWF in OSAS patients (uncomplicated and complicated).

Fig. (9): Correlation between OSAS severity manifested as number of desaturation episodes and estimated levels of PAI-1 and vWF in OSAS patients (uncomplicated and complicated).
Fig. (10): Correlation between OSAS severity manifested as lowest SaO₂ saturation (%) and estimated levels of PAI-1 and vWF in OSAS patients (uncomplicated and complicated).

Fig. (11): Correlation between presence of OSAS-induced cardiovascular complication and estimated parameters.
DISCUSSION

It has been recognized that OSAS is one of the important risk factors of cardiovascular disorders, including hypertension, ischemic heart disease and cerebrovascular diseases. (23). Although OSA-related autonomic dysfunction and OSA-induced hypoxic stress may be dependently or independently involved in the development of cardiovascular disorders, the exact mechanism remains to be elucidated. (23). The present study tried to investigate the plasma levels of endothelial damage parameters and fibrinolysis-inhibiting enzyme PAI-1 as possible risk factors related to OSAS-induced cardiovascular complication and as a trial to define an appropriate screening parameter for early detection of OSAS adult patients at risk of cardiovascular complications.

The study included 60 patients; 45 males and 15 females with M:F ratio of 3:1, such masculine predilection agreed with Chorostowska-Wynimko et al., (24) who reported a similar frequency of males and females in their series of OSAS patients.

Mean recorded ESS score was significantly higher in OSAS patients complicated by either HT or IHD compared to those had OSAS and patients had OSAS+IHD had significantly higher frequency of desaturation episodes compared to those with OSAS+HT or those with uncomplicated OSAS. These data signified that the occurrence of OSAS-induced cardiovascular complications is related to the severity of OSAS as judged subjectively by ESS score or objectively using pulse oximeter as the frequency of desaturation episodes during sleep. These findings go in hand with Bayram et al., (25) who reported that hypertension was more frequently seen in patients with OSAS than in patients without OSAS and that HT frequency increased in parallel to the severity of OSAS and with Tavil et al., (26) who evaluated the right ventricular function in patients with OSAS and to determine the association between OSAS severity and right ventricular dysfunction and found both right ventricular systolic and diastolic functions are impaired in patients having OSAS with or without HT. Also, Kono et al., (27) investigated whether the components of metabolic syndrome were associated with OSAS in non-obese patients and found the percentage of hypertensive patients were significantly higher in the group with OSAS and a significantly higher percentage of patients with OSAS had at least two of the following: hypertension, hyperglycemia, and dyslipidemia and concluded that OSAS was associated with hypertension, dyslipidemia, and hyperglycemia. It is possible that OSAS may predispose even non-obese patients to the development of metabolic syndrome.

Mean estimated plasma levels of studied parameters were significantly higher in patients compared to control levels with significantly higher levels in patients with complicated OSAS.
compared to those with uncomplicated OSAS and those with IHD without OSAS. However, estimated levels in patients with uncomplicated OSAS were non-significantly different from those with IHD only. These data illustrated the impact of OSAS on cardiovascular risk factors that were non-significantly higher in uncomplicated OSAS but significantly higher in complicated OSAS compared to those with IHD without OSAS. These findings agreed with that previously reported in literature; von Kanel et al., found that the increased coronary risk in OSA might be partially relate to a prothrombotic state, and found an independent association between higher d-dimer levels and poor sleep quality in the elderly, and higher d-dimer levels and higher stage 2 sleep in distressed dementia caregivers. Moreover, Wolk et al., found markers of disturbed sleep are associated with enhanced coagulability and thus potentially higher risk of cardiovascular disease, even in non-apneics. Mallon et al., found that poorer sleep efficiency and greater sleep fragmentation was predictive of elevated levels of sTF and VWF and had been shown to predict coronary artery disease mortality in middle-aged men at 12-year follow-up.

According to the findings of the current study, vWF and sTF being as endothelial activation markers that may indicate endothelial cell damage at a very early stage, so poor sleep quality and disturbed sleep architecture manifested as significantly higher ESS score and frequency of desaturation episodes could contribute to atherosclerosis by eliciting increases in vWF and sTF that will clinically manifest many years later. In support of such explanation, there was a positive significant correlation between estimated factors and occurrence of cardiovascular complications and between estimated vWF level and ESS score and frequency of desaturation episodes and a negative significant correlation with lowest SaO2 levels.

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