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ORIGINAL ARTICLE

Stepped approach for prediction of syndrome Z in patients attending sleep clinic: a north Indian hospital-based study

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Abstract
Purpose Syndrome Z is the occurrence of metabolic syndrome (MS) with obstructive sleep apnea. Knowledge of its risk factors is useful to screen patients requiring further evaluation for syndrome Z.
Methods Consecutive patients referred from sleep clinic undergoing polysomnography in the Sleep Laboratory of AIIMS Hospital, New Delhi were screened between June 2008 and May 2010, and 227 patients were recruited. Anthropometry, body composition analysis, blood pressure, fasting blood sugar, and lipid profile were measured. MS was defined using the National Cholesterol Education Program (adult treatment panel III) criteria, with Asian cutoff values for abdominal obesity.
Results Prevalence of MS and syndrome Z was 74% and 65%, respectively. Age, percent body fat, excessive daytime sleepiness (EDS), and ΔSaO_2 (defined as difference between baseline and minimum SaO_2 during polysomnography) were independently associated with syndrome Z. Using a cutoff of 15% for level of desaturation, the stepped predictive score using these risk factors had sensitivity, specificity, positive predictive value, and negative predictive value of 75%, 73%, 84%, and 61%, respectively for the diagnosis of syndrome Z. It correctly characterized presence of syndrome Z 75% of the time and obviated need for detailed evaluation in 42% of the screened subjects.
Conclusions A large proportion of patients presenting to sleep clinics have MS and syndrome Z. Age, percent body fat, EDS, and ΔSaO_2 are independent risk factors for syndrome Z. A stepped predictive score using these parameters is cost-effective and useful in diagnosing syndrome Z in resource-limited settings

Keywords Metabolic syndrome · Obstructive sleep apnea · Syndrome Z · Prediction · Risk factors · North Indian

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Introduction

Obstructive sleep apnea (OSA) is associated with various cardiovascular risk factors [1] and increased cardiovascular morbidity and mortality [2, 3]. The co-occurrence of cardiovascular risk factors such as insulin resistance, dyslipidemia, hypertension, and obesity is called metabolic syndrome (MS) [4]. Studies have shown that OSA is associated with hypertension [5, 6], insulin resistance [7, 8], dyslipidemia [9], and metabolic syndrome [10] as a whole. Sharma et al. observed the prevalence of MS to be 77% and 40% in patients with and without OSA, respectively [11] in a north Indian community-based study. However, obesity is considered an important confounder in this relationship due to its independent association with OSA and the components of MS [12–14].

The co-occurrence of OSA with MS is known as syndrome Z. Not much data are available on the prevalence and risk factors of syndrome Z. This knowledge is important given the possible synergistic effect of MS and OSA on cardiovascular risk. A study from Singapore showed a 96% prevalence of syndrome Z in patients with MS [15]. An Indian community-based study showed a prevalence of 4.5% [11]. Diagnosis of syndrome Z is laborious and expensive requiring overnight polysomnography and fasting blood tests.

The present study was performed to determine the prevalence and risk factors of syndrome Z and MS in an urban north Indian population presenting to the sleep clinic with symptoms of OSA. We further attempted to calculate a score to predict presence of syndrome Z suitable for resource-limited settings.

Methods

Consecutive patients referred to the sleep laboratory for polysomnography (PSG) from the sleep-related breathing disorders clinic of All India Institute of Medical Sciences (AIIMS) hospital, New Delhi between June 2008 and May 2010 were evaluated for enrolment. Males and females, aged 30–65 years and naïve to CPAP treatment were included. Patients having hypothyroidism, chronic renal failure, chronic liver disease, coronary artery disease, and left ventricular dysfunction were excluded. Approval was obtained from the AIIMS ethics committee, and a written informed consent was taken from each participant.

Sleep assessment

All subjects underwent overnight 16-channel PSG conducted by trained technicians using Rembrandt 7.3 version PSG machine (Medicare Technologies, USA) as described previously [16]. Sleep data were scored manually according to standard criteria [17] by technicians blinded to clinical data. Apnea and hypopnea were defined as per the recommendations of the American Academy of Sleep Medicine [18]. OSA was defined as apnea–hypopnea index (AHI)>5. Excessive daytime somnolence (EDS) was defined as a score greater than 10 on the Epworth Sleepiness Scale (ESS).

