Michalis Agrafiotis[1], Artemis Galanou[1], Dimosthenis Fletsios[1], Anastassia Chassiotou[1], Diamantis Chloros[1], Paschalis Steiropoulos[2]

[1]Department of Pulmonary Medicine, "Georgios Papanikolaou" General Hospital of Thessaloniki, Exohi, Greece
[2]Department of Pneumonology, Medical School, Democritus University of Thrace, Alexandroupolis, Greece

Functional Comorbidity Index and health-related quality of life in patients with obstructive sleep apnea

Abstract

Introduction: The role of comorbidities in determining health-related quality of life (HRQL) in obstructive sleep apnea (OSA) patients has not been thoroughly investigated. Commonly used comorbidity tools, such as Charlson Comorbidity Index (CCI), have been designed with mortality as the outcome variable. A new tool, the Functional Comorbidity Index (FCI), has been especially developed to assess the effect of comorbidities on the "physical functioning" subscale of the Medical Outcomes Short Form-36 Health Survey (SF-36). 1) To determine the role of FCI in the prediction of the effect of comorbidities on HRQL in OSA. 2) To determine whether FCI and CCI are equally robust in predicting the effect of comorbidities on HRQL in OSA.

Material and methods: Two hundred and fifty-five OSA patients were enrolled. Patients completed the SF-36 and the Medical Outcomes Study Sleep Scale (MOS-SS) forms, while their comorbidity status was assessed by FCI and CCI. The SF-36 physical (PCS-36) and mental component summary (MCS-36) scores were also calculated.

Results: PCS-36 was predicted by FCI ($p < 0.001$), male gender ($p = 0.001$), BMI ($p = 0.002$) and the "awakening with "breathlessness/headache" MOS-SS subscale ($p = 0.011$) ($R^2 = 0.348$). Among these predictors, FCI exerted the most important quantitative effect. MCS-36 was predicted only by the "sleep disturbance" ($p = 0.005$) and the "awakening with breathlessness/headache" MOS-SS subscales ($p < 0.001$) ($R^2 = 0.221$).

Conclusions: In patients with OSA, FCI is an independent predictor of the physical aspect of their HRQL. FCI is more robust than CCI in assessing the effect of comorbidities on HRQL in OSA.

Key words: obstructive sleep apnea, multimorbidity, functional outcome, headache, sleepiness, obesity, dyspnoea

Adv Respir Med. 2022; 90: 9–16

Introduction

Multimorbidity is very common in patients with obstructive sleep apnea (OSA) and appears to exert a significant effect on their health-related quality of life (HRQL) [1–4] . Therefore, adjustment for comorbidities is essential to understand the relative contributions of various factors in determining HRQL in OSA and to assess the effectiveness of therapeutic interventions.

Although there is a multitude of comorbidity indices, the majority of them are calibrated to predict mortality or administrational outcomes (e.g. length of hospital stay). Thus, the Charlson Comorbidity Index (CCI), which grades multimorbidity according to the presence or absence of 19 diseases/disorders, has been originally designed to predict 1-year mortality [5]. A new comorbidity tool, the Functional Comorbidity Index (FCI), employs the Medical Outcomes Study Short Form-36 Health Survey (SF-36) "physical functioning" subscale as the outcome variable and has been especially designed to assess the effect of comorbidities on HRQL. FCI calculation is based on a list of 18 diseases/disorders which may affect daily functioning [6].

FCI has been tested in various patient groups, including acute respiratory distress syndrome

Address for correspondence: Michalis Agrafiotis, Department of Pulmonary Medicine, "Georgios Papanikolaou" General Hospital of Thessaloniki, Exohi, Greece, Papanikolaou Ave, 57010 Exohi, Greece, e-mail: m.agrafiotis@gmail.com

DOI: 10.5603/ARM.a2022.0001 | Received: 29.12.2020 | | ISSN 2451–4934 | e-ISSN 2543–6031

(ARDS) survivors [7], chronic rhinosinusitis [8], stroke [9] , injury [10] and primary care patients [11]. Fan et al reported an excellent FCI interobserver variability in patients with acute lung injury [12]. In a study involving patients with OSA, FCI displayed a stronger correlation with the SF-36 "physical functioning" subscale, as compared to CCI. However, in this study a direct comparison between the two tools in the prediction of HRQL was not performed [2].

