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Clinical characteristics of sleep apnea in middle-old and oldest-old inpatients: symptoms and comorbidities

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Short title: Obstructive sleep apnea in geriatric patients

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Abstract

Background: Obstructive sleep apnea (OSA) is prevalent in older adults but still underdiagnosed for many reasons, such as underreported symptoms, non-specific ones because of the comorbidities and polypharmacy, or the social belief of sleep problems as normal with aging.

Objectives: To identify salient symptoms and comorbidities associated with OSA, diagnosed by nocturnal respiratory polygraphy in geriatric inpatients.

Method: We conducted a retrospective, cross-sectional study in a sample of 102 geriatric inpatients from a French Geriatric University Hospital. We reviewed medical records to collect demographic, medical information including comorbidities, the geriatric cumulative illness rating scale (CIRS-G), subjective sleep-related symptoms and data of overnight level 3 portable sleep polygraphy recording.

Results: Among classic OSA symptoms, only excessive daytime sleepiness ($p=0.02$) and nocturnal choking ($p=0.03$) were more prevalent in older inpatients with OSA ($n=64$) than in those without ($n=38$). The prevalence of comorbidities and mean CIRS-G scores were not different between groups except for the lower prevalence of chronic obstructive pulmonary disease and the higher level of creatinine clearance in OSA patients. Multivariate analysis showed OSA was associated with excessive daytime sleepiness ($OR=2.83$, $p=0.02$) in symptoms-related model and with composite CIRS-G score ($OR 1.26$, $p=0.04$) in comorbidities-related model.

Conclusions

Only excessive daytime sleepiness and comorbidity severity (composite CIRS-G score) were associated with the objective diagnosis of OSA, while other usual clinical OSA symptoms and comorbidities in geriatric inpatients were not. These findings emphasize the importance

of excessive daytime sleepiness symptom, when reported in comorbid older patients, strongly suggesting OSA and requiring adequate nocturnal exploration.

INTRODUCTION

Recognizing obstructive sleep apnea (OSA) is important in older patients, because of serious health consequences and available therapy. Sleep-disordered breathing is frequent: the prevalence of moderate to severe sleep-disordered breathing is 23.4% in women and 49.7% in men in a general population and is more important in participants aged 60 years or older [1]. In community-dwelling older adults, it is occurring in up to 56% of women and 70% of men. OSA is associated with greater risk of cardiovascular and metabolic disorders, cognitive impairment, functional decline, and frailty in older patients [2–4]. Severe OSA is associated with severity of multimorbidity [5]. Consequently, they need greater healthcare resources than those without OSA, and than middle-aged patients with OSA [6,7]. In addition, OSA is treatable by continuous positive airway pressure therapy, which decreases the sleepiness, fatigue, depressive symptoms, and improves quality of life, even in older patients, resulting in functional outcomes comparable to that of younger adults [8].

However, OSA remains under-diagnosed in the older patients. This may be explained by the difficulties to recognize the OSA symptoms for many reasons. Indeed the typical clinical presentation exists in aged individuals, but symptoms are often underreported, non-specific because of the comorbidities and polypharmacy, underdiagnosed by clinicians, or the social belief of sleep problems as normal with aging. Older patients sleeping alone could not report if they snore and/or have breathing pauses during the night. Snoring, high body mass index (BMI), and breathing pauses were found to be less associated with OSA in older persons [9]. With respect to excessive daytime sleepiness (EDS), a key symptom for OSA, there are substantial difficulties in establishing its existence in older people for various reasons: the high prevalence of sleepiness unrelated to OSA and generally multifactorial in older adults, in particular due to comorbidities and pharmacological treatments; a different perception of this symptom by the older patient; and the social perception of sleepiness as a

normal symptom in the older population, even by clinicians [10–12]. The Epworth Sleepiness Scale (ESS) is the most used tool to detect the subjective sleepiness but underestimates it in older patients [13–15]. Among some existing screening tools for OSA, the Berlin questionnaire has been widely used [16]. It is based on self-reported major symptoms (snoring, stopped breathing, fatigue, sleepiness) and hypertension. However, a study did not validate its use in older people, showing a very low specificity of the Berlin questionnaire for the OSA diagnosis, at only 39% [17]. The another screening OSA questionnaire, STOP-BANG, based on symptoms, age or BMI is not also sufficiently accurate in the older population [18]. And these studies were conducted in independent community-dwelling seniors, and not in comorbid older patients [17,18]. Other symptoms such as nocturia, fatigue, insomnia, memory and mood disorders are quite frequent and non-specific in geriatric patients because of the coexisting multiple comorbidities. These comorbidities will certainly impacts the clinical presentation of OSA in older individuals, and some authors have even suggested sleep apnea in geriatric patients as a unique syndrome [19]. Moreover, a symptom of OSA as fatigue/tiredness is included in the frail phenotype, considering that frailty is a geriatric condition characterized by an increased vulnerability to external stressors, and is one of the leading cause of morbidity and premature mortality in older people [20–22].