General assessment, anthropometry, and blood pressure measurements

Blood pressure, body weight, body composition analysis, neck circumference (NC), neck length, waist circumference, hip circumference and biceps, triceps, subscapular, and suprailiac skin fold thicknesses were measured as described previously [19]. Percentage predicted neck circumference (PPNC) was computed using Davies and Strading formula as, PPNC=(1,000×NC)/[(0.55×Height)+310] [20]. Habitual smoking and drinking were defined as smoking or alcohol intake for at least 3 days a week, respectively.

Biochemical tests

At the end of the sleep study the next morning, blood samples were taken, and the following tests were done: fasting blood sugar (by glucose oxidase method), fasting plasma insulin (by ELISA), and lipid profile [total cholesterol, triglyceride, and HDL cholesterol by immunocolorimetric assay, LDL cholesterol calculated using Friedewald equation [21]].

Metabolic syndrome

Metabolic syndrome was defined as per the National Cholesterol Education Program—Adult Treatment Panel III criteria [22], with the cutoff for defining abdominal obesity taken as waist circumference ≥90 cm in males and ≥80 cm in females as recommended by the World Health Organization for South Asians [23, 24].

Statistical analysis

Statistical analysis was performed using Stata 9.2 for Windows (Stata Corporation, College Station, TX, USA). Continuous variables were summarized as mean±SD or median (range) and categorical variables as proportions, *n* (%). Comparison between groups was done by Student's *t* test and Mann–Whitney test for parametric and nonparametric variables, respectively and chi-square test for categorical variables. A p value of <0.05 was considered statistically significant. Prevalence of MS and syndrome Z were calculated with 95% confidence intervals (CI). Multivariable analysis using stepwise binary logistic regression was done with MS as the outcome variable. Component variables of MS were excluded from this analysis. Parameters differing between groups at $p<0.1$ significance level on univariate analysis were included. A similar analysis was done for syndrome Z. Once risk factors for syndrome Z were derived, an equation was constructed with the adjusted odds ratio to develop a scoring system, after excluding PSG variables. Receiver operating characteristic (ROC) curve was drawn. A cutoff level with a high sensitivity (95%) was chosen and subjects categorized as high or low risk for syndrome Z. ROC curve was then plotted for maximum oxygen desaturation in the high-risk group patients. A cutoff for the level of desaturation that had a high specificity and acceptable sensitivity was chosen. Patients with desaturation above this cutoff were designated as having syndrome Z. Finally, cross-tabs were constructed for the whole group together and sensitivity, specificity, positive, and negative predictive values were calculated.

Results

Two hundred and twenty-seven patients were studied. Of these, 187 (82%) had OSA. MS was present in 168 (74%) [95% CI, (68–79%)] the subjects and 148 (65%) [95% CI, (59–71%)] had syndrome Z.

Associations and risk factors for metabolic syndrome

The characteristics of patients with MS are shown in Table 1. They were more likely to be older, female, have EDS, spend higher percent of sleep time in hypoxia (SpO_2 <90%), have more desaturation during sleep (ΔSaO_2: defined as baseline saturation−minimum saturation during sleep study), and have higher AHI compared to non-MS subjects. They were more obese with higher body fat content. Age, gender, body mass index (BMI), biceps skin fold thickness, PPNC, percent body fat, fat mass, AHI, ESS, SpO_2<90%, and ΔSaO_2 were included in the multivariate analysis. Increasing age, SpO_2<90%, and percent body fat were independent predictors of MS (Table 2).

Associations and risk factors for syndrome Z

The characteristics of patients with syndrome Z are shown in Table 3. Patients with syndrome Z were more likely to have EDS, be smokers, have obesity with higher body fat content and PPNC, and have higher AHI, SpO_2<90%, and ΔSaO_2 values. Age, BMI, biceps skin fold thickness, PPNC, percent body fat, fat mass, EDS, SpO_2<90%, ΔSaO_2, minimum saturation, and smoking status were included in the multivariate analysis. AHI was excluded as it was a defining criterion for syndrome Z. Increasing age,