Hence, the aim of this study is twofold; first to investigate the role of FCI as a predictor of HRQL in OSA patients; second to explore whether FCI and CCI are equally robust as predictors of HRQL in these patients.

Material and methods

Patient recruitment and assessment

This was a cross-sectional, observational study which took place between 05/07/2018 and 30/04/2019. Patients were recruited from the Outpatient Sleep Clinic of the Department of Pulmonary Medicine of the "Georgios Papanikolaou" General Hospital of Thessaloniki, Exohi, Greece. Patients with probable OSA were interviewed, clinically examined, and subsequently scheduled for sleep studies within 3–4 weeks. Exclusion criteria were previous diagnosis or treatment of OSA, unstable medical or psychiatric disease, central sleep apnea, non-respiratory sleep disorders, pregnancy and age <18 years. On initial evaluation, all interviewees completed 3 questionnaires: the Epworth Sleepiness Scale [13], SF-36 [14] and the Medical Outcomes Study Sleep Scale (MOS-SS) [15]. In addition, the interviewer scored CCI [5] and FCI scales [6], based on each patient's history and clinical findings.

ESS is an 8-item questionnaire designed to evaluate excessive daytime sleepiness (EDS) [13]. SF-36, a generic HRQL tool comprising 36-items, interrogates 8 major health domains for a recall period of 4 weeks [14]. This 8-factor structure can be collapsed into a 2-factor structure representing the physical and the mental SF-36 summary components, i.e. the Physical Summary Score (PCS-36) and the Mental Summary Score (MCS-36), with higher values indicating better HRQL [16, 17]. A validated Greek SF-36 translation and normative Greek data for individual and summary subscales have been previously published [18, 19].

MOS-SS is a 12-item non-specific questionnaire designed for evaluating sleep across 6 individual domains for a recall period of 4 weeks. These domains include: 1) "sleep disturbance", i.e. the ability to fall asleep and maintain sleep 2) "snoring" 3) "awakening with breathlessness or headache" 4) "sleep adequacy", i.e. the ability of sleep to provide restoration 5) "sleep quantity", i.e. the amount of sleep in hours 6) "somnolence", i.e. daytime drowsiness or sleepiness. Except for "sleep quantity", all the other items are reported on an 0-100 scale.

Higher scores for "sleep disturbance", "snoring", "awakening with sleepiness/headache" and "somnolence" and lower scores for "sleep quantity" and "adequacy" indicate worse sleep quality and more severe sleep problems. MOS-SS also yields two summary scores, "sleep problems indices I and II" with higher scores suggesting worse sleep quality [15]. A validated Greek translation of the MOS-SS questionnaire has recently become available [20].

CCI calculation assigns a weighted score on each of 19 conditions/comorbidities (range 0–37) [5]. FCI is calculated based on a list of 18 diseases/disorders with a score of 1 assigned to each of them, if present, and a score of 0, if absent. FCI total score is derived by summing up all individual scores (range: 0–18) [6].

Sleep studies

Patients underwent either type I studies (in-laboratory polysomnographies) or attended type III studies (in-laboratory cardiorespiratory polygraphies). The choice of the study type was exclusively based on equipment availability. Type I studies setup included electroencephalography (F3, F4, C3, C4, O1, O2), electrooculography and submental electromyography; thoracic and abdominal motion was assessed by respiratory inductance plethysmography (RIP), oxygenation by pulse oximetry (SaO_2) and airflow by nasal pressure (NP) cannulas and oronasal (ON) thermal devices. Type III studies setup included NP cannula for airflow, pulse oximetry for oxygenation and RIP thoracic/abdominal belts for respiratory effort assessment; a microphone for recording snoring was used in both types of studies. A minimum of 4 hours of total sleep (type I studies) or total recording time (type III studies) was required to consider a study acceptable. Sleep staging was performed according to the American Academy of Sleep Medicine guidelines [21]. With respect to respiratory variables, an apnea was scored when there was a drop in peak airflow signal (ON thermistor or NP canula) excursion by > 90% lasting for ≥ 10 seconds; a hypopnea was scored when there was a > 30% drop in peak airflow signal (NP cannula) excursion lasting ≥ 10 seconds and