Finally, studies on older people focus on a population over 65 years of age, mostly the youngest-old population aged 65 to 74 years, but the older population is very heterogeneous. The heterogeneity comes not only from the different age groups (youngest-old, aged 65 to 74 years; middle-old, 75 to 84 years; and oldest-old, ≥ 85 years), but also from their variable health status marked by comorbidities, various functional status and clinical setting such as community dwelling or hospital setting [23]. Most of the existing studies were conducted among community dwelling older adults who are often younger, fitter and independent than geriatric inpatients [9,17,18]. Given the heterogeneity of the older people, it is important to

study this latter population. Gamaldo et al. have used a large national healthcare database to comprehensively examine trends in sleep disturbance diagnoses such as OSA among hospitalized older adults in the United States from 2002 to 2012, and whether co-morbidities and outcomes are related to disturbance status [24]. Using clinical diagnostic codes (the International Classification of Diseases Ninth revision, Clinical Modification ICD-9-CM), this previous study observed that while rates of sleep disturbances such as OSA were increasing within hospital settings, the relatively low rates, especially in middle old and oldest old subgroups, might reflect that many older adults' sleep disorders remained underdiagnosed. To date, very few studies on OSA have been conducted in old inpatients [24–26]. To our knowledge, no study has been done in the very old inpatients with detailed comorbidities and objective diagnosis of OSA. Improving the diagnosis of OSA, a highly prevalent but underdiagnosed sleep disorder, is important in this population. Therefore, the aim of this study is to identify symptoms and comorbidities associated with the diagnosis of OSA established using a level 3 portable sleep testing in geriatric inpatients aged 75 and over. We hypothesized that usual OSA-related symptoms (snoring, EDS, observed apnea or nocturnal choking, morning headache, nocturia, insomnia symptoms including difficulty of initiating and/or maintaining sleep overnight, dissatisfaction with sleep) might not be associated with the diagnosis of OSA in geriatric inpatients. Furthermore, we hypothesized that geriatric inpatients with more severe comorbidity will be more likely to be diagnosed with OSA.

METHODS

We retrospectively analyzed the medical records of inpatients aged 75 and over, who had undergone a level 3 portable sleep testing, the nocturnal polygraphy (NP) in a French University geriatric hospital, between April 2009 and June 2014. All patients who have undergone nocturnal recording for OSA diagnosis were eligible. Of 160 patients with NP

recording, we excluded 49 because of missing clinical data, recording failure, or insufficient recording time <5 hours, and 9 central sleep apnea. A total of 102 patients were included. The ethics Institutional Review board (IRB00003888, IORG0003254, FWA00005831) of the French Institute of Medical Research and Health (Inserm) has approved the study protocol (approval N° 18-487). An information letter with possibility of opposing medical data collection was previously sent to the patients, informed consent was thus waived in this context. The database was declared to the French National Commission on Informatics and Liberty (CNIL, Paris, France). Data were collected anonymously by a team of medical doctors.

Clinical data

A geriatrician collected retrospectively information about demographics and medical conditions with systematic review of medical record and hospitalization report for each patient. The comprehensive geriatric assessment performed routinely during their geriatric hospitalization included BMI, as well as the patients' living situation (alone and where (home, nursing home), the score of autonomy in daily living (ADL) Katz scale, cognitive status (including Mini Mental State Examination MMSE score), as well as cardiovascular, respiratory, psychiatric and ophthalmic comorbidities, and prostate disease for men, and the cumulative illness rating scale for geriatrics (CIRS-G) scores. Daily alcohol consumption of more than 30 g in men or 20 g in women defined chronic alcoholism. The cumulative illness rating scale for geriatrics (CIRS-G) score was used to quantify burden of comorbidities in older patients in 14 organ categories, with a 0 to 4 grading scale of impairment in each organ category: the "total" CIRS-G score was the sum of each of the 14 individual system scores and the "composite" CIRS-G score was calculated as the number of categories with a score of 2 or greater [27]. We also collected for each patient biological data including hemoglobin

(g/dL), albumin (g/L) and creatinine clearance (CrCl - mL/min - calculated with the Cockcroft and Gault method). At the time of nocturnal polygraphy, physicians had asked patients for subjective symptoms suggesting sleep apnea (snoring, EDS, observed apnea or nocturnal choking, morning headache, nocturia, insomnia symptoms including difficulty of initiating and/or maintaining sleep overnight, dissatisfaction with sleep) that were usually present at their home. These symptoms were asked once the clinical condition had stabilized, and extracted from the request file for nocturnal recording. EDS was reported either by the patient or the primary caregiver but not assessed by the Epworth sleepiness scale (ESS) considering its limitations in the older population [15].

