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Risk of sedation for diagnostic esophagogastroduodenoscopy in obstructive sleep apnea patients

**Cha LM *et al*.** Risk of sedative EGD in OSA

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**Abstract**

**AIM:** Toinvestigate whether patients with obstructive sleep apnea (OSA) are at risk of sedation-related complications during diagnostic esophagogastroduodenoscopy (EGD).

**METHODS:** A prospective study was performed in consecutive patients with OSA, who were confirmed with full-night polysomnography between July 2010 and April 2011. The occurrence of cardiopulmonary complications related to sedation during diagnostic EGD was compared between OSA and control groups.

**RESULTS:** During the study period, 31 patients with OSA and 65 controls were enrolled. Compared with the control group, a higher dosage of midazolam was administrated (*P =* 0.000) and a higher proportion of deep sedation was performed (*P =* 0.024) in OSA group. However, all adverse events, including sedation failure, paradoxical responses, snoring or apnea, hypoxia, hypotension, oxygen or flumazenil administration, and other adverse events were not different between two groups (all *P >* 0.1). Patients with OSA were not predisposed to hypoxia with multivariate logistic regression analysis (*P =* 0.068).

**CONCLUSION:** In patients with OSA, this limited sized study did not disclose an increased risk of cardiopulmonary complications during diagnostic EGD under sedation.

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**Key words:** Conscious sedation; Obstructive sleep apnea; Endoscopy; Complications; Safety

**Core tip:** Patients with obstructive sleep apnea (OSA) are known to be vulnerable to cardiopulmonary complications during deep sedation and anesthesia, however, little is known about the risk of conscious sedation during esophagogastroduodenoscopy (EGD). This prospective study evaluated the cardiopulmonary complications related to conscious sedation during diagnostic EGD between OSA group (*n =* 31) and control group (*n =* 65). All adverse events, including sedation failure, paradoxical responses, snoring or apnea, hypoxia, hypotension, oxygen or flumazenil administration, and other adverse events were not different between groups. Therefore, the risk of cardiopulmonary complications during diagnostic EGD under sedation may not be increased in patients with OSA.

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**INTRODUCTION**

Esophagogastroduodenoscopy (EGD) is generally a safe procedure, and has been routinely performed with sedation in the general population. Sedation reduces patient discomfort by inducing analgesia and amnesia and improves patient tolerance during EGD[1-3]. However, sedation itself is also the cause of many potentially serious adverse events during EGD. The frequency of serious adverse events associated with EGD is about 0.5%[4,5], and over 50% of these adverse events are cardiopulmonary complications related to the sedation[4-6]. The most common cardiopulmonary adverse event is hypoxia, although its incidence is variable depending on the definition of hypoxia, the patient population, and the level of sedation[7-9].

Obstructive sleep apnea (OSA) is characterized by intermittent and recurrent episodes of partial or complete obstruction of the upper airway during sleep. The administration of sedatives in patients with OSA may worsen obstruction of the pharynx and depression of the upper airway muscles[10]. Therefore, patients with OSA are known to be vulnerable to cardiopulmonary complications during deep sedation and anesthesia[10-13].However, little is known about the adverse events of moderate sedation for diagnostic EGD in patients with OSA. Khiani *et al*[14]reported that there was no significant difference in the rates of hypoxia during EGD with sedation between high- and low-risk OSA cases, but patients with confirmed OSA were not included in this study.

The purpose of this study was to determine whether patients with confirmed OSA undergoing diagnostic EGD under sedation are more likely to become hypoxic. A prospective, case-control study was performed to compare the rate of hypoxia between an OSA group and a control group during diagnostic EGD under sedation.

**MATERIALS AND METHODS**

***Patient population***

A prospective study was performed in consecutive patients with OSA, who were recruited from a sleep center laboratory at the Kyung Hee University Hospital in Gang Dong, Seoul, Republic of Korea between July 2010 and April 2011. Patients with confirmed OSA who underwent EGD under moderate sedation for their routine health checkup at initial diagnosis or at a follow-up visit in an outpatient clinic were considered eligible for this study. Consecutive healthy subjects, who underwent EGD under moderate sedation for a routine health checkup between February 2011 and April 2011, were also enrolled for the control group. As the prevalence of gastric cancer is high in Korea, healthy subjects often routinely perform screening EGD for regular medical check-up without any gastrointestinal symptoms in Korea. The occurrence of hypoxia and other cardiopulmonary complications related to sedation for diagnostic EGD were compared between an OSA and a control groups.