Table 1 Comparison of subjects with and without metabolic syndrome

Characteristic	Metabolic syndrome present (n=167)	Metabolic syndrome absent (n=60)	OR (95% CI)	P value
Age (year)	46±9	43±10	1.04 (1.00–1.07)	.029
Male (%)	125 (75)	53 (88)	0.39 (0.17–0.93)	.034
Epworth sleepiness score[a]	12(6–15)	9 (5–15)	1.06 (1.00–1.12)	.034
Excessive daytime sleepiness	112 (67)	24 (40)	3.05 (1.66–5.62)	<.001
Smokers	36 (22)	9 (15)	1.56 (0.70–3.46)	.277
Alcohol consumers	36 (22)	15 (25)	0.82 (0.41–1.65)	.584
Apnea–hypopnea index (events/h)[a]	38 (13–51)	10 (1–31)	1.03 (1.01–1.04)	<.001
SpO_2<90% (%)[a,b]	9.8 (2.7–32.9)	1.6 (0.1–8.5)	1.05 (1.02–1.08)	<.001
Minimum saturation (%)	71.4±5.4	80.2±10.9	0.95 (0.92–0.97)	<.001
ΔSaO_2 (%)[a,c]	22.4 (13.6–32.6)	13.2 (7.9–22.7)	1.06 (1.03–1.09)	<.001
ΔSaO_2<10	19 (11)	19 (32)	1.00	
ΔSaO_2≥10 and <20	52(31)	22 (37)	2.4 (1.05–5.30)	.040
ΔSaO_2≥20 and <30	50 (30)	11 (18)	4.5 (1.8–11.3)	.001
ΔSaO_2≥30	54 (28)	8 (13)	5.8 (2.1–15.4)	<.001
BMI (kg/m^2)	33.5±7.0	27.7±6.9	1.08 (1.02–1.13)	.005
BMI<25	9 (5.4)	15 (25)	1.00	
BMI 25–30	55 (32.9)	20 (33.3)	4.58 (1.77–12.11)	.002
BMI>30	103 (61.7)	25 (41.7)	6.87 (2.69–17.49)	<.001
Percent body fat	33.4±7.1	30.2±7.4	1.10 (1.05–1.14)	<.001
Fat mass (kg)[a]	27 (22–35)	21 (16–28)	1.06 (1.03–1.10)	<.001
PPNC (%)	99±9	96±10	1.03 (1.00–1.07)	.060
TSFT (mm)	20±8	19±8	1.02 (.99–1.06)	.224
SSFT (mm)	29±7	27±8	1.02 (0.98–1.07)	.249
BSFT (mm)	15±6	12±6	1.08 (1.03–1.14)	.004
SIFT (mm)	35±8	33±8	1.03 (0.99–1.07)	.164

BMI body mass index, *PPNC* percentage predicted neck circumference, *TSFT* triceps skin fold thickness, *SSFT* subscapular skin fold thickness, *BSFT* biceps skin fold thickness, *SIFT* suprailiac skin fold thickness

[a] Data presented as median (range). All other data presented as mean±SD or n (%)

[b] SpO_2<90% (%)=percentage of total sleep time spent in hypoxia (SpO_2<90%)

[c] ΔSaO_2 (%)=baseline saturation−minimum saturation during sleep study

Table 2 Risk factors for metabolic syndrome

Characteristic	Adjusted OR (95% CI)	*P* value
Age (for 1 year increase)	1.04 (1.00–1.08)	.034
SpO_2<90% (%)[a] (for 1% increase)	1.04 (1.01–1.07)	.003
Percent body fat (%) (for 1% increase)	1.09 (1.04–1.14)	<.001

[a] SpO_2<90% (%)=percentage of total sleep time spent in hypoxia (SpO_2<90%)

percent body fat, EDS, and ΔSaO_2 were independent predictors (Table 4).

Prediction score for syndrome Z

Using age, percent body fat, and EDS the following score was derived: score=(EDS×1.67)+(percent body fat×0.07)+(age×0.03) where EDS=1 if present and 0 if absent. This score had an area under the ROC curve of 77.5% (95% CI, 70.9–84.0%) (Fig. 1). A cutoff value of 3.3 had sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 95%, 29%, 71%, and 74%, respectively. One hundred ninety-six patients were deemed high risk for syndrome Z by this score. Degree of desaturation was plotted on the ROC curve for these subjects with syndrome Z as binary variable (Fig. 2). AUC was 75.0% (95% CI, 66.9–83.1%). With a desaturation cutoff of 15%, the sensitivity, specificity, PPV, and NPV for diagnosis of syndrome Z for the whole group was 75%, 73%, 84%, and 61%, respectively, and 132 patients were classified as syndrome Z.