Overnight respiratory recording

One-night respiratory recordings were performed during the hospitalization using an ambulatory respiratory polygraphic system (CIDELEC CID 102) with the following recorded parameters: nasal airflow, snoring, thoraco-abdominal respiratory movements, pulse oximetry (SpO₂), position, and electrocardiography. All recordings were visually analyzed, and manually scored by 2 physicians specialized in sleep disorders. Hypopnea was defined as a $\geq 30\%$ reduction in airflow lasting for ≥ 10 s and associated with $\geq 3\%$ oxygen desaturation [28]. Apnea was defined as the absence of airflow lasting ≥ 10 s. Number of hypopneas and apneas per hour defined the apnea-hypopnea index (AHI). The oxygen desaturation index (ODI) was defined as the number of $\geq 4\%$ arterial oxygen desaturations per hour of recording. OSA patients were defined according to the International Classification of Sleep Disorders (ICSD-3) with an apnea-hypopnea index (AHI) ≥ 15 /h even in the absence of associated symptoms or disorders, predominantly obstructive respiratory events.

Statistical analysis

Statistical analyses were performed with SPSS 24 (IBM, Armonk, New York). Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test. Quantitative variables were analyzed using Student's t-test or the Mann-Whitney's test, depending on whether the distribution was normal or not. Results are presented as the mean \pm standard deviation (SD) or medians, unless otherwise stated. Independent variables (factors/comorbidities or relevant clinical symptoms) were examined for their association with OSA using two multivariate logistic forward stepwise regressions to calculate odds ratios (ORs) and corresponding 95% confidence intervals (95%CI). ORs with a p value < 0.23 on univariate analysis were used to define which covariates should be incorporated into a multivariate analysis. A first multivariate logistic regression for associations between OSA (dependent variable) and factors/comorbidities (gender, chronic obstructive pulmonary disorder, history of stroke, atrial fibrillation, weight, CIRS composite and creatinine clearance CrCl: OSA-associated comorbidities model analysis) was performed. A second multivariate logistic regression for associations was performed between OSA and relevant clinical symptoms (gender, EDS, observed apnea or nocturnal choking, snoring, nocturia, insomnia, dissatisfaction with sleep, morning headache, memory complaint, mood disorders: OSA-related symptoms model analysis). A P-value of < 0.05 was used as a cut-off for statistical significance.

RESULTS

Participants' characteristics

Among 102 patients, 62.7% were diagnosed OSA and 37.3% were not (table 1). These patients were 62.7% females with a mean age 85.5 ± 4.9 years. Between OSA and non-OSA patients, no difference was found regarding age, BMI, ADL, living situation, total and composite CIRS-G score, reason for hospitalization (respiratory, heart failure, confusion, cognitive impairment, infection, stroke, falls, weight loss, seizure), and comorbidities

excepted for COPD being more prevalent in non-OSA patients. Biological data showed a lower CrCl in non-OSA patients, but both groups showed moderate renal failure (> 45 mL/min).

	All patients N = 102	OSA N = 64	non-OSA N= 38	p value
Clinical characteristics				
Females (%)	62.7	56.3	73.7	0.07 †
Age, yrs (Mean ± SD)	85.5 ± 4.9	85.4 ± 4.8	85.9 ± 5.2	0.61 ¶
Weight, kg (Mean ± SD)	71.6 ± 13.1	73.5 ± 12.4	68.5 ± 14	0.06 ¶
BMI, kg/m ² (Mean ± SD)	26.7 ± 5.1	27.3 ± 4.9	25.7 ± 5.2	0.13 ¶
ADL (Mean ± SD)	4.7 ± 1.4	4.6 ± 1.5	4.8 ± 1.4	0.52 ‡
Nursing home (%)	12.7	9.3	18.4	0.18 †
Living alone at home (%)	63.7	64.1	63.2	0.92
CIRS-G scores (Mean ± SD)				
• Total CIRS-G	12.3 ± 4.9	12.9 ± 5.2	11.2 ± 4.2	0.21 ‡
• Composite CIRS-G	4.4 ± 2.1	4.7 ± 2.2	3.9 ± 1.8	0.15 ‡
Hypertension (%)	85.3	87.5	81.6	0.41 †
Dyslipidemia (%)	47.0	48.4	44.7	0.71 †
Diabetes mellitus (%)	32.4	37.5	23.7	0.15 †
Actual Smoking (%)	9.8	7.8	13.2	0.38 §
Chronic alcohol addiction (%)	13.7	14.1	13.2	0.89 §
Heart failure (%)	41.2	40.6	42.1	0.88 †
Ischemic heart disease (%)	34.3	39.1	26.3	0.19 †
Atrial fibrillation (%)	38.7	43.8	29.0	0.13 †