Patients with confirmed OSA between 18 and 70 years old who provided informed consent were eligible for this study. The diagnosis of OSA was confirmed based on the results of full-night, in-laboratory polysomnography. Asymptomatic patients who scored higher than 15 on the apnea hypopnea index or respiratory disturbance index were diagnosed with OSA, as were patients with symptoms or signs of disturbed sleep who scored higher than 5 on the hypopnea index or respiratory disturbance index[11]. Patients who declined to participate in the study; were younger than 18 years or older than 70 years; had an EGD examination within the last 12 wk; were pregnant; had a history of substance abuse; were in poor health as determined by a score greater than grade III in the American Society of Anesthesiologists(ASA) classification; had lung disease requiring home oxygen; had baseline oxygen saturation less than 90% as measured by a pulse oximetry without sedation; or had previous gastric surgery were excluded from the study.

A study coordinator administered a questionnaire to patients, which included questions about alcohol consumption, cigarette smoking, or co-morbidities such as hypertension or diabetes mellitus(DM).Current smokers were defined as those who smoked at least one cigarette per day for the previous 12 mo and alcohol consumption was defined as drinking over 40 g of alcohol per day. Hypertension was defined as a blood pressure of ≥ 140 mmHg or taking anti-hypertensive medication. DM was defined as fasting glucose of ≥ 126 mg/dL or previously diagnosed DM. All data were collected and stored securely.

***Esophagogastroduodenoscopy and sedation***

Esophagogastroduodenoscopys (EGDs) were performed by an expert staff endoscopist (J.M.C) in a standard manner using a standard video scope (EG-590WR; Fujinon Inc., Saitama, Japan). Sedation was performed in accordance with guidelines published by the American Society of Gastroenterological Endoscopy[2]. An individualized dose of midazolam was administered by registered nurses according to study protocol based on patient age and weight. In this study, sedation was initiated with a standard dose of midazolam at 0.07 mg/kg[15,16]. Those not adequately sedated 180 s later were provided an additional 1-2 mg of midazolam until the patient reached a state of moderate sedation or until the maximum dose of 0.1 mg/kg had been administered. The goal was to achieve moderate sedation (*i.e.*, conscious sedation), which was defined as depression of consciousness during which the patient responds purposefully to verbal command, either alone or accompanied by light tactile stimulation[3]. The level of sedation was evaluated by an independent nurse using the Modified Observer’s Assessment of Alertness/Sedation (MOAA/S) scale[17], 2 min after initiation of sedation and when the EGD was inserted. MOAA/S scores range from 0 to 6, and moderate sedation was defined as a MOAA/S score from 3 to 4. The total duration of the EGD was recorded with a stopwatch, from the beginning of sedation until the end of the procedure. During EGD, the following data were collected: midazolam dose, MOAA/S score, total duration of EGD, oxygen administration, patient physiologic parameters (*e.g*., SaO2 and systolic blood pressure), whether the patient snored during the procedure, and episodes of hypoxia or other cardiopulmonary complications. Potential complications were described to patients before the procedure, and all patients provided verbal and written consent prior to the EGD under sedation. After EGD, patients were observed for at least 30 min in a recovery room for possible complications.

***Monitoring and data collection***

All outcome parameters during the procedure were assessed by the endoscopist and registered nurses. Baseline blood pressure and SaO2 were recorded before administration of midazolam. All patients were continuously monitored for blood pressure, SaO2, respiratory activity, and electrocardiography during the procedure. The assistant nurse’s responsibilities were limited to sedating and monitoring ventilatory effort, which was visually monitored by chest excursions, respiratory effort, and respiratory rate at regular intervals. A change in tone denoted a rise or fall in saturation, and alarms were set to sound if the value fell below 90%. Oxygen was supplemented when the oxygen saturation level dropped to between 81%-89% for more than 15 s*,* or below 80% more than 5 s.

