Original Research

Clinical Characteristics of Patients with Acute Coronary Syndrome at High Clinical Suspicion for Obstructive Sleep Apnea Syndrome

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Introduction: The risk of a cardiovascular event increases with the number of cardiovascular risk factors. The aim of this study was to identify patients with acute coronary syndromes (ACS) who were at high clinical suspicion for obstructive sleep apnea syndrome (OSAS). We also report the clinical characteristics of ACS patients at high clinical suspicion for OSAS.

Methods: We studied 158 consecutive patients who satisfied the entry criteria (mean age 57.1 ± 8.7 years, 68% males) and were admitted to a tertiary university hospital. The risk of OSAS was assessed using the Berlin questionnaire. In addition, all patients were required to have excessive sleepiness as demonstrated by a score >10 on the Epworth Sleepiness Scale (ESS).

Results: Fifty four (34.2%) patients were at high clinical suspicion. On admission, patients at clinical suspicion for OSAS had significantly more often a history of hypertension (92.6% vs. 55.8%, $p<0.0001$) or diabetes mellitus (37% vs. 15.4%, $p=0.0049$); significantly higher mean ESS (14.83 ± 3.02 vs. 5.83 ± 3.33, $p<0.0001$), systolic blood pressure (149.9 ± 34.2 vs. 128.4 ± 23.6 mmHg, $p<0.0001$), diastolic blood pressure (87.7 ± 17.4 vs. 76.2 ± 12.1 mmHg, $p<0.0001$), and body mass index (32.3 ± 4.6 vs. 27 ± 3.8 kg/m^2, $p<0.0001$); and a lower glomerular filtration rate (79.5 ± 21.2 vs. 87.5 ± 22.2 ml/min/1.73 m^2, $p=0.048$). Patients at high clinical suspicion for OSAS more often had onset of acute chest pain between midnight and 5.59 am compared to the patients at low clinical suspicion (42.6% vs. 26%; $p<0.05$). The mortality (7.4% vs. 1%; $p=0.03$) was greater in patients at high clinical suspicion.

Conclusions: This study demonstrates that one out of every three ACS patients was diagnosed with a high clinical suspicion for OSAS. The prevalence of cardiovascular risk factors among ACS patients at high clinical suspicion for OSAS was high when compared with patients at low clinical suspicion. This finding calls for physicians to perform routine screening and individual evaluation of myocardial infarction patients for sleep disorders, especially when they are obese, or have hypertension or chest pain in the night hours.

The risk of a cardiovascular event increases with the number of cardiovascular risk factors, such as hypertension, diabetes, obesity, dyslipidemia or sleep disordered breathing. The prevalence of sleep disordered breathing among patients with cardiovascular disease has been shown to be up to 3 times greater than in the population without.[1-4] Obstructive sleep apnea syndrome (OSAS) is the most common type of sleep apnea, associated with a 70% relative increase in the risk of cardiovascular morbidity and mortality.[5] OSAS is present in a large proportion of patients with hypertension and in those with other cardiovascular disorders, including stroke, atrial fibrillation and coronary artery disease. The

blood pressure changes, hypoxemia, and sympathetic activation frequently observed in OSAS patients may lead to plaque rupture, coronary thrombosis, and, as a consequence, to acute myocardial infarction. OSAS is characterized by repetitive interruption of ventilation during sleep, caused by collapse of the pharyngeal airway. Screening of patients for OSAS can be accomplished by several different methods.

The aim of this study was to use the Berlin Questionnaire (BQ) and Epworth Sleepiness Scale (ESS) to identify patients at high clinical suspicion for obstructive sleep apnea syndrome (OSAS) among consecutively admitted patients with acute coronary syndromes (ACS) who had undergone invasive treatment. We also report the clinical characteristics of the study population.

Methods

Study design, setting, and selection of patients

We studied 158 consecutive patients who satisfied the entry criteria (mean age 57.1 ± 8.7 years, 68% males) and were admitted to our tertiary university hospital, which provides 24-hour Cardiology Intensive Care Unit services. We excluded post-cardiac-arrest patients. The study protocol was approved by the Regional Ethics Committee. Informed consent was obtained from each patient before participation in the study.

