Title: Predictive factors facilitate identification of potential aortic dissection in patients with obstructive sleep apnea syndrome

Authors:

Dandan Jiang, MD[ac], Qu Chen, MD[bc], Xiangyang Yao, MD[a], Chunping Dong, MD[a], Weiming Su, MD[a], Dinghui Wu, MD[a]

[a]: Department of Internal Medicine, Xinglin Branch of The First Affiliated Hospital of Xiamen University, Xiamen, Fujian Province, People's Republic of China.

[b]: Department of Cardiovascular Surgery, The First Affiliated Hospital of Xiamen University, Xiamen, Fujian Province, People's Republic of China.

[C]: The first two authors contributed equally to this work.

Email:

Dandan Jiang: jddcmu@163.com

Qu Chen: cmuchenqu@163.com

Xiangyang Yao: xmxyyao@sina.com

Chunping Dong: jianyankuangren@sina.com

Weiming Su: sugedehao@sina.com

Dinghui Wu: dinghuizhijia@sina.com

Disclosures: The authors of this manuscript have no relationships with industry to disclose.

Sources of Funding: None.

Date Availability Statement: The raw data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study.

Address for Correspondence

Dinghui Wu, MD

Department of Internal Medicine, Xinglin Branch of The First Affiliated Hospital of Xiamen University, No. 55 Zhenhai Road, Siming District, Xiamen City, Fujian Province, 36100, People's Republic of China

Tel.: +86 18650129649

Fax: +86 0592-2137106

29Email: dinghuizhijia@sina.com

30**Running Head:** Identification of potential aortic dissection

31**Word Coun**t: 3447

Abstract

Objective: Investigating potential predictors of aortic dissection development in high-risk hypertensive patients with obstructive sleep apnea syndrome (OSAS).

Methods: Hypertensive patients with aortic dissection, admitted to hospital between January 2010 and July 2020, was diagnosed with OSAS by overnight sleep study with polysomnography (PSG).

Results: Male was liable to aortic dissection compared to female in both groups (84.7% and 86% respectively) .There were actually significant differences with regard to neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), mean platelet volume (MPV) / platelet count (PLT) ratio and D-dimer that we concerned about and were of great value in aortic dissection as previously reported. As multivariable regression analysis revealed, NLR (odds rate [OR], 2.258, 95% confidence interval [CI], 1.464-3.482, P<0.05), MPV/PLT (OR, 2.743, 95%CI, 1.713-4.392, P<0.05) and apnea and hypopnea index (AHI) (OR, 1.746,95% CI, 1.225-1.320, P<0.05) were all independent risk factors for aortic dissection. receiver operating characteristic curves analysis of NLR, MPV/PLT, AHI and combination of indicators for aortic dissection revealed combination of NLR, MPV/PLT ratio and AHI is of outstanding predictive value with sensitivity of 0.904 and specificity of 0.847. At the thresholds of 4.41 for NLR and 5.14 for MPV/PLT and 35.95 for AHI, 87.5% of all studied patients were expected to be correctly diagnosed with regard to aortic dissection.

Conclusion: Inflammation, platelet alteration is crucial for initiation and progression of aortic dissection. Combined detection of NLR, MPV/PLT ratio and AHI could assist sleep physicians to identify clinically silent or potential aortic dissection in patient comorbidity OSAS and hypertension.

Key words: aortic dissection, obstructive sleep apnea syndrome, outcomes

Abbreviation:

AD: aortic dissection

AAD: acute aortic dissection

AHI: apnea and hypopnea index

AUC: area under curve

BMI: body mass index

CPAP: continuous positive airway pressure

CRP: C-reactive protein

FDP: fibrinogen degradation product

LC: lymphocyte count

LC%: lymphocyte percentage

MPV: mean platelet volume

MPV/PLT ratio: mean platelet volume/platelet count)

NE%: neutrophil percentage

NLR: neutrophil to lymphocyte ratio

OSAS: Obstructive sleep apnea syndrome

PDW: platelet distribution width

PLR: platelet to lymphocyte ratio

PLT: platelet count

PSG: polysomnagraphy

ROC: receiver operating characteristic

WBC: white cell count

Introduction

Obstructive sleep apnea syndrome(OSAS) is a common clinical condition , which is characterized by apnea or hypopnea with recurrent collapse of upper airway tract during sleep, mainly shortening sleep duration and lowering sleep quality through intermittent hypoxia, fragmentation and other pathophysiological mechanisms[1].The reason for so much attention paid to OSAS by clinicians and researchers is that OSAS has yielded various complications including cognitive impairment, cardiovascular disease, pulmonary disease, endocrine dysfunction, and neuropsychiatric problems[2-4],among which cardiovascular diseases are given top priority due to higher incidence, acute onset and worse prognosis. In recent years, prevalence and lethal outcome of comorbidity of OSAS and aortic dissection(AD) arouse more and more attention from clinicians and researchers[5-7].