Sedation failure was defined as any procedure that required the use of flumazenil for successful completion of the procedure, or that was terminated by the endoscopist due to patient agitation. Hypoxia was defined as a pulse oximeter measurement of SaO2 less than 90% for at least 5 s. Paradoxical response was defined as hostility, rage and even physical violence, necessitating the restraint of such patients after the administration of midazolam. Hypotension was defined as systolic blood pressure less than 90 mmHg or a drop in systolic blood pressure of more than 20 mmHg from baseline systolic blood pressure.

***Ethics***

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved ethically by the Institutional Review Board of the Kyung Hee University Hospital at Gangdong (KHNMC IRB 2010-013). All patients provided informed written consent.

***Statistical analysis***

The prevalence of hypoxia related to moderate sedation for diagnostic EGD was assumed to be approximately 0.5% in control group, as the risk of hypoxia in diagnostic EGD with moderate sedation was approximately 0.5% in previous studies[4,5,8,18]. We assumed that a difference in hypoxia rate of 20% between the OSA and control groups was clinically significant and would be sufficient for clinicians to avoid sedation in patients with OSA. It was calculated that 56 participants (28 in each group) would be required to have an 80% chance of ruling out a 20% difference with 95% confidence (one-sided analysis).

Continuous data are described by mean and SD. Categorical data are presented as numbers and percentages. Continuous variables were compared using the *t-*test. Categorical variables were compared using the 2 test or Fisher’s exact test, when appropriate. We computed OR and 95% confidence intervals (95%CI) using logistic regression analysis. A *P* value < 0.05 was considered significant. All statistical analyses were performed using SPSS statistical software version 13.0 (SPSS Inc., Chicago, IL).

**RESULTS**

During the study period, 61 patients with OSA were eligible. Data of 31 patients with OSA were analyzed after exclusion of 30 patients: unwillingness to participate in the study (*n =* 22), EGD examination within the last 12 wk (*n =* 6) and previous gastric surgery (*n =* 2). For control group, 69 subjects were eligible and data of 65 subjects also analyzed after exclusion of 4 subjects: unwillingness to participate (*n =* 2) and an EGD examination within the last 12 wk (*n =* 2). In total, 31 patients with confirmed OSA and 65 control subjects were enrolled in this study. The study group of 96 subjects included 50 men (52.1%) and 46 women(47.9%), with a mean age of 48.3 years. Mean BMI was 24.2 kg/m2, and 24.0% (*n =* 23) of subjects were classified as overweight and 37.5% (*n =* 36) of subjects were classified as obesity according to Asia-Pacific guidelines. In total, a mean dose of 5.0 mg midazolam was used for sedation of diagnostic EGD.

Table 1 shows the patient characteristics and baseline clinical data of the two study groups, including age, sex, height, weight, BMI, smoking and drinking status, Charlson’s comorbidity score, history of hypertension or DM, baseline blood pressure and SaO2. As expected, higher proportion of males, subjects with a higher BMI and subjects with hypertension were more frequently included in the OSA group than those in the control group. However, other clinical variables and baseline SaO2 were not different between the two groups.

Table 2 shows the procedural characteristics and adverse events in the two study groups. A higher dosage of midazolam was administrated in the OSA group than in the control group (*P <* 0.001), which makes sense considering midazolam doses were based on the weight, and patients with OSA weighed more on average. MOAA/S score were not significantly different between two groups. The target level of sedation for this study was moderate sedation, and 58.3% of subjects reached moderate sedation while 41.7% reached deep sedation. For the level of sedation, the proportion of deep sedation was significantly higher in OSA group than in control group (*P =* 0.024). Most patients (99.0%) reached the target level of sedation within 2 minutes, and only one in the OSA group needed an additional dose of sedatives. The frequency of all adverse events, including sedation failure, paradoxical responses, snoring or apnea, hypoxia, hypotension, oxygen or flumazenil administration, and other adverse events was not different between two groups (all *P >* 0.1). In cases of hypoxia, only one (3.2%) patient became transiently hypoxic in the OSA group, and seven cases (10.8%) became transiently hypoxic in the control group (*P* = 0.211). In total, 96.8% of patients remained stable without oxygenation supplementation in the OSA group, and 99.8% remained stable without oxygenation supplementation in the control group (*P =* 0.588).