Discussion

The 74% prevalence of MS seen in this study is higher than the 43% prevalence in our previous community-based study

Table 3 Comparison of subjects with and without syndrome Z

Characteristic	Syndrome Z present (*n*=148)	Syndrome Z absent (*n*=79)	OR (95% CI)	*P* value
Age (year)	46±8	44±9	1.03 (0.99–1.06)	.103
Male (%)	116 (78)	62 (78)	0.99 (0.51–1.93)	.986
Epworth sleepiness score[a]	12 (9–16)	7(4–13)	1.12 (1.06–1.18)	<.001
Excessive daytime sleepiness	109 (74)	27 (34)	5.38 (2.98–9.7)	<.001
Smokers	35 (24)	10 (13)	2.14 (1.00–4.59)	.051
Alcohol consumers	36 (24)	15 (19)	1.37 (0.70–2.70)	.360
Apnea–hypopnea index (events/hr)[a]	42 (21–55)	5 (1–20)	1.05 (1.04–1.07)	<.001
SpO_2<90% (%)[a,b]	12.5 (4.1–35.8)	1 (0.1—6.7)	1.07 (1.04–1.11)	<.001
Minimum saturation (%)	69±15	82±10	0.92 (0.89–0.94)	<.001
ΔSaO_2 (%)[a,c]	23.0 (15.7–33.6)	11.6 (7.6–21.4)	1.10 (1.06–1.14)	<.001
ΔSaO_2<10	8 (5)	30 (38)	1.00	
ΔSaO_2≥10 and <20	45 (30)	29 (37)	5.82 (2.34–14.44)	<.001
ΔSaO_2≥20 and <30	50 (34)	11 (14)	17.05 (6.16–47.13)	<.001
ΔSaO_2≥30	45 (30)	9 (11)	18.75 (6.51–54.04)	<.001
BMI (kg/m^2)	33.8±6.8	30.2±7.6	1.09 (1.04–1.12)	.001
BMI <25	6 (4)	18 (23)	1.00	
BMI 25-30	44 (30)	31 (39)	4.26 (1.52–11.95)	.006
BMI >30	98 (66)	30 (38)	9.80 (3.57–26.92)	<.001
Percent body fat	33.4±9.1	27.6±9.3	1.08 (1.04–1.12)	<.001
Fat mass (kg)	31.5±14.1	23.4±12.0	1.06 (1.03–1.09)	<.001
PPNC (%)	100±8	95±10	1.08 (1.04–1.11)	<.001
TSFT (mm)	20±8	19±9	1.02 (.99–1.05)	.273
SSFT (mm)	29±7	27±9	1.03 (0.99–1.07)	.131
BSFT (mm)	15±6	12±6	1.09 (1.04–1.15)	.001
SIFT (mm)	35±8	34±9	1.03 (0.99–1.06)	.149

[a] Data presented as median (range). All other data presented as mean±SD or n (%)

[b] SpO_2<90% (%)=percentage of total sleep time spent in hypoxia (SpO2<90%)

[c] ΔSaO_2 (%)=baseline saturation−minimum saturation during sleep study

BMI body mass index, *PPNC* percentage predicted neck circumference, *TSFT* triceps skin fold thickness, *SSFT* subscapular skin fold thickness, *BSFT* biceps skin fold thickness, *SIFT* suprailiac skin fold thickness

Table 4 Risk factors for syndrome Z

Characteristic	Adjusted OR (95% CI)	*P* value
Age (for 1 year increase)	1.04 (1.00–1.09)	.051
Excessive daytime sleepiness	3.95 (2.01–7.78)	<.001
Percent body fat (%) (for 1% increase)	1.07 (1.02–1.11)	<.001
ΔSaO_2 (%)[a]		
ΔSaO_2 <10	1.00	
ΔSaO_2 10–20	6.31 (2.31–17.24)	<.001
ΔSaO_2 20–30	11.24 (3.75–33.70)	<.001
ΔSaO_2 >30	11.84 (3.78–37.03)	<.001

[a] ΔSaO_2 (%)=baseline saturation−minimum saturation during sleep study

[11]. The prevalence of syndrome Z in this study was 65% compared to 4.5% in that study. Our study being sleep clinic-based is expected to have a higher prevalence due to referral bias. Also, average BMI in our study was much higher in both MS and non-MS groups, and 82% of our patients had OSA compared to 27% in that study. The only previous hospital-based study on syndrome Z [15] had a 96% prevalence of syndrome Z. This is because all their patients had MS, while in our population only 74% patients had MS.