History of stroke (%)	36.3	40.6	23.7	0.23 [†]
COPD (%)	22.5	15.6	34.2	0.03 [†]
Asthma (%)	10.8	9.4	13.2	0.74 [§]
Restrictive pulmonary disease (%)	7.8	9.3	5.3	0.70 [§]
Cognitive impairment (%)	55.9	50.0	65.8	0.12 [†]
MMSE (Mean ± SD, range 0-30)	21.5 ± 5.6	21.2 ± 6.3	21.3 ± 5.2	0.51 [‡]
Depression (%)	41.2	39.1	44.7	0.57 [†]
Ophthalmic disease (%)	59.8	62.5	55.3	0.47 [†]
Prostatic disease (%) (in 38 men)	68.4	71.4	60	0.50 [†]
Number of medications	7.7 ± 3.5	8.1 ± 3.3	7.0 ± 3.7	0.09 [‡]
Albumin (Mean ± SD, g/dL)	34.3 ± 4.4	34.2 ± 4.1	34.5 ± 4.8	0.79 [¶]
CrCl (Mean ± SD, mL/min)	54.4 ± 18.8	57.5 ± 20.0	49.1 ± 15.4	0.05 [‡]
Hemoglobin (Mean ± SD, g/dL)	12.5 ± 2.1	12.7 ± 2.4	12.1 ± 1.3	0.28 [‡]
Reason for hospitalization (%)				
Respiratory failure	13.7	9.4	21.1	0.14 [§]
Heart failure	14.7	18.8	7.9	0.16 [§]
Delirium	6.9	9.4	2.6	0.25 [§]
Cognitive impairment	7.8	4.7	13.2	0.14 [§]
Infection	2.9	3.1	2.6	1.00 [§]
Stroke	6.9	7.8	5.3	1.00 [§]
Falls	14.7	17.2	10.5	0.40 [§]
Weight loss	5.9	6.2	5.3	0.53 [§]
Seizure	2.0	3.1	0	0.53 [§]
Others	24.5	20.3	31.5	0.29 [†]
Symptoms suggesting sleep apnea (%)				

EDS	73.5	81.3	60.5	0.02 [†]
Snoring	44.1	46.9	39.5	0.46 [†]
Observed apnea, nocturnal choking	18.6	25.0	7.9	0.03 [†]
Nocturia	33.3	39.1	23.7	0.11 [†]
Insomnia symptoms	33.3	28.1	42.1	0.14 [†]
Dissatisfaction with sleep	18.6	18.8	18.4	0.96 [†]
Morning headache	9.8	7.8	13.2	0.38 [§]
Memory loss complaint	29.4	31.3	26.3	0.59 [†]
Mood disorders	52.9	53.1	52.6	0.96 [†]
Nocturnal polygraphy parameters				
AHI (/hour) (Mean ± SD)	27.4 ± 21.4	40.0 ± 17.0	6.5 ± 5.0	< .0001 [‡]
Waking SpO2 (%)	94.9 ± 2.6	94.8 ± 3.0	95 ± 1.8	0.66 [‡]
Mean SpO2 (%)	91.2 ± 3.9	90.8 ± 4.5	91.8 ± 2.8	0.40 [‡]
Minimal SpO2 (%)	78.3 ± 9.9	75.1 ± 10.0	83.1 ± 7.4	< .0001 [‡]
SpO2 < 90% (% time)	26 ± 32.6	28.7 ± 32.1	21.9 ± 33.5	0.02 [‡]
ODI (/hour)	21 ± 20.7	31.2 ± 19.8	5.6 ± 9.6	<.0001 [‡]