To determine independent predictors of a hypoxia, we performed logistic regression analysis adjusted for age, sex, smoking, alcohol, DM, hypertension, BMI (< 25 *vs* ≥ 25 kg/m2), midazolam dose (< 5 *vs* ≥ 5 mg), and OSA (Table 3). In this analysis, all variables including the confirmed diagnosis of OSA were not predispose to risk of hypoxia (OR = 0.117, 95%CI = 0.012-1.168, *P =* 0.068).

**DISCUSSION**

This is the first prospective study to evaluate the risk of sedation for diagnostic EGD in patients with OSA. Although higher doses of midazolam were administrated and higher proportion of deep sedation were performed in the OSA group than in the control group, all adverse events associated with sedation for diagnostic EGD were not significantly different between the two study groups. In addition, the confirmed diagnosis of OSA was not predisposed to hypoxia with multivariate logistic regression analysis.

Anesthesia and deep sedation have been shown to increase pharyngeal collapse, decrease ventilator response, and impair the arousal response, leading to cardiopulmonary complications in patients with OSA[10-13,19-22]. However, little is known about the risk of sedation for diagnostic EGD, which is usually targeted for moderate sedation, in patients with OSA. The risk of hypoxia associated with sedation for diagnostic EGD in patients with OSA might be lower than expected due to the following three reasons: First, the sedation level for diagnostic EGD is generally targeted for moderate sedation. The risk of hypoxia in patients with OSA might be lower in cases of moderate sedation than deep sedation or anesthesia because increasing depth of sedation is associated with a progressive increase in upper airway collapsibility[23,24]. Second, diagnostic EGD is of relatively short procedure, which may be associated with a lower risk of hypoxia, as longer endoscopic procedures were associated with increased risk of hypoxia compared to shorter endoscopic procedures[25]. Finally, the position of patient during diagnostic EGD is in the left lateral decubitus position, which may be associated with a lower risk of hypoxia. Patients who undergo anesthesia or surgery in the supine position may be at greater risk of upper airway collapsibility than those who are in the left lateral decubitus position. Therefore, the risk of hypoxia associated with sedation for diagnostic EGD in patients with OSA might not be high.

As patients with OSA are classified at increased risk for sedation-related complications[26], physicians are often reluctant to recommend sedation for diagnostic EGD. However, the risk of sedation for diagnostic EGD in patients with OSA is not supported by the direct evidence. Our findings suggest that the risk of sedation for diagnostic EGD in patients with OSA might be rare, if any. In the literature, hypoxia has been used as a surrogate for cardiopulmonary outcomes, and its reported incidence during gastrointestinal endoscopy under sedation ranges widely from 10% to 70%[9,18,27-38]. Although, the study methodology, definition of hypoxia, patient populations, type of endoscopy, use of supplemental oxygen, and type of sedatives should be considered for the interpretation of risk factor of hypoxia during endoscopy under sedation, a confirmed diagnosis of OSA rarely pointed out as a risk factor of hypoxia during endoscopy under moderate sedation.

This study is unique as this is the first prospective study that evaluated the risk of sedation for diagnostic EGD in patients with OSA. Khiani *et al*[14] suggested that patients at risk for OSA can safely undergo sedation for routine endoscopic procedures, however, only the Berlin questionnaire was used for OSA risk stratification and patients with OSA were not included in this study. Sharara *et al*[39] suggested that snoring during colonoscopy is a strong predictor of OSA, however, only sleep questionnaire was also used in this study. Mador *et al*[40] showed that presence of OSA does not clearly increase the risk of cardiopulmonary complications in endoscopy procedures under moderate sedation, which is a consistent finding with ours. Although all patients with OSA were confirmed with overnight polysomnography in this study, it was also limited due to its retrospective nature and nonstandard definition of hypopnea. Furthermore, the method of sedation is not controlled, and EGD and colonoscopy were analyzed together in this retrospective analysis. In contrast, our prospective study included all patients with confirmed OSA with a polysomnography and evaluated adverse effects with pre-defined criteria. As an OSA diagnosis is confirmed in only 50%-60% of subjects suspected of having OSA with questionnaire[41,42], subjects without OSA might be included in previous questionnaire based studies[14,39].