Aortic dissection is a life-threatening emergency lacking effective therapeutic medication remedies up to now. It derives from a tear in the intimal layer of aorta resulting in the entry of blood to the space between the intima and media , which is usually accompanied with the classic symptoms “severe tear pain” described by the suffered patients on the onset of acute aortic dissection. Compared to acute aortic dissection,the symptoms and prognosis of chronic aortic dissection usually are slightly better. The majority of patients with acute aortic dissection (AAD) have died even before they reach the emergence room. As a wealth of study indicates, the patients of aortic dissection missed optimal medical treatment and instant rescue have a mortality rate of 50-68% during the first 48 hours after onset, with a mean mortality of up to 1% per hour, and reaches as high as 90% within 3 months from occurrence [8].

Recently, more and more observational studies have demonstrated a high prevalence of previously undiagnosed OSAS in patients with aortic dissection[9-11].Lack of effective indicators for identification is responsible for the tragedy, which motivates us to investigate the underlying relation between them.As is reported, the prevalence of OSAS is up to 80% in case of refractory hypertension[12].While hypertension, especially refractory hypertension, is a corroborated independent risk factor associated with aortic dissection, whether initiation or progression. Constant hypertension will exert persistent transmural pressure on aortic wall, which is likely to exacerbate aortic dissection further to rupture on account of huge shear stress. Thus, there may be shared pathogenesis in incidence and development of secondary hypertension and aortic dissection in patients with OSAS given the intimate connection among them. Endothelial dysfunction of aorta wall and subsequent atherosclerosis, increased negative intrathoracic pressure and shear stress, secondary hypertension and vulnerable aortic medial structure brought about by OSAS maybe major

contributors to the emergence of aortic dissection [13].

Up till now, former researches demonstrated that several significant predictive factors could be applied to evaluate prognosis and mortality of hospitalized patients with aortic dissection including neutrophil to lymphocyte ratio(NLR)[14],platelet to lymphocyte ratio（PLR）[15],D-dimer[16],fibrinogen degradation product(FDP)[17],C-reactive protein(CRP)[18].Inspired by this, we hypothesize that these significant, readily available and inexpensive serum markers will help facilitate identification of potential aortic dissection from high-risk hypertensive patients with OSAS. Additionally, arterial hypertension is a determined risk factor for aortic dissection and, on the other hand, several studies have shown OSAS to be widely prevalent in hypertensive patients [19],thus a control group of hypertensive patients was included.

METHODS

Patient selection

Study group: Hypertensive patients with aortic dissection, admitted to the Department of Cardiac surgery, First Affiliated Hospital of Xiamen University between January 2010 and July 2020, was diagnosed with OSAS by overnight sleep study with polysomnography（PSG），were recruited(n=94).Inclusion criteria were as follows: first admission after the onset of aortic dissection symptoms，hypertension diagnosed after admission or with hypertension history.

Control group: Hypertensive patients(n=85) well-matched age, gender, BMI and other baseline characteristics with study group, was diagnosed with OSAS by overnight sleep study with polysomnography（PSG）,were chosen from sleep center in our hospital during the same time range with study group. Inclusion criteria were as follows: hypertension diagnosed after admission or with hypertension history.

The common exclusion criteria of two groups were as follows: age less than 10 or more than 80, chronic respiratory diseases, recent history of neoplasm, autoimmune disease, infectious disease, systemic inflammatory disease, acute renal failure, acute limb ischemia, patients with unstable hemodynamics, hypoxemia, myocardial ischemia/infarction, conscious disturbance, pericardial tamponade, and paraplegia.

Baseline characteristics of patients in two groups were collected once admission, including age, male/female, height, weight, history of diabetes mellitus, smoking, drinking. For all patients, body mass

index (BMI, kg/m^2) was calculated as the weight(kg) divided by height^2 (m^2).

This study complied with the Declaration of Helsinki, and the study protocol was approved by the Human Ethical Committee of the First Affiliated Hospital of Xiamen University. All participants in this study provided written informed consent.