The initial screening interview addressed patient's cardiovascular risk factors. Every study patient underwent full transthoracic echocardiographic screening between the third and fifth day. The studies were carried out using a Philips iE 33 device with a 2.5-3.5 MHz transthoracic probe.

Evaluation of clinical suspicion for OSAS

The risk of OSAS was assessed using the BQ. In addition, all patients in the high clinical suspicion group were required to have excessive sleepiness as demonstrated by a score >10 on the ESS. The content of the BQ and ESS has been previously described in detail.[6,7]

The overnight sleep study was performed only in those patients who had a high clinical suspicion of OSAS. Patients underwent an overnight sleep study using a portable device for diagnosing the sleep disorders (Embletta X30; Flaga, Reykjavik, Iceland) to confirm the OSAS. The data were scored manually according to the recommendations of the American Academy of Sleep Medicine.[8] When the apnea-hypopnea index exceeded 5 per hour the OSAS diagnosis was confirmed. Apnea was defined as a cessation of airflow lasting 10 seconds. Hypopnea was defined as a recognizable transient reduction (but not complete cessation) of breathing for 10 seconds or longer, a decrease of greater than 50% in the amplitude of a validated measure of breathing, or a reduction in amplitude of less than 50% associated with oxygen desaturation of 4% or more.

Endpoint definitions

The primary endpoint of the present study was all-cause mortality during the 30-day follow-up period. The composite endpoint was all-cause mortality during the 30-day follow-up and/or a duration of hospitalization >14 days.

Statistical analysis

All analyses were performed using SAS statistical software version 8.02 (SAS Institute, Inc., Cary, NC). Continuous data are presented as mean ± standard deviation and were compared using the Mann–Whitney test or Student t-test. Categorical variables were compared using either χ^2 or Fisher exact tests. The analysis of variance was used to compare multiple variables. A p-value <0.05 was considered statistically significant, with confidence intervals of 95%.

Results

Characteristics of study patients

The baseline characteristics of the study population are given in Table 1. All study patients had a first myocardial infarction, confirmed by an increase in serum cardiac troponin I concentrations (above 0.1 ng/mL): 105 patients had ST-elevation myocardial infarction, 51 patients had non ST-elevation myocardial infarction, and 2 patients had myocardial infarction in the presence of new-onset left bundle-branch block.

Fifty four (34.2%) of the 158 patients were at high clinical suspicion and 104 (65.8%) at low clinical suspicion for OSAS. On admission, high clinical suspicion OSAS patients were significantly more likely to have a history of hypertension (92.6% vs. 55.8%, $p<0.0001$) and diabetes mellitus (37% vs. 15.4%, $p=0.0049$) compared to the patients at low risk. In

Table 1. Baseline characteristics according to the clinical suspicion of obstructive sleep apnea syndrome.