The present study has several limitations. First, 30 OSA cases were excluded from 61 eligible patients with confirmed diagnosis of OSA. However, there was minimal selection bias, if any, as data was prospectively collected and patients were excluded based on criteria determined before starting enrollment. One reason for the high rate of exclusions in our study is that most patients with OSA were concerned about sedation risks. They have been recommended for a diagnostic EGD without sedation due to hypoxia risk for a long time. Therefore, out study may have a helpful clinical implication for them. Second, the sample size was small because we only included confirmed OSA cases. At the inception of this study, we estimated that OSA group would comprise a much larger number of cases and improve the power of this study. The sample size of our study was small (*n =* 96), however, the statistical significance may be sufficiently verified with our study design as only 56 participants were required in our sample size calculation. Third, there is a limitation for the generalizability of our results to all patients with OSA because our patients were recruited from a single university outpatient clinic, and procedures were purely diagnostic EGD with midazolam alone. Our results cannot be generalized to EGDs that will include therapy or more extensive diagnosis such as Barrett’s surveillance or sedation with propofol or opioids.

In conclusion, this limited sized study did not disclose an increased risk of cardiopulmonary complications during diagnostic EGD with moderate sedation in patient with OSA. This suggests that the majority of patients with OSA would safely undergo diagnostic EGD with sedation. However, our findings should be more clearly established in the future large studies.

**COMMENTS**

***Background***

Obstructive sleep apnea (OSA) is characterized by intermittent and recurrent episodes of partial or complete obstruction of the upper airway during sleep. The administration of sedatives in patients with OSA may worsen obstruction of the pharynx and depression of the upper airway muscles. Therefore, patients with OSA are known to be vulnerable to cardiopulmonary complications during deep sedation and anesthesia. However, little is known about the adverse events of moderate sedation for diagnostic esophagogastroduodenoscopy (EGD) in patients with OSA.

***Research frontiers***

The research hotspot is to investigate whether patients with OSA are at risk of sedation-related complications during diagnostic EGD.

***Innovations and breakthroughs***

This is the first prospective study to evaluate the risk of sedation for diagnostic EGD in patients with OSA. Although higher doses of midazolam were administrated and higher proportion of deep sedation were performed in the OSA group than in the control group, all adverse events associated with sedation for diagnostic EGD were not significantly different between the two study groups. In addition, the confirmed diagnosis of OSA was not predisposed to hypoxia with multivariate logistic regression analysis. This study is outstanding in that the risk of sedation for diagnostic EGD in patients with OSA was investigated prospective design with pre-defined criteria and all OSA patients were confirmed of their diagnosis with full-night, in-laboratory polysomnography. Although the diagnosed of OSA were made with questionnaire in previous studies, subjects without OSA might be included as an OSA diagnosis is confirmed in only 50-60% of subjects suspected of having OSA with questionnaire.

***Applications***

As patients with OSA are classified at increased risk for sedation-related complications, physicians are often reluctant to recommend sedation for diagnostic EGD. In fact, most patients with OSA were concerned about sedation risks in our study, as they have been recommended for a diagnostic EGD without sedation for a long time. However, the risk of sedation for diagnostic EGD in patients with OSA is not supported by the direct evidence. Therefore, out study may have a helpful clinical implication for patient with OSA when they perform diagnostic EGD under sedation.

***Terminology***

OSA: The diagnosis of OSA was confirmed based on the results of full-night, in-laboratory polysomnography. Asymptomatic patients who scored higher than 15 on the apnea hypopnea index or respiratory disturbance index were diagnosed with OSA, as were patients with symptoms or signs of disturbed sleep who scored higher than 5 on the hypopnea index or respiratory disturbance index; Moderate sedation: The level of sedation was evaluated by an independent nurse using the Modified Observer’s Assessment of Alertness/Sedation (MOAA/S) scale, and moderate sedation was defined as a MOAA/S score from 3 to 4; Hypoxia: Hypoxia was defined as a pulse oximeter measurement of SaO2 less than 90% for at least 5 seconds.

***Peer review***

It is generally a well-written paper: it has an excellent Core Tip section to “advertise” the paper, well-summarized results section adding meaningfully to the existing literature on an important subject and the rest of the sections are also well-written. The bibliography is focused and well-researched. The results are interesting and suggest that the majority of patients with OSA would safely undergo diagnostic EGD with sedation.