Table 1: Patients' characteristics

ADL: activities of daily living; AHI: apnea-hypopnea index; BMI: body mass index;
CIRS: cumulative Illness Rating Scale; COPD: Chronic obstructive pulmonary disease; CrCl:
creatinine clearance; EDS: excessive daytime sleepiness; MMSE: Mini Mental State

Examination; ODI: oxygen desaturation index (number of decrease in the oxygen saturation \geq 4%)

¶ Student's t-test; † Pearson's χ^2 test; § Fisher exact; ‡ Mann-Whitney test; in bold: $p < .05$

OSA-related comorbidities

To identify which comorbidities are associated with the diagnosis of OSA, we performed an OSA associated comorbidities model analysis, including as covariates: gender, chronic obstructive pulmonary disorder, history of stroke, atrial fibrillation, weight, CIRS composite and creatinine clearance CrCl (Table 2). OSA was positively associated with composite CIRS-G score (OR 1.26, 95% CI 1.01-1.57, $p=0.04$) and CrCl (OR 1.03, 95%CI 1.01-1.06, $p=0.02$), and negatively with COPD (OR 0.31, 95%CI 0.11-0.85, $p=0.02$) while no association to other comorbidities was found ($p > 0.05$). To explore the variables that mediate associations between COPD and OSA, we checked the role of these interaction variables (atrial fibrillation, stroke, ischemic heart disease) for potential confounding effects. The p-value for the two interactions was not statistically significant. Others interacting variables (depression, insomnia, actual smoking, heart failure, hypertension) were also checked (based on the univariate analysis between COPD vs no COPD) and the p-values were not significant.

Variables	β	p-value	OR (95% CI)
COPD	-1.179	0.02	0.31 (0.11-0.85)
Composite CIRS	0.214	0.04	1.26 (1.01-1.57)
CrCl	0.031	0.02	1.03 (1.01-1.06)

Table 2: Multivariate forward logistic analysis results for the OSA associated comorbidities model analysis.

The model was significant ($\chi^2 = 14.99$, $p = 0.002$, Nagelkerke $R^2 = 0.175$).

β : partial regression coefficient; CIRS: Cumulative Illness Rating Scale; COPD: Chronic obstructive pulmonary disease; CrCl: Creatinine clearance; OR: (EXP (β), Odds Ratio value of the corresponding variable with 95% Confidence Interval. In bold: $p < .05$

OSA-related symptoms

Subjective clinical symptoms of OSA and objective polygraphy parameters are presented in table 1. OSA patients reported significantly more EDS and more observed apnea or nocturnal choking than non-OSA patients; the other usual OSA symptoms were not statistically different between groups. EDS was not different between severe OSA patients (n=46, mean AHI = 46 ± 16 /h, 80% EDS) and moderate OSA (n=18, mean AHI= 23 ± 4.7 /h, 83% EDS; $p=1$).

To identify which symptoms are associated with the OSA diagnosis, we performed an OSA-related symptoms model analysis, including as covariates: gender, EDS, observed apnea or nocturnal choking, snoring, nocturia, insomnia, dissatisfaction with sleep, morning headache, memory complaint, mood disorders (Table 3). OSA was statistically associated only with EDS (OR=2.83, 95% CI=1.14-6.98, $p=0.02$) and the other covariates were not significantly associated with the odds of having OSA.

Variables	β	p-value	OR (95% CI)
Excessive Daytime sleepiness	1.039	0.02	2.83 (1.14-6.98)

Table 3: Multivariate forward logistic analysis results for the OSA-related symptoms model.

The model was significant ($\chi^2 = 5.14$, $p = 0.02$, Nagelkerke $R^2 = 0.067$).

β : partial regression coefficient; OR: (EXP (β), Odds Ratio value of the corresponding variable with 95% Confidence Interval.

Concerning the potential gender differences in OSA related symptoms, the forward step-wise logistic regression model including gender in the OSA-related symptoms model analysis showed that gender was not associated with OSA (p=0.12). Moreover, in the univariate analysis among OSA patients, there was no difference in OSA related symptoms between women and men, except for insomnia complaint and mood disorders (table 4).

Symptoms suggesting sleep apnea (%)	OSA	OSA	p-value
	Women	Men	
EDS	70	79	0.34 †
Snoring	41	50	0.36 †
Observed apnea, nocturnal choking	17	21	0.63 †
Nocturia	27	45	0.06 †
Insomnia symptoms	41	21	0.04 †
Dissatisfaction with sleep	20	16	0.57 †
Morning headache	14	2.6	0.09 §
Memory loss complaint	28	32	0.71 †
Mood disorders	61	39	0.04 †

Table 4: OSA Patients' symptoms between women and men.