Most of the factors associated with MS on univariate analysis, including age, female gender, BMI, AHI, ESS, SpO_2<90%, and ΔSaO_2 have been shown be associated with MS in our community-based study [11]. In addition, some more parameters of obesity such as BSFT, PPNC, percent body fat, and fat mass were found to be significantly associated with MS. To determine independent association of these factors with MS and the role of obesity

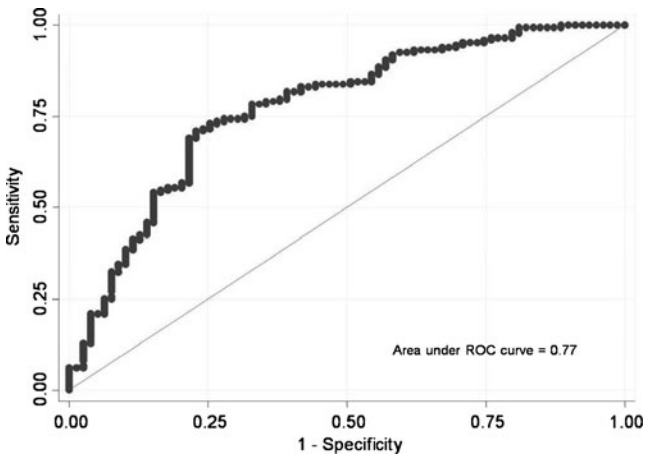

Fig. 1 Receiver–operating characteristics curve plotted for the equation derived from age, percent body fat, and excessive daytime somnolence to evaluate its utility in prediction of syndrome Z

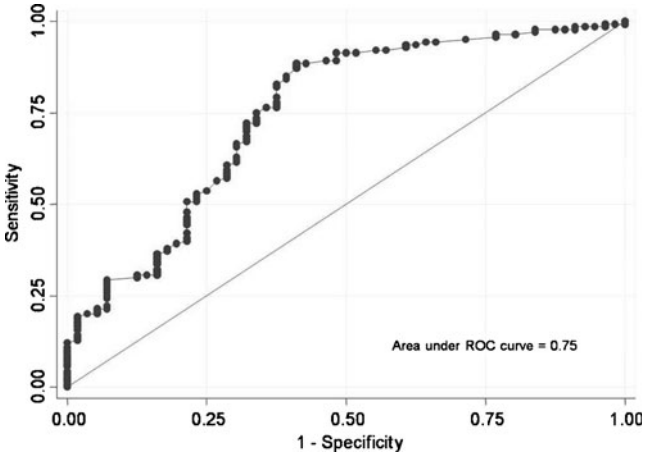

Fig. 2 Receiver–operating characteristics curve plotted for the level of desaturation in patients with a score above 3.3 on the equation derived from age, percent body fat, and excessive daytime somnolence to evaluate its utility in prediction of syndrome Z

in MS, stepwise logistic regression was done. Age, percent body fat, and SpO_2<90% were independently associated with MS. After removing percent body fat for its possible masking role on BMI, female gender, AHI, and ΔSaO_2 were also independent predictors of MS (data not shown). BMI, the universally used tool to define obesity, was not a predictor. Therefore, obesity alone cannot account for the relationship between OSA and MS, although a high body fat composition does play a significant role. This suggests that percent body fat may be a better measure than BMI in screening patients for MS and syndrome Z. Every 1% increase in percent body fat increases the risk of MS by 9%, while every 1 year increase in age, increases the risk of MS by 4%. Every unit increase in SpO_2<90% increases the risk of MS by 4%. These results are in agreement with our previous study [11]. Female gender predisposes to MS, despite females having a lower risk of OSA due to lack of testosterone and protective effect of female hormones on sleep disordered breathing. Our previous study [11] found a similarly higher incidence of MS in females. This is probably because females have a higher percent body fat, which was an independent risk factor for MS in the present study. Another possibility is that men might be coming more often to the hospital with OSA as it impairs their occupational capabilities while women may come to the hospital for obesity-related complaints and are subsequently diagnosed as having MS. The independent association of AHI, SpO_2<90%, and ΔSaO_2 with MS suggests the central role of hypoxia and OSA in the development of MS. This is supported by previous human [25] and mice [26] studies showing the role of intermittent hypoxia in the development of insulin resistance and MS.