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**Table 1 Characteristics and baseline clinical data of subjects in the obstructive sleep apnea and control groups**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **OSA group**  **(*n* = 31)** | **Control group**  **(*n* =65 )** | ***P*-value** |
| Patient characteristics |  |  |  |
| Age (yr)  Sex (male), *n* (%)  Height (meters)  Weight (kg)  BMI (kg/m2)  Smoking, *n* (%)  Drinking, *n* (%)  Charlson score (points)  Hypertension, *n* (%)  Diabetes mellitus, *n* (%) | 51.3 ± 9.6  23 (74.2)  167.1 ± 6.8  74.3 ± 11.2  26.5 ± 3.0  9 (29.0)  11 (35.5)  1.0 ± 0.2  10 (32.3)  4 (12.9) | 47.1 ± 11.8  27 (41.5)  164.4 ± 8.0  62.6 ± 12.0  23.1 ± 3.3  9 (13.8)  24 (36.9)  1.0 ± 0.0  9 (13.8)  7 (10.8) | 0.082  0.003  0.104  0.000  0.000  0.075  0.891  0.325  0.034  0.759 |
| Baseline clinical data |  |  |  |
| Systolic BP (mmHg)  Diastolic BP (mmHg)  SaO2 (%) | 127.6 ± 16.9  79.3 ± 10.6  97.6 ± 1.7 | 114.3 ± 22.2  66.1 ± 14.4  98.0 ± 2.2 | 0.004  0.000  0.418 |

OSA: Obstructive sleep apnea; BMI: Body mass index; BP: Blood pressure; SaO2: Arterial oxygen saturation.

**Table 2 Procedural characteristics and adverse events in the obstructive sleep apnea and control groups *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **OSA group**  **(*n* =31 )** | **Control group**  **(*n* = 65)** | ***P*-value** |
| EGD data  Duration of EGD (s )  Midazolam dosage (mg)  MOAA/S score (points, at 2 min)  Level of sedation for EGD  Moderate sedation  Deep sedation  Adverse events  Sedation failure  Paradoxical responses  Snoring or apnea  Hypoxia (SaO2< 90%)  Hypotension  Other adverse events  Oxygen administration  Flumazenil administration | 261.4 ± 79.6  5.3 ± 0.9  2.5 ± 1.2  13 (41.9)  18 (58.1)  0 (0)  4 (12.9)  5 (16.1)  1 (3.2)  0 (0)  0 (0)  1 (3.2)  0 (0) | 304.4 ± 154.2  4.5 ± 0.8  2.9 ± 1.0  43 (66.2)  22 (33.8)  0 (0)  4 (6.2)  7 (10.8)  7 (10.8)  0 (0)  0 (0)  1 (0.2)  0 (0) | 0.074  0.000  0.146  0.024  -  0.268  0.458  0.211  -  -  0.588  - |

OSA: Obstructive sleep apnea; EGD: Esophagogastroduodenoscopy; MOAA/S: Modified Observer’s Assessment of Alertness/Sedation; SaO2: arterial oxygen saturation.

**Table 3 Multivariate logistic regression analysis of possible risk factors for a hypoxia**

|  |  |  |
| --- | --- | --- |
| Parameter | OR (95%CI) | *P* value |
| Age (continuous)  Sex (female *vs* male)  Smoking (No. *vs* Yes)  Alcohol (No. *vs* Yes)  Diabetes mellitus (No. *vs* Yes)  Hypertension (No. *vs* Yes)  Body mass index (< 25 *vs* ≥ 25 kg/m2)  Midazolam dose (< 5 *vs* ≥ 5 mg)  OSA (No *vs* Yes) | 1.056 (0.958-1.164)  1.003 (0.153-6.563)  0.753 (0.056-10.127)  0.592 (0.095-3.706)  1.842 (0.187-18.128)  1.102 (0.120-10.117)  1.304 (0.192-8.845)  10.726 (0.815-141.100)  0.117 (0.012-1.168) | 0.276  0.997  0.830  0.576  0.601  0.932  0.786  0.071  0.068 |

OSA: Obstructive sleep apnea.