Diagnosis of aortic dissection

The diagnosis of aortic dissection was based on morphological findings by enhanced computer tomographic (CT) scan with or without typical clinical symptoms including a sudden onset of severe chest pain, back pain radiating to the neck or shoulders.

Polysomnography

PSG consisted of recordings of electroencephalogram (EEG, C4/A1 and C3/A2), right and left electrooculogram (EOG), submental electromyogram (EMG), and electrocardiogram (ECG), chest and abdominal excursion, airflow (detected by a nasal-oral thermocouple and oxygen saturation (SaO2) by finger pulse oximetry. Apnea was defined as the cessation of airflow through nose and mouth for a period of longer than ten seconds. Hypopnea was defined as a reduction in thoracic and abdominal movements to 50% or less associated with at least a 4% fall in oxygen saturation. The apnea-hypopnea index (AHI) was defined by the number of events per hour of recording.

Hematological parameters

For patients in control group, blood samples were obtained in the morning after overnight PSG examination，for the study group，within 24 hours after admission. All blood samples sent within 1 hour after venipuncture to avoid alterations in parameters with prolonged storage at room temperature. The biochemical parameters include white cell count(WBC)，neutrophil percentage(NE%),lymphocyte count(LC#)and percentage(LC%),platelet count(PLT), mean platelet volume(MPV)，platelet distribution width(PDW),C-reactive protein (CRP), fibrinogen degradation product (FDP),and D-dimer were evaluated. Some indicators were calculated by investigator such as NLR (neutrophil to lymphocyte ratio), PLR (platelet to lymphocyte ratio), MPV/PLT ratio (mean platelet volume/platelet count).

Data statistics

Quantitative variables are presented as mean±standard deviation if normally distributed, mean(interquartile range) if abnormally distributed. Continuous variables were compared by means of Student’s t-test for normally distributed data, and nonparametric Mann–Whitney U test for abnormally

distributed data. Categorical variables were compared by chi-square tests. Multiple liner regression was used to test multicollinearity, binary logistic regression analysis was used to determine independent risk factor for aortic dissection, controlling for potential confounders. A receiver operating characteristic curve analysis was performed to investigate the predictive performance of variables according to the logistic regression analysis model，alone and as a bundle. Data analysis was performed using SPSS Statistics for Windows, Version 20.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Baseline characteristics for two groups are presented in **Table 1**. As expected based on matching criteria ,no significant difference was observed between two groups for demographic data and clinical history. Male was liable to aortic dissection compared to female in both groups（84.7% and 86% respectively）.The majority of patients in both groups were accompanied with tobacco use, drinking and glucometabolic disorder, however, no significance difference was found between groups with regard to clinical history.

Table 2 illustrates the results of logistic regression analysis concerning biochemical variables and AHI of two groups. WBC and CRP as traditionally classic inflammatory indexes showed no significant difference between two groups, even though patients with aortic dissection had higher level of WBC and CRP in comparison with control group(7.63±1.71 versus 7.24±1.49,p=0.114,5.89(1.81) versus 4.21(2.39),p=0.833,respectively).We also found lower PLT in study group compared to control group, but with no significant difference between them(167.22±30.35 versus 173.23±39.93,p=0.263).The percentage of neutrophil and lymphocyte as WBC subtype showed significant difference between two groups, as well as lymphocyte count. Of note, there were actually significant differences with regard to NLR,PLR,MPV/PLT ratio and D-dimer that we concerned about and were of great value in aortic dissection as previously reported.

To get what were related independently with aortic dissection, we conducted binary multivariate logistic regression analysis. As **Table 3** showed, NLR (OR, 2.258, 95%CI, 1.464-3.482, P<0.05), MPV/PLT (OR, 2.743, 95%CI, 1.713-4.392, P<0.05) and AHI (OR, 1.746, 95%CI, 1.225-1.320, P<0.05) were all independent risk factors for aortic dissection. To evaluate predictive performance of indicators selected from

logistic regression analysis, we plotted the ROC curves with them, individually and as a bundle for combination. AUC value and cut-off value, sensitivity and specificity got from Youden index were showed **Table 4**. ROC curves analysis of NLR, MPV/PLT, AHI and combination of indicators for aortic dissection revealed that AUC value of 0.782 (95%CI, 0.715-0.848, P<0.01),0.783(95%CI, 0.717-0.849, P<0.01), 0.838 (95%CI, 0.781-0.896, P<0.01), 0.93(95%CI, 0.892-0.967, P<0.01), respectively. (**Figure 1**)