† Pearson's χ^2 test; § Fisher exact;

DISCUSSION/CONCLUSION

This study focused on the symptoms and comorbidities associated with OSA in geriatric inpatients. To our knowledge, our study is the first one performed in well-characterized very old inpatients with an objective OSA diagnosis by polygraphy.

We have used CIRS-G, a comorbidity scale for geriatrics patients registering all coexisting diseases and assessing the severity of diseases according to their impact of disability. Interestingly, OSA was associated with the CIRS-G “composite” score, reflecting the comorbidity severity [27]. A previous study has shown a dose-response relationship between the comorbidities “number” and a high risk for OSA screened by questionnaire, not confirmed by recordings [29]. Moreover, severe OSA diagnosed by polysomnography was associated with the morbidity severity assessed by a self-report questionnaire, the Disease Burden Morbidity Assessment, in middle-aged patients [5], while the CIRS-G is from objective data collected by physicians. Our finding that the comorbidity burden was independently associated with OSA is important, considering a report that comorbidities do not mask the effect of OSA on mortality for inpatients ≥ 50 years old, but OSA possibly worsens the prognosis of comorbid subjects [30].

Concerning the comorbidities associated with OSA, limited data are available in older inpatients. The United States’ nationwide study among older inpatients (aged over 65 years old), examined trends over time, and assessed whether comorbidities and other individual-level and hospital-level characteristics were related to a sleep disturbance diagnosis (i.e., insomnia, OSA, or other sleep disturbance) and hospitalization outcomes [24]. In this study, many comorbidities had independent positive associations with OSA: rheumatoid arthritis, congestive heart failure, depression, diabetes, hypertension, hypothyroidism, neurological disorders, pulmonary circulation disorders, renal failure, and most importantly obesity [24]. However, the clinical diagnostic codes using ICD-9-CM, given by a health provider, were used to estimate OSA; it is unclear what diagnostic tests were given to assess the symptoms/signs common to OSA. In our study, there were no clinically relevant comorbidities associated with the objective diagnosis of OSA. Indeed, we found no association between OSA and cardiovascular comorbidities, in contrast to the literature

[31,32]. Our result concerning CrCl should be interpreted carefully because the odds ratio is low, although a previous meta-analysis showed that OSA is significantly associated with poorer renal function [33]. OSA was negatively associated with COPD in our study, and there are conflicting results in older patients in the literature [34], reflecting the different investigated populations and the possible survival bias against the association COPD-OSA. Moreover, in our study COPD was a reported medical history and not severe without oxygen dependency and considering that the limit of normal SpO₂ in older patients was reported to be 91%. Thus, our finding on COPD is less clinically significant. These comorbidities common in geriatric patients may overshadow the association between comorbidity types and OSA. These results underline the importance of the global comorbidity burden to be considered in OSA.

The usual symptoms were not associated with the diagnosis of OSA in our geriatric population, except for EDS. It was reported that traditional symptoms suggesting OSA (snoring, high BMI) were not significantly associated with OSA, while the sensation of not feeling well-rested, nocturia, and EDS were independently associated with OSA in community-dwelling independent older adults [9]. Our study was different from Endeshaw's, with very old inpatients (mean age 85.5 years old) from acute geriatric ward, dependant in ADL, and the comorbidities may be more prevalent than in the community-dwelling setting and may overshadow the OSA symptoms. To date, no study has investigated in very old inpatients aged over 75 years including clinical symptoms and comorbidities (using a validated comorbidity scale) associated with an objective diagnosis of OSA. Few studies on OSA with older inpatients have been reported. Shear et al. have reported that two of every 5 general medicine inpatients older than 50 years were screened at "high risk" for OSA using the Berlin questionnaire, without confirming the diagnosis of OSA [25]. Moreover, they have considered as eligible "older patients", ambulatory, community-dwelling adults aged 50