BMI, biceps skin fold thickness, PPNC, percent body fat, fat mass, ESS, EDS, AHI, SpO2<90%, ΔSaO_2,

minimum saturation, and smoking status were found to be associated with syndrome Z on univariate analysis. The absence of an association of syndrome Z with gender could be because females are more prone to MS while males are more prone to OSA, thereby negating the effect of gender on syndrome Z. Smoking status was associated with syndrome Z, but not MS, possibly due to its association with OSA [19, 27]. Multivariate analysis showed that a 1-year increase in age increased risk of syndrome Z by 4% while presence of EDS increased the risk fourfold. Every unit increase in percent body fat increased risk by 7% and increasing desaturation increases risk six-, 11-, and 12-fold for ΔSaO_2 10–20%, 20–30%, and >30% compared to ΔSaO_2<10%. This reiterates the role of hypoxia and body fat in development of both MS and syndrome Z. Age is a common risk factor for OSA [19] and MS [11] and thus a risk factor for syndrome Z. EDS is a risk factor probably because of its association with OSA [28]. As seen with MS, BMI was not an independent predictor for syndrome Z.

With a cutoff of 3.3, the scoring system required only 196 of the 227 patients to be further evaluated, allowing 31 (14%) of the patients to be screened out in the clinic itself. Only eight patients (3.5% of the sample) were falsely excluded. In the second step, overnight oximetry data were used because performing PSG for all high-risk cases would not be cost-effective due to low specificity at this cutoff (56 of 196 high-risk cases did not have syndrome Z). With a cutoff of 15% desaturation in the second step, the score correctly differentiated syndrome Z from non-syndrome Z 75% of the time. Only 132 of the 227 patients (58%) seen in the outpatient clinic would need PSG and blood testing by this approach. A high PPV of 84% resulted in only 21 false positives among these 132 patients. This method ensures that patients finally selected for PSG and blood testing will only be those with a high probability of actually having syndrome Z. This stepped approach, consisting of easily measured demographic, anthropometric, and oximetry parameters can be used as a tool to screen individuals requiring further evaluation for syndrome Z, thereby decreasing the cost and work load of performing a full night polysomnography and fasting blood tests.

We recommend that in resource-limited settings, where facilities for PSG are costly and limited with long waiting lists, patients be screened on the basis of this score and overnight oximetry performed if score is more than 3.3. If maximal desaturation is more than 15% then PSG and blood testing should be done. If score is less than 3.3, the patient can be safely reassured and investigations avoided. Since the sensitivity of the score is only 75%, in patients with score more than 3.3 but desaturation less than 15% we recommend evaluation for MS by blood investigations with PSG being considered on a case by case basis.

Limitations of this study include: (1) prone to referral bias with more symptomatic patients being referred to the hospital; (2) matching for confounders, chiefly obesity, age, and gender, was not done. Since this would have led to a substantially smaller sample size of the control group with reduction in the statistical power of the study, we felt a regression analysis with a higher sample size and statistical power would be better; (3) the scoring system is valid only for symptomatic patients presenting to hospitals and not for screening in the community.

The strengths of the present study include (1) a large sample size of 227 patients; (2) the overnight, supervised, in-hospital PSG study was performed in all patients for diagnosis, and exclusion of OSA; (3) AHI cutoff of ≥5 events per hour was used to define OSA as per the results of the Sleep Heart Health Study; and (4) compared to previous community-based studies [11, 29], we have recruited a more symptomatic group of patients, allowing extrapolation to the patient population seen in daily clinical practice.

This is the first hospital-based prospective study to investigate the risk factors of MS and syndrome Z from India. They are associated with OSA, increasing age and high body fat percent independent of BMI. Prevalence of MS and syndrome Z in patients attending sleep clinics for symptoms of OSA is very high. Therefore, these patients should be screened as early detection and correction may result in significant decrease in morbidity and mortality. The stepped prediction approach for syndrome Z is useful and cost-effective in identifying patients requiring further evaluation, especially in resource-limited settings. Further prospective studies in other cohorts will be required to validate the results of this scoring system.

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