Individually analyzed, MPV/PLT ration showing excellent predictive performance of AD displayed perfect sensitivity of 1.00 but relatively lower specificity of 0.424, AHI with sensitivity of 0.713 but higher specificity of 0.843 showing the higher value in ruling out AD. Similar to AHI, NLR also presented relatively better specificity. Of note, combination of NLR, MPV/PLT ratio and AHI is of outstanding predictive value with sensitivity of 0.904 and specificity of 0.847. At the thresholds of 4.41 for NLR and 5.14 for MPV/PLT and 35.95 for AHI, 87.5% of all studied patients were expected to be correctly diagnosed with regard to aortic dissection.

DISCUSSION

Obstructive sleep apnea syndrome (OSAS) is closely associated with arterial hypertension, which is a mainly independent risk factor for aortic dissection [20]. And an increasing number of reports have verified the prevalence of patients comorbidity OSAS and aortic dissection[9-11]. Saruhara et al. showed that patients with aortic diseases frequently suffered from moderate to severe OSAS and recommended that screening for OSAS may be helpful for early detection of patients with aortic diseases[21].Gabriel et al. also suggested patients of aortic dissection, specially complaining of severe snoring and unrefreshing sleep, should be considered to take the PSG examination in their clinical management[19].As we know, repetitive episodes of apnea and hypopnea which is measured by AHI to evaluate severity of OSAS frequently occur during sleep duration of OSAS patients every night and will increase gradually due to be undiagnosed or misdiagnosed.

As of now, it has been unclear about the underlying mechanism implicated in the association of OSAS and aortic dissection, while there are some hypotheses yet. Inspiratory effort to restore ventilation against occluded airway contributes to a series of neurohumoral alteration through pathophysiological mechanisms such as intermittent hypoxia, hypercapnia, increased negative intrathoracic pressure and sleep fragmentation. We will discuss them in the following section. At first, hypoxia induced and subsequent arousal induced by apneic episode provoke sympathetic activation, which is demonstrated in both animal and human studies[22-23],and it will motivate initiation and accelerate progression of hypertension. Thus, end-apneic arterial blood pressure repetitively surges and usually develops into refractory hypertension with resistance to common anti-hypertensive medication. At the same time, increased negative intrathoracic pressure can be observed

during OSAS. Suzuki M et al. suggested from their research that the negative end-apnoeic pressures were quantified in one in vivo study 53.6±2.9 cmH2O and peak pressure of 147.4 cmH2O [24]. Compared with physiological inspiration pressure of around 5 to 8 cmH2O in healthy subjects [25]. The obvious pressure difference produces an increase in transmural pressure across the aorta and shear stress of aortic wall, which could lead to impaired vascular function and propensity of dissection [26] will arise as a consequence. Furthermore, chronic systematic inflammation, oxidative stress, endothelial dysfunction and atherosclerosis due to intermittent hypoxia during sleep duration of OSAS patients may be other factors responsible for aortic dissection.

All the mentioned pathophysiological mechanisms act as risk factors for aortic dissection characterized by high mortality and noted with the most frequent complications being recurrent dissection, aortic dilation and even abrupt aortic rupture. Accordingly, expeditious and accurate diagnosis as well as discrimination from high-risk population such as hypertensive patients with OSAS are of vital importance to curb the catastrophe. Some serum biochemical markers reportedly associated with prognosis of aortic dissection is hypothesized to be expected to be potentially ideal predictive indexes. So the present study is to explore the value of NLR,PLR,MPV/PLT,D-Dimer and AHI, which is readily and rapidly available，widely applied and inexpensive, to find the appropriate candidates for identifying aortic dissection from hypertensive patients with OSAS.

In our study, among all the hematological parameters with significant differences compared to control subjects, we selected some potential markers closely related with development or prognosis of aortic dissection in previous researches. However, logistic regression analysis revealed that NLR, MPV/PLT ration and AHI were all independent risk factors for aortic dissection getting rid of the confounding factors. ROC curve analysis demonstrated MPV/PLTA ration is characteristic with excellent sensitivity but lower specificity, while AHI holds satisfactory specificity. The AUC of combined prediction of NLR,MPV/PLT ratio and AHI for aortic dissection is 0.930 with sensitivity of 0.904 and specificity of 0.847.