years or older (mean age 65 years old) who were cognitively intact; all these characteristics are far from the geriatric setting. Another study done in hospitalized adults (general medicine ward, n=66, mean age 53 years old) and older adults (geriatric ward, n=36, mean age 82 years old), reported that nearly 80% of hospitalized adults are at risk of sleep apnea, using the prospectively administered STOP-BANG and ISNORED questionnaires [26]. There was no confirmation of OSA, no clinical characteristics described, and individuals with cognitive impairment were excluded, a condition associated with OSA diagnosis, thus limiting comparison with our study. Concerning the comorbidities associated with OSA, limited data are available in older inpatients. The United States' nationwide study among older inpatients (aged over 65 years old), examine trends over time, and assess whether co-morbidities and other individual-level and hospital-level characteristics are related to a sleep disturbance diagnosis (i.e., insomnia, OSA, or other sleep disturbance) and hospitalization outcomes [24]. In this study, many comorbidities had independent positive associations with OSA: rheumatoid arthritis, congestive heart failure, depression, diabetes, hypertension, hypothyroidism, neurological disorders, pulmonary circulation disorders, renal failure, and most importantly obesity [24]. However, the clinical diagnostic codes (ICD-9-CM), given by a health provider, were used to estimate OSA; it is unclear what diagnostic tests were given to assess the symptoms/signs common to OSA, unlike to our study.

Screening OSA questionnaires (e.g Berlin or STOP-BANG) based on symptoms, age or BMI are not sufficiently accurate in the older population [17,18]. These studies were conducted in independent community-dwelling seniors. The existing OSA screening tool for older patients, the "Observation-based nocturnal sleep inventory", is based on nighttime observation of apneic episodes [15]. These results show how it is difficult to suggest OSA from only clinical symptoms in older population. Despite the fact that sleepiness was not assessed by the ESS considering its limitations in older population [15], the EDS reported by

the patient or caregiver was the only symptom statistically associated with OSA in our very old geriatric inpatients. Although there are many other causes of EDS in older people, these results emphasize its importance and encourage us to suspect OSA in co-morbid older patients. Studies performed specifically in older patients have reported that severe OSA not treated with CPAP is associated with mortality, and adequate CPAP treatment may reduce this risk [35]. The general view is to treat if OSA patients are symptomatic, whether they are young or old adults, but for example, the question of whether non-sleepy OSA should be routinely treated or not is controversial. It should be emphasized that the clinical picture of OSA in older is different; our study confirmed that only EDS and comorbidity severity were associated with the objective OSA. Diurnal dysfunction secondary to recurrent sympathetic arousals and hypoxemia during sleep are not universal findings in OSA. The evidence for successful treatment of asymptomatic OSA is not strong. However, the evidence for a direct link between untreated OSA and cardio-metabolic consequences is important, even though treatment does not always fully reverse the abnormalities. How to apply these data on a daily basis on older patients remains difficult [35]. And treatment is also challenging in older patients; among 64 OSA patients of our study, CPAP was not prescribed in 18.7% (n=12; severe dementia, moderate OSA without significant symptoms and without severe cardiorespiratory comorbidity, positional moderate OSA), 50% of patients refused or discontinued CPAP in the days following CPAP (n=32), and finally CPAP was prescribed and accepted in 31.3% (n=20) of the patients. Among the 20 patients treated by CPAP, 75% (n=15) were under CPAP at 3 months, with a mean adherence of 3hrs 34min per night. Ten patients had an adherence of more than 4h/night with >80% of days, out of the 15 patients still treated at 3 months (66,7%). In the future, studies on CPAP use in very old patients (≥ 75 years old) are needed to have an extensive view on this important point.

Prior studies showed gender differences in OSA related symptoms. In our study, there was no difference in OSA related symptoms between women and men in the univariate analysis among OSA patients, except for insomnia complaint and mood disorders, that are less specific of OSA. Moreover, the forward step-wise logistic regression model including gender in the OSA-related symptoms model analysis showed that gender was not associated with OSA. It was also reported that in a general community healthy youngest old population, females reported the cardinal symptoms of OSA less frequently and had a higher risk of having had, or being treated for, mood and anxiety disorders as in middle-aged studies [36]. Although depression and anxiety scores were higher in females with OSA, comparison of females with and without OSA showed that there were no significant differences between groups for anxiety and depression scores, as well as for previous psychiatric treatment. Therefore, sex differences in personality characteristics, more than the presence of OSA, contribute to clinical spectrum in females with OSA.

Strengths and limitations of the study

In this study, data were obtained from inpatients with very old age and well-characterized comorbidities who were representative of geriatric inpatients. Furthermore, OSA was diagnosed using nocturnal recording, more reliable than screening questionnaires.

Some limitations need to be addressed. Monocentric hospital setting, retrospective method with lack of data about ethnicity, cross-sectional design with a relatively small sample size of our study limit its generalization. Of note, Hnin et al. have highlighted that anatomical traits (i.e., obesity, fat distribution, and craniofacial structure) underlie differences in OSA prevalence and severity between ethnic groups; but obesity appears to be the most important factor [37]. However, our patient population was not obese and the mean BMI was $27.3 \pm 4.9 \text{ kg/m}^2$ in OSA group, and most of them came from European descent.