	Low-clinical suspicion	High-clinical suspicion	p
General characteristics (% or mean ± SD):			
Number of patients	104 (65.8%)	54 (34.2%)	
Age (years)	57.07 ± 9.06	57.21 ± 8.07	0.924
Male	69 (66.3%)	38 (70.4%)	0.738
High risk of obstructive sleep apnea based on Berlin Questionnaire	3 (2.9%)	54 (100%)	<0.0001
Epworth Sleepiness Scale	5.83 ± 3.33	14.83 ± 3.02	<0.0001
Epworth Sleepiness Scale >10	8 (7.7%)	54 (100%)	<0.0001
History of hypertension, n (%)	58 (55.8%)	50 (92.6%)	<0.0001
Diabetes mellitus, n (%)	16 (15.4%)	20 (37%)	0.0049
Dyslipidemia, n (%)	49 (47.1%)	22 (40.7%)	0.582
Smokers, n (%)	59 (56.7%)	28 (51.8%)	0.677
Family history, n (%)	23 (22.1%)	17 (31.5%)	0.275
Characteristics on admission (% or mean ± SD):			
Triglycerides (mg/dL)	148.79 ± 94.59	169.69 ± 69.78	0.007
Low-density lipoprotein (mg/dL)	117.96 ± 36.37	107.57 ± 36.25	0.116
High-density lipoprotein (mg/dL)	44.63 ± 15.33	42.22 ± 12.36	0.332
High sensitivity C-reactive protein (mg/L)	11.06 ± 18.41	24.32 ± 36.47	0.068
Creatine kinase isoenzyme MB mass (ng/mL)	79.76 ± 150.28	52.74 ± 97.27	0.343
Cardiac troponin I (ng/mL)	25.33 ± 46.13	19.97 ± 33.84	0.548
GFR (MDRD), ml/min/1.73 m^2	87.52 ± 22.16	79.5 ± 21.18	0.048
Heart rate, beats/minute	80.48 ± 21.76	83.35 ± 13.74	0.036
Systolic blood pressure, mmHg	128.36 ± 23.57	149.91 ± 34.2	<0.0001
Systolic blood pressure >140 mmHg	18 (20.2%)	31 (57.4%)	<0.0001
Diastolic blood pressure, mmHg	76.18 ± 12.06	87.65 ± 17.49	<0.0001
Diastolic blood pressure >90 mmHg	8 (9%)	17 (31.5%)	0.0013
Body mass index (kg/m^2)	26.99 ± 3.81	32.3 ± 4.63	<0.0001
Body mass index >30 kg/m^2	22 (22.7%)	32 (64%)	<0.0001
Angiography, n (%):			
Multivessel disease	26 (25%)	13 (24.1%)	0.87
2-vessel disease	25 (24%)	8 (14.8%)	0.28
1- vessel disease	44 (42.3%)	25 (46.3%)	0.89
without occlusion	9 (8.7%)	8 (14.8%)	0.35
Characteristics at discharge:			
B-type natriuretic peptide, pg/mL	18.47 ± 22.17	83.41 ± 153.15	0.0001
Hospitalization duration (days)	8.7 ± 4.04	10.4 ± 5.24	0.016

GFR – glomerular filtration rate; MDRD – Modification of Diet in Renal Disease formula.

addition, patients at high clinical suspicion for OSAS had significantly higher mean resting heart rate (83 ± 14 vs. 80 ± 22 beats per minute, p=0.036), systolic blood pressure (149.9 ± 34.2 vs. 128.4 ± 23.6 mmHg, p<0.0001), diastolic blood pressure (87.7 ± 17.4 vs. 76.2 ± 12.1 mmHg, p<0.0001), body mass index (32.3 ± 4.6 vs. 27 ± 3.8 kg/m^2, p<0.0001); higher levels of C-reactive protein (24.3 ± 36.5 vs. 11.1 ± 18.4 mg/L, p=0.068); and significantly lower glomerular filtration rate (79.5 ± 21.2 vs. 87.5 ± 22.2 mL/min/1.73 m^2, p=0.048). There was no statistically significant difference in the patients' mean age (57.07 ± 9.06 vs. 57.21 ± 8.07 years, p=0.924) or the presence of dyslipidemia (47.1% vs. 40.7%, p=0.582). The high clinical suspicion OSAS patients had significantly higher mean triglyceride levels (169.69 ± 69.78 vs. 148.79 ± 94.59 mg/dL, p=0.007)) as compared to the low clinical suspicion patients. There was no statistically significant difference in low-density lipoprotein (117.96 ± 36.37 vs. 107.57 ± 36.25 mg/dL, p=0.116) or high-density lipoprotein (44.63 ± 15.33 vs. 42.22 ± 12.36 mg/dL, p=0.332). There was no statistically significant difference between the subgroups in cardiac troponin I levels (19.97 ± 33.84 vs. 25.33 ± 46.13 ng/mL, p=0.548) or creatine kinase isoenzyme MB mass (52.74 ± 97.27 vs. 79.76 ± 150.28 ng/mL, p=0.343). All measurements were performed on admission in the emergency department.

According to the reported time of onset of acute chest pain experienced by every patient, four subgroups were established (A: midnight - 5.59 am; B: 6 am - 11.59 am; C: noon - 5.59 pm; D: 6 pm - 11.59

pm). Patients admitted to the hospital with a suspected ACS who were at high clinical suspicion for OSAS more often had their onset of acute chest pain between midnight and 5.59 am compared to the patients at low clinical suspicion (42.6% vs. 26%, $p<0.05$). There were no differences in the other three subgroups (Figure 1).