Inflammation as a key pathophysiological feature plays an important role in the initiation and progression of aortic dissection [15]. The idea of chronic systemic inflammation is highly correlated with aortic dissection were also elucidated by former researches[27-28].Inflammation contributes partly to the occurrence and progression of AD and local chronic inflammation causing aortic medial degeneration are involved in the pathophysiology of AD[29-30]. It has been testified that traditional inflammatory hematological parameters such as white cell blood count (WBC)and C reactive protein (CRP) [31] as well as inflammation-

related cytokine and chemokine such as plasm interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), matrix metalloproteinase-9 (MMP-9) and endotoxins [27] are found increased in acute aortic dissection. Similarly, Zhixuan Bai and his colleagues concluded from their study that pathological observation of the aortic tissue showed inflammatory cells infiltration and elastic fiber destruction, which destroy the aortic medial structural strength in the aortic dissection patients than aortic aneurysm ones [32]. Furthermore, ischemia and hypoxia of downstream organ caused by decreased blood perfusion due to false lumen formation in aortic dissection aggravate systemic inflammation.

Neutrophil to lymphocyte ratio (NLR) is newly recognized as a novel inflammatory marker that is easy to obtain, inexpensive and widely available, and seems to aid in risk stratification in cardiovascular disease, in addition to traditional markers [33-34]. Increased NLR implies higher inflammatory burden, which is a reflection of two different but complementary immune pathways. Lymphopenia is a predictor of adverse outcomes in chronic ischemic disease, heart failure, and acute coronary syndromes [35]. NLR combines the effect of nonspecific active inflammation by neutrophil and specific immune regulation by lymphocyte and tends to be a parameter more stable than other leukocytic parameter which is easily altered by hydration status and blood sampling. Of note, NLR is reported a predictor in the asymptomatic general population of cardiovasular patients across the spectrum of coronary artery disease including stable angina and acute coronary syndromes [36], following elective or urgent revascularization (percutaneous coronary intervention and coronary artery bypass grafting , in heart failure as well as after repair of abdominal aortic aneurysms [37].In our study, NLR is significantly higher in study group and justified as an independent risk factor of aortic dissection, which is partially consistent with the former result which demonstrates NLR is higher in aortic dissection compared to chronic aortic aneurysm and health controls[38].Up till now, most researches focus on investigating NLR as long-term prognostic predictor of AD, and our study affirmed its significance on predictive assessment of aortic dissection from high-risk population, to our best knowledge, is firstly reported.

Active coagulation and fibrinolysis go all through the process of aortic dissection, in which platelet plays a pivotal role in every chain. Mechanical injury of the aorta results in release of tissue factors into the circulation, which leads to activation of extrinsic pathway of the coagulation cascade and fibrinolytic system with subsequent thrombus formation within the false lumen[39]. Thrombocytopenia is a result presumably due to platelet consumption associated with enhanced fibrinolysis within the false lumen and inflammation motivation during aortic dissection[15].Mean platelet volume (MPV) can reflect both PLT activation and low grade systemic inflammation, so it is also referred as a reflection of both proinflammatory and

prothrombotic conditions[40].Higher MPV, which could occur because of thrombosis and inflammation in AD, in conjunction with thrombocytopenia results in increased MPV/PLT ration. Similar to NLR, we think that MPV/PLT ratio is more reliable than platelet or MPV alone, which is more sensitive to prethrombotic status in initiation of aortic dissection. In our study, MPV/PLT differs significantly between groups and is also justified as an independent risk factor (OR,2.743, 95%CI, 1.713-4.392, P<0.05) in multivariate logistic regression analysis although the degree of platelet lowering in study group fail to attain the significant level. Milne AA et al reported that reduced PLT count and increased MPV values were found in unruptured abdominal aortic aneurysms[41]. Previous studies have demonstrated MPV/PLT as significant diagnostic and prognostic indicator for aortic dissection [42]. These conclusions are all in tune with ours. As of note, D-dimer is a fibrin fragment whose elevation is induced by the coagulation cascade and associated with fibrinolysis , which is well recognized to be associated with various vascular diseases involved with thrombosis[43].It has been reported recently to be applied in acute aortic dissection [44], but its diagnostic accuracy is always restricted by fairly low specificity. So other alternatives for diagnosis with higher specificity is expected to be found, more researches are needed to testify the role of MPV/PLT played in aortic dissection.