Although a polysomnography including EEG recording with sleep study was not performed, the diagnosis of OSA was confirmed by an overnight respiratory recording. One overnight recording may have limitation, but it allowed an objective diagnosis of OSA and not estimated by a questionnaire [29]. Endeshaw et al. had published clinical characteristic of OSA in older adults, using an overnight ambulatory sleep recording as our study, but they had studied in community-dwelling older participants who were independent in their instrumental activities of dialing living [9]. Because older population is heterogeneous, our study provided new information on clinical characteristic of OSA in geriatric inpatients.

Symptoms suggesting sleep apnea are often underreported or non-specific among older patients, and maybe not reliable in case of cognitive impairment. To limit this bias, symptoms suggesting sleep apnea were asked from both patients and caregivers if possible to be complete. Moreover, MMSE scores of the participants are around $21.5 \pm 5.6 / 30$, considered as mild to moderate cognitive impairment (mild — MMSE score of between 21 and 24, and moderate — MMSE score of between 10 and 20). Finally, there was no difference in MMSE scores and also in the percentage of cognitive impairment between OSA and non-OSA patients in our study. As older population is very heterogeneous, with differences, not only in living situation, but also in comorbidity burden and dependency, the aim of our study was to describe comorbidities and symptoms related to OSA in geriatric older inpatients with complex health problems, including dementia. Therefore we have detailed clinical characteristics to have a global view of these aged geriatric inpatients, and we have kept the representability of a geriatric unit, with patients with their comorbidities, including cognitive impairments. In our study, we have focused on usual symptoms, thus representing another limitation. Other symptoms (e.g., fatigue, palpitation, depression) were not asked. The EDS was not evaluated by the Epworth questionnaire in our study considering its limitations in the older population [5], but was reported either by the patient or the primary caregiver. Onen et

al. have reported that among all non demented older subjects complaining EDS, only 24% of them had an abnormal ESS score (>10). Almost 60 % of subjects and close relatives were not able to answer at least one question on the ESS [5]. The ESS may underestimate sleepiness severity in older subjects. The EDS was also not evaluated by Multiple Sleep Latency Test because while the test is a valuable and widely used diagnostic tool for narcolepsy and idiopathic hypersomnia, the use of Multiple Sleep Latency Test in other sleep disorders, including OSA is not well established [38]. This test measures how long it takes the patient to fall asleep during the day in a quiet environment, comprising 5 scheduled naps, separated by a two-hour break, in one day. In the absence of a questionnaire or tool evaluating EDS, suitable for older patients, EDS reported either by the patient or the primary caregiver can be considered sufficiently indicative to suspect sleep apnea in comorbid geriatric patients.

Lastly, other data such as duration of hospitalization, sleep duration, history of OSA and CPAP or other treatment in the past, were not collected in this study.

Despite these limitations, our study has clinical implications. OSA is highly prevalent in geriatric inpatients and we have shown that most of the usual OSA-related symptoms and comorbidities were not associated with the diagnosis of OSA. EDS, either self-reported or reported by caregiver, was the only OSA-related symptoms associated with OSA in this population. Usual OSA-related comorbidities were not associated with OSA in geriatric inpatients, probably because comorbidities may overshadow the association between comorbidity types and OSA. The severity of global comorbidity burden was indeed associated with the diagnosis of OSA, thus this aspect has to be considered in OSA.

CONCLUSION

Very few parameters were found to be associated with the diagnosis of OSA in geriatric inpatients: only EDS and comorbidity severity (CIRS-G “composite” score) were

associated with OSA. Multiple comorbidities may overshadow the usual OSA-related symptoms and comorbidities. These results emphasize the importance of suspecting OSA in comorbid sleepy older patients. Future Challenges in OSA in older patients include, among others, identification of other signs and uncommon symptoms that could be more specific to OSA in older patients with a validation of specific questionnaires, and treatment with CPAP in very old age (over 75 years).

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Conflict of interest

The authors have no conflict of interest to declare.

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Author contributions

AM and KK participated in study concept and design, acquisition of subjects and/or data, analysis and interpretation of data, and wrote the manuscript. MD conducted statistical analysis and participated in the interpretation of data. CL participated in the data collection. KK and VNM participated in acquisition of subjects and/or data. JM and EP participated in the preparation of the manuscript.

Ethical statement

The ethics Institutional Review board (IRB00003888) has approved the study protocol. Patients were informed of the possibility of objecting medical data collection, and informed consent was thus waived in this context.

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