associated with a 3% desaturation. The presence of respiratory effort throughout the whole event or at the last part of it indicated an obstructive or a mixed apnea, respectively; otherwise a central apnea was scored [21, 22]. For type I studies, AHI was calculated as the number of apnoeic/hypopnoeic events divided by the total sleep time; for type III studies, the respiratory event index (REI) was calculated as the number of apnoeic/hypopnoeic events divided by the total recording time. Percentage of time with a $SpO_2 < 90\%$ was calculated by dividing the respective time by the total sleep (type I studies) or the total recording time (type III studies). Oxygen desaturation index (number of times with a saturation > 3% per hour, ODI) and minimum oxygen saturation during the study (min SaO_2) were calculated accordingly.

Definitions

EDS was defined based on an ESS > 10 [23]. Sleep hypoxemia was defined based on a time with a $SaO_2 < 90\%$ higher than 10% [24]. OSA was diagnosed in patients with an AHI/REI > 5/hour, when the majority of apnoeic/hypopnoeic events were obstructive. The severity of OSA was graded as follows: mild for 5 < AHI/REI ≤ 14.9; moderate for 15 ≤ AHI/REI ≤ 29.9 and; severe for AHI/REI ≥ 30 [23].

Statistical analysis

Histograms and normal Q-Q plots were inspected to disclose any departure from normality. Continuous variables are presented as mean ± standard deviation (SD) or as median (25^{th} percentile, 75^{th} percentile) as appropriate and categorical variables as frequency counts and as proportions. FCI and CCI are presented as ranges and as percentages of individual scores. Bivariate correlations between variables were assessed with Spearman's rank order correlation coefficient (rho). Independent-samples t-test was used for comparisons between males and females for PCS-36 and MCS-36 scores. Z-test was used to compare PCS-36 and MCS-36 scores to normative Greek data. Multiple linear regression equations with all independent variables entered in one step were developed to determine the independent predictors of PCS-36 and MCS-36. F-statistic was used to assess the global model significance. The percentage of the dependent variable variance explained by the model was determined by adjusted R squared (R^2). All statistical tests were two-tailed and a $p < 0.05$ was assumed to indicate statistical significance. Statistical procedures were performed with the Statistical Package for Social Sciences (SPSS), version 23 (IBM corporation, Armonk, NY, USA).

Ethics

The Scientific Council Ethics Subcommittee of the "Georgios Papanikolaou" General Hospital of Thessaloniki approved the study protocol (1017/05.07.2018) and all patients gave written informed consent for their enrolment into this strictly observational, cross-sectional study.

Results

Descriptive statistics

Two-hundred and fifty-five patients with an established diagnosis of OSA and acceptable sleep studies were enrolled into the study. Demographic, clinical and sleep study data are summarized in Table 1. Their mean age was 51 ±

Table 1. Demographic, clinical and sleep study data of patients (N = 225)

Variable	Value
Age [years][1]	51.0 ± 11.2
Gender, n (%)	Males: 193 (75.7) Females: 62 (24.3)
BMI [kg/m^2][1]	33.8 ± 10.6
ESS[2]	9 (6, 12)
EDS, n (%)[2]	92 (36.4)
Study type, n (%)	Type I: 215 (84.3) Type III: 40 (15.7)
FCI score, n (%)[3]	0: 42 (16.5) 1: 86 (33.7) 2: 70 (27.5) 3: 29 (11.4) 4: 22 (8.6) 5: 5 (2.0) 7: 1 (0.4)
CCI score, n (%)[3]	0: 196 (76.9) 1: 39 (15.3) 2: 13 (5.1) 3: 6 (2.4) 5: 1 (0.4)
AHI/REI (events/hour)[2]	39.1 (18.4, 66.2)
OSA severity distribution	Mild: 53 (20.8) Moderate: 46 (18) Severe: 156 (61.2)
ODI (events/hour)[2]	34.1 (16.4, 60.1)
Time with $SaO_2 < 90\%$ (%)[2]	9 (1, 34.6)
minSaO_2 (%)[2]	79 (71, 85)
Sleep hypoxemia, n (%)	122 (47.8)

[1]mean ± SD; [2]median (25^{th} percentile, 75^{th} percentile); [3]percentages of each individual score