OSAS is characterized by hypoxia and sleep fragmentation due to frequent arousals, which are the results from apnea or hypopnea. AHI signifies the total number of events of apnea and hypopnea per hour during sleep duration and proportional arousals or microarousals follow subsequently after every apneic episode, as a result, AHI is the most important index representing severity of OSAS.As is mentioned in the former content, sympathetic activation, increased intrathoracic pressure and transmural pressure of aorta, oxidative stress, endothelial dysfunction and atherosclerosis are all possible causative essentials for aortic dissection. Moreover, elastic fiber of aorta media could be injured by systemic inflammation and oxidative stress in patients with OSAS, which will give rise to medial degeneration and further to aortic dissection. Bai et al. found the uniaxial tensile test value for evaluating elastic fiber strength and medial degeration is negatively correlated with the serum and tissue homogenized concentration of IL-6 and TNF-α.In other words, OSAS is closely associated with aortic dissection and the intensity of aortic medial fiber is in negative relation with serum inflammatory cytokines[32]produced in OSAS patients. Although these pathophysiological hemodynamic and neurohumoral changes occur during sleep, their consequences persist for 24 h in fact[45].

As is mentioned above, we speculate that higher AHI will increase the risk of aortic dissection, which is demonstrated by the present study. We have shown that AHI is an independent risk factor for aortic dissection irrespective of other confounders. In addition, Gabriel Sampol et al affirmed that a higher AHI was found in patients with aortic dissection compared with a control group of hypertensive patients[46].Mitsumasa Hata et al. suggested that sleep disorders are considered one of the risk factors for the occurrence of acute aortic dissection in patients of active ages[10] and advocate that timely and appropriate treatment is essential to prevent refractory hypertension and subsequent AD. Besides，Xuemin Zhang et al. conducted the study between the patients of Stanford's Type B AD and the patients of suspected OSAS patients with similar symptoms, and they found that OSAS was independently associated with Stanford's Type B AD (odds ratio 1.063, 95% confidence interval: 1.010-1.120; P= 0.020) and in the follow-up prospective study, two patients developed finally into aortic dissection and both of them had serious OSAS diagnosed previously[47].

Additionally, Limitations of this investigation should be mentioned，first，our study was a single-center study with a relatively small population，which may have influenced the statistical power of our results. Further prospective studies incorporating more patients aimed to substantiate our findings are warranted. secondly, we did not make a contrast with other concomitant cardiovascular diseases as control group in determining these markers. In addition, we cannot judge whether they are constant predictor of aortic dissection due to lack of tracing subsequent change of NLR and MPV/PLT ratio during hospitalization.

Summary

In conclusion, inflammation, platelet alteration is crucial for initiation and progression of aortic dissection. Combined detection of NLR, MPV/PLT ratio and AHI could assist sleep physicians to identify clinically silent or potential aortic dissection in patient's comorbidity OSAS and hypertension. Further multicenter randomized controlled trials are warranted to verify our finding and explore whether CPAP might be a possible precautionary measure to prevent aortic dissection in potential patients with severe OSAS.

Figure 1 Receptor operating characteristic curves

Table 1 Clinical and demographic characteristics of control group

Table 2: Serum biochemical parameters and AHI of control group and study group

Table 3: Binary logistic regression analysis of NLR, PLR, MPV/PLT, D-Dimer and AHI for aortic dissection

Table 4: Receptor operating characteristic curves of NLR, MPV/PLT, AHI and combination of all three variables for aortic dissection

References

1. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea [published correction appears in Physiol Rev. Physiol Rev. 2010;90:47-112.

2. Banks S, Dinges DF. Behavioral and physiological consequences of sleep restriction. J Clin Sleep Med. 2007;3(5):519-528.

3.Meerlo P, Sgoifo A, Suchecki D. Restricted and disrupted sleep: effects on autonomic function, neuroendocrine stress systems and stress responsivity. Sleep Med Rev. 2008;12(3):197–210.

4.Mirrakhimov AE. Obstructive sleep apnea and kidney disease: is there any direct link? Sleep Breath. 2012;16(4):1009–16

5.Kohler M, Pitcher A, Blair E, Risby P, Senn O, Forfar C, Wordsworth P, Stradling JR. The impact of obstructive sleep apnea on aortic disease in Marfan's syndrome. Respiration. 2013;86(1):39-44.

6.Wang L, Chen J, Li G, et al. The Prevalence of Sleep Apnea in Type B Aortic Dissection: Implications for False Lumen Thrombosis. Sleep. 2017;40(3):zsw071.

7.Gaisl T, Bratton DJ, Kohler M. The impact of obstructive sleep apnoea on the aorta. Eur Respir J. 2015 Aug;46(2):532-44.