All patients underwent primary percutaneous intervention. None of the patients received thrombolytic therapy. Five (9.2%) patients at high clinical suspicion for OSAS, and 8 (7.7%) patients at low clinical suspicion for OSAS were referred for coronary artery bypass graft surgery.

High clinical suspicion OSAS patients had significantly larger left ventricular diastolic diameter (52.2 ± 7.3 vs. 48.2 ± 5.1 mm, $p=0.01$), a thicker interventricular septum (12.6 ± 2.4 vs. 11.5 ± 1.7 mm, $p=0.0028$), and a higher left ventricular mass index

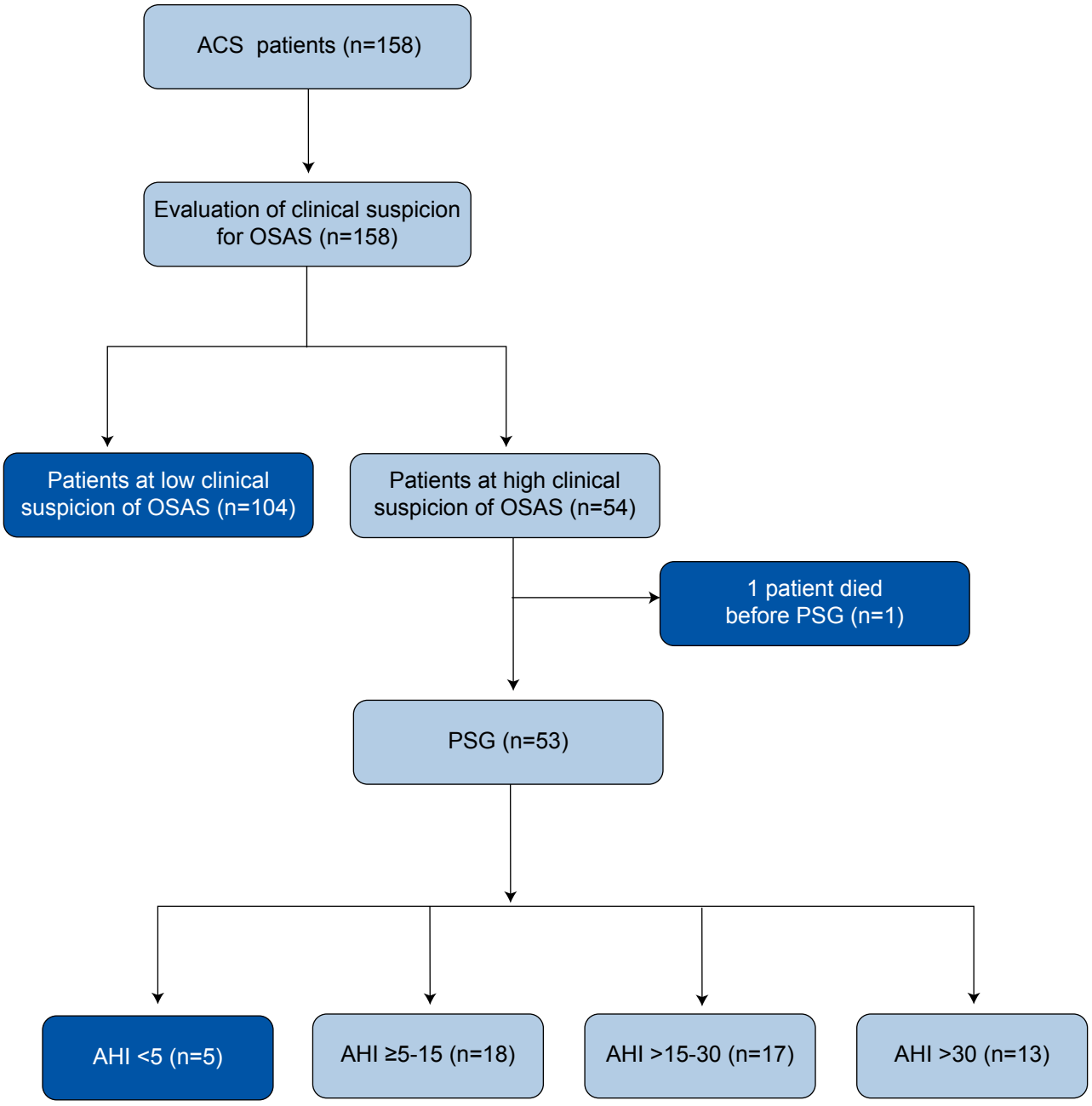

Figure 1. Flow diagram of study participants. ACS – acute coronary syndrome; AHI – apnea/hypopnea index; OSAS – obstructive sleep apnea syndrome; PSG – polysomnography.