8.AApostolakis E, Akinosoglou K. What's new in the biochemical diagnosis of acute aortic dissection: problems and perspectives. Med Sci Monit. 2007;13(8):RA154-RA158.

9.Sampol G, Romero O, Salas A, et al. Obstructive sleep apnea and thoracic aorta dissection. Am J Respir Crit Care Med. 2003; 168(12): 1528–1531.

10.Hata M, Yoshitake I, Wakui S, et al. Sleep disorders and aortic dissection in a working population. Surg Today. 2012; 42(4): 403–405.

11.Saruhara H, Takata Y, Usui Y, Shiina K, Hashimura Y, Kato K, Asano K, Kawaguchi S, Obitsu Y, Shigematsu H, Yamashina A. Obstructive sleep apnea as a potential risk factor for aortic disease. Heart Vessels. 2012 Mar;27(2):166-73.

12.Netchitaïlo M, Destors M, Bosc C, Pépin JL, Tamisier R. Syndrome d’apnées du sommeil. Stratégies diagnostiques dans les différents contextes cliniques [Obstructive sleep apnea syndrome. Diagnostic strategies in various clinical settings]. Presse Med. 2017;46(4):404-412.

13.Wang L, Chen J, Li G, et al. The Prevalence of Sleep Apnea in Type B Aortic Dissection: Implications for False Lumen Thrombosis. Sleep. 2017;40(3):71.

14.Sun G, Yang Y, Chen Z, et al. Neutrophil to Lymphocyte Ratio Predicts Outcome of Stroke by Cervicocranial Arterial Dissection. Front Med (Lausanne). 2020;7:598055.

37815.Sbarouni E, Georgiadou P, Kosmas E, Analitis A, Voudris V. Platelet to lymphocyte ratio in acute aortic 379dissection. J Clin Lab Anal. 2018;32(7):e22447.
38016.Itagaki R, Kimura N, Mieno M, et al. Characteristics and Treatment Outcomes of Acute Type A Aortic 381Dissection With Elevated D-Dimer Concentration. J Am Heart Assoc. 2018;7(14):e009144.
38217.Kitada, S., Akutsu, K., Tamori, Y., Yoshimuta, T., Hashimoto, H., & Takeshita, S. (2008). Usefulness of 383fibrinogen/fibrin degradation product to predict poor one-year outcome of medically treated patients with 384acute type B aortic dissection. The American journal of cardiology, 101, 1341–1344.
38518.Sbarouni E, Georgiadou P, Analitis A, Voudris V. Significant changes in platelet count, volume and size 386in acute aortic dissection. Int J Cardiol. 2013;168: 4349-4350.
38719.Sampol G, Romero O, Salas A, et al. Obstructive sleep apnea and thoracic aorta dissection. Am J Respir 388Crit Care Med. 2003;168):1528-1531.
38920.Hagan PG, Nienaber CA, Isselbacher EM, et al. The International Registry of Acute Aortic Dissection 390(IRAD): new insights into an old disease. JAMA. 2000;283: 897-903.
39121.Saruhara H, Takata Y, Usui Y, et al. Obstructive sleep apnea as a potential risk factor for aortic disease. 392Heart Vessels 2012; 27:166e73.
39322.Brooks D, Horner RL, Kozar LF, Render-Teixeira CL, Phillipson EA. Obstructive sleep apnea as a cause 394of systemic hypertension. Evidence from a canine model. J Clin Invest. 1997;99(1):106-109.
39523.Peker Y, Hedner J, Norum J, Kraiczi H, Carlson J. Increased incidence of cardiovascular disease in 396middle-aged men with obstructive sleep apnea: a 7-year follow-up. Am J Respir Crit Care Med. 3972002;166:159-165.
39824.Suzuki M, Ogawa H, Okabe S, et al. Digital recording and analysis of esophageal pressure for patients 399with obstructive sleep apnea-hypopnea syndrome. Sleep Breath 2005; 9: 64–72.
40025.Rhoades RA, Bell DR, eds. Medical Physiology: Principles for Clinical Medicine. 4th Edn. Philadelphia, 401Lippincott Williams and Wilkins, 2013.
40226.Ryan S, Taylor CT and McNicholas WT. Selective activation of inflammatory pathways by intermittent 403hypoxia in obstructive sleep apnea syndrome. Circulation 2005; 112: 2660–2667.
40427.Liu X, Wang G, Zhang T. The analysis of the levels of plasma inflammation-related cytokines and 405endotoxins in patients with acute aortic dissection. Clin Hemorheol Microcirc. 2020;76(1):1-7.
40628.Cuschieri J, Bulger E, Schaeffer V, et al. Early elevation in random plasma IL-6 after severe injure is 407associated with development of organ failure. Shock. 2010;34(4):346.
40829.del Porto F, Proietta M, Tritapepe L, et al. Inflammation and immune response in acute aortic 409dissection. Ann Med. 2010;42(8):622-629.

41030.He R, Guo DC, Estrera AL, et al. Characterization of the inflammatory and apoptotic cells in the aortas of 411patients with ascending thoracic aortic aneurysms and dissections. J Thorac Cardiovasc Surg. 4122006;131(3):671-678.
4133.1Li M, Luo N, Bai Z, et al. A canine model of multiple organ dysfunction following acute type-A aortic 414dissection. Surg Today. 2012;42(9):876.
41532.Bai Z, Gu J, Shi Y, Meng W. Effect of inflammation on the biomechanical strength of involved aorta in 416type A aortic dissection and ascending thoracic aortic aneurysm: An initial research. Anatol J Cardiol. 4172018;20(2):85-92.
41833.Bhat T, Teli S, Rijah J, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert 419Rev Cardiovasc Ther 2013;11:55-9
42034.Guasti L, Dentali F, Castiglioni L, et al. Neutrophils and clinical outcome in patients with acute coronary 421syndromes and/or cardiac revascularization. A systemic review on more than 34000 subjects. Thromb 422Haemost 2011;16:591-9
42335.Ommen SR, Gibbons RJ, Hodge DO, Thomson SP. Usefulness of the lymphocyte concentration as a 424prognostic marker in coronary artery disease. Am J Cardiol. 1997;79(6):812-814.
42536.Arbel Y, Finkelstein A, Halkin A, et al. Neutrophil/lymphocyte ratio is related to the severity of coronary 426artery disease and clinical outcome in patients undergoing angiography. Atherosclerosis. 2012;225(2):456-427460.
42837.Park JJ, Jang HJ, Oh IY, et al. Prognostic value of neutrophil to lymphocyte ratio in patients presenting 429with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Am J 430Cardiol. 2013;111(5):636-642.
43138.Sbarouni E, Georgiadou P, Analitis A, Voudris V. High neutrophil to lymphocyte ratio in type A acute 432aortic dissection facilitates diagnosis and predicts worse outcome. Expert Rev Mol Diagn. 2015;15(7):965-433970.
43439.Zhang J, Jiang Y, Gao C, Feng J, Wang A. Risk factors for hospital death in patients with acute aortic 435dissection. Heart Lung Circ. 2015;24(4):348-353.
43640.Azab B, Torbey E, Singh J, et al. Mean platelet volume/platelet count ratio as a predictor of long-term 437mortality after non-ST-elevation myocardial infarction. Platelets. 2011;22(8):557-566.
4384.1Milne AA, Adam DJ, Murphy WG, Ruckley CV. Effects of asymptomatic abdominal aortic aneurysm on 439the soluble coagulation system, platelet count and platelet activation. Eur J Vasc Endovasc Surg. 4401999;17(5):434-4

442.Li DZ, Chen QJ, Sun HP, et al. Mean platelet volume to platelet count ratio predicts in-hospital complications and long-term mortality in type A acute aortic dissection. Blood Coagul Fibrinolysis. 2016;27(6):653-659.
443.Dong J, Duan X, Feng R, et al. Diagnostic implication of fibrin degradation products and D-dimer in aortic dissection. Sci Rep. 2017;7:43957.
444.Sodeck G, Domanovits H, Schillinger M, et al. D-dimer in ruling out acute aortic dissection: a systematic review and prospective cohort study. Eur Heart J. 2007;28(24):3067-3075.
445.Gaisl T, Bratton DJ, Kohler M. The impact of obstructive sleep apnoea on the aorta. Eur Respir J. 2015;46(2):532-544.
446.Sampol G, Romero O, Salas A, et al. Obstructive sleep apnea and thoracic aorta dissection. Am J Respir Crit Care Med. 2003;168(12):1528-1531.
447.Zhang X, Zhang T, Zhang X, et al. Obstructive sleep apnea syndrome: a risk factor for Stanford's type B aortic dissection. Ann Vasc Surg. 2014;28(8):1901-1908.