(175.9 ± 60.8 vs. 140.6 ± 34 g/m, p=0.0003) compared to the patients at low clinical suspicion. There was no statistically significant difference in left ventricular ejection fraction (49.79 ± 8.75% vs. 49.88 ± 8.73%, p=0.953).

Patients at high clinical suspicion for OSAS had a longer hospitalization duration (10.4 ± 5.2 vs. 8.7 ± 4 days, p=0.0004) and higher mean B-type natriuretic peptide (BNP) levels at the time of their hospital discharge (83.4 ± 153.2 vs. 18.5 ± 22.2 pg/mL, p=0.0001).

In addition, mortality (7.4% vs. 1%, p=0.03), and the composite endpoint (20.4% vs. 5.8%, p=0.01) were more frequent in patients at high clinical suspicion for OSAS.

Confirmation of OSAS

Fifty-three patients underwent an overnight sleep study (one patient of the initial group of 54 died before the overnight sleep study). In total, 48 patients (90.6%) were diagnosed as having OSAS with an apnea-hypopnea index >5. Subsequently, patients were divided into 3 groups, classified according to the results of the sleep study (apnea-hypopnea index) as: mild OSAS in 18 (37.5%) patients, moderate OSAS in 17 (35.4%) patients, and severe OSAS in 13 (27.1%) patients.

Discussion

The results of our studies confirm the previous finding[4] that over 30% of myocardial infarction patients have OSAS. It came to our attention that none of the study patients was ever diagnosed with OSAS. The results of our study strongly reinforce the previous notion, that OSAS is common and under-diagnosed among patients with myocardial infarction.[9,10] All patients should receive education about sleep and proper sleep hygiene, OSAS, and the risks of driving while sleepy.

The BQ and ESS have often been used and reported in their Polish version for predicting OSAS, in a population of over 1000 patients.[11,12] These sleep questionnaires, supported by portable devices, might be very helpful in the risk stratification of ACS patients.

Our study also confirmed previous findings that patients who were at high clinical suspicion for OSAS had significantly higher systolic and diastolic blood pressure on admission. It was also observed that the number of conventional risk factors, such as hypertension and/or diabetes, in patients at high risk of OSAS was higher than in those at low clinical suspicion. It was shown previously that OSAS is associated with poor blood pressure control, especially during the night hours.[13] Nocturnal hypertension is an important parameter that has a poor correlation with office blood pressure values.[14] It requires additional screening, including ambulatory blood pressure monitoring, in patients at high risk—such as those with OSAS. Treatment of OSAS, which includes continuous positive airway pressure as well as intensive pharmacotherapy, may both lower the patient's blood pressure, also during the night hours, and protect his heart from damage. In addition, it has also been found that these patients are more often obese and male. Indeed, results from other studies show that obesity and male sex are clearly risk factors for OSAS. Control of body mass index is frequently recommended as means to improve OSAS among obese patients.[15] The previous results also indicate that obese patients have lower levels of plasma BNP compared to patients with a normal body mass index.[16] Paradoxically, we observed that obese patients at high clinical suspicion of OSAS had a higher mean BNP level at discharge. It has been a long-standing observation that higher levels of BNP at discharge may be a predictor of cardiovascular morbidity and mortality in the long-term observation of OSAS patients.

OSAS is also associated with elevated levels of plasma C-reactive protein, a well known marker of inflammation and of cardiovascular risk.[17] We found

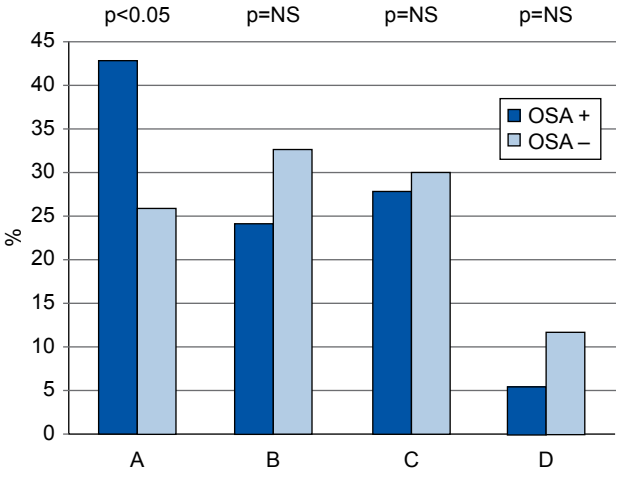

Figure 2. Onset of chest pain according to the clinical suspicion of obstructive sleep apnea syndrome (A: midnight - 5.59 am; B: 6 am - 11.59 am; C: noon - 5.59 pm; D: 6 pm - 11.59 pm).

that the ACS patients at high clinical suspicion for OSAS had higher mean C-reactive protein levels compared to the patients at low clinical suspicion; this may be prognostic for a worse outcome.

Our data confirmed previous results[18] that, in patients with sleep-disordered breathing, glomerular filtration rate is reduced; thus, even mild renal disease, as assessed by the estimated glomerular filtration rate, should be considered as a major risk factor for cardiovascular complications.[19]

We have shown that mean levels of triglycerides were higher in patients at high clinical suspicion for OSAS. To deal with this problem, patients with OSAS need statins to significantly reduce their cardiovascular risk. Myocardial infarction patients with OSAS who undergo stent implantation may be at higher risk of restenosis and/or in-stent thrombosis[20,21] on account of their OSAS status, since the treatment of OSAS has been associated with reductions in circulating inflammatory and thrombogenic factors.[22]

Patients at high clinical suspicion for OSAS have an increased risk of acute myocardial infarction during the night. We observed that patients admitted to the hospital with suspected ACS who were at high clinical suspicion for OSAS often had their onset of acute chest pain between midnight and 5.59 am. The results of this study confirm previous evidence, showing that patients with a nocturnal onset of acute myocardial infarction should be evaluated for OSAS.[23,24] In addition, patients at high clinical suspicion for OSAS also need significantly longer hospitalization compared to those with a low clinical suspicion of OSAS. The time to discharge was representative of that in other Polish cardiac centers of this type, based on a comparison with the data from the Polish National Registry on Acute Coronary Syndromes – the largest one of its kind in Europe.

Previous studies have suggested that OSAS significantly increases cardiovascular morbidity and mortality.[5,25] Our results confirmed this finding: patients at high clinical suspicion for OSAS have significantly higher mortality compared to the patients at low clinical suspicion. ACS patients at high clinical suspicion for OSAS should be treated using continuous positive airway pressure, which can lower blood pressure, partially reverse metabolic abnormalities, and reduce the risk of cardiovascular complications.[26-28]

Our study has some limitations. First, we did not performed an overnight sleep study in patients at low clinical suspicion for OSAS. However, only 2.9% patients were at high clinical suspicion for OSAS based on the BQ. The other limitation of the study is the relative small number of patients involved, which might impact on the study's statistical power. It might also be of clinical importance to analyze data in the subgroup of patients who were at high clinical suspicion of OSAS based on the BQ and had excessive daytime sleepiness by the ESS, compared to those who were at high clinical suspicion of OSAS and did not have excessive daytime sleepiness. However, because of the insufficient number of patients in the second subgroup (n=3) we could not perform such a comparison with statistical significance.

In conclusion, one ACS patient in every three was diagnosed with high clinical suspicion for OSAS. The prevalence of cardiovascular risk factors among patients at high clinical suspicion of OSAS was high when compared with patients at low clinical suspicion. A high clinical suspicion of OSAS was also associated with an increase in the risk of adverse cardiac events in myocardial infarction patients. Physicians should routinely screen and evaluate myocardial infarction patients for sleep disorders, especially when they are obese, have hypertension, and suffer from chest pain in the night hours.

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