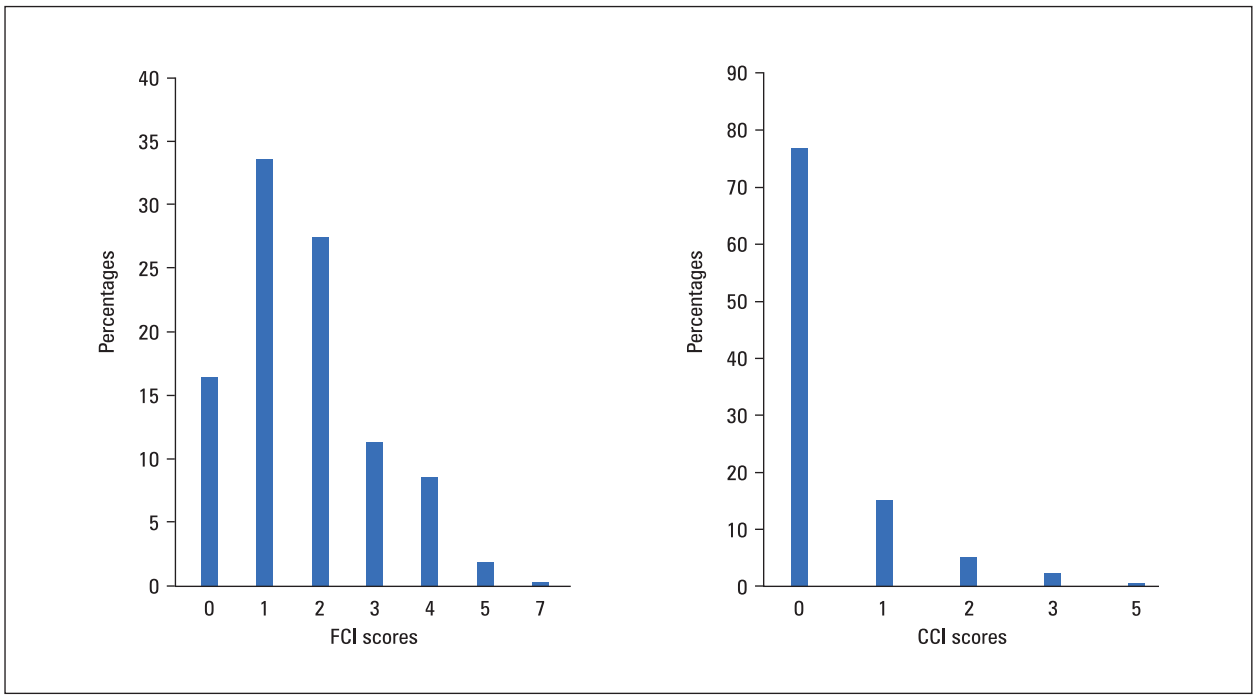

Figure 1. Distribution of FCI and CCI scores expressed as percentages of total patient population

11.2 years and 75.7% were males. Their median ESS was 9 (6, 12) with 36.4% presenting with EDS. Most patients (84.3%) underwent type I sleep studies, while attended type III studies were performed in the rest (15.7%). Their median AHI/REI was 39.1 (18.4, 66.2)/hour, with 20.8% suffering from mild OSA, 18% from moderate OSA and 61.2% from severe OSA. Sleep hypoxemia was observed in 47.8%. FCI score was ≤ 2 in 77.6% and ≤ 4 in 97.6% of the patients; on the other hand, 92.2% of the patients had a CCI score ≤ 1 and 76.9% had a score of 0 (Figure 1). Regarding FCI diseases/disorders, obesity was the most common (64.7%), followed by upper gastrointestinal disease (29%), degenerative disk disease (10.6%), diabetes (10.2%) and depression (10.2%) (Table 1). Among the CCI diseases/disorders, diabetes without end-organ damage was the most common (7.1%), followed by congestive heart failure (5.5%), myocardial infarction (4.7%) and diabetes with end-organ damage (4.4%) (Table 2).

Health-related quality of life

Based on normative Greek data [18, 19], both mean PCS-36 and MCS-36 were significantly reduced in our cohort of Greek patients with OSA (43.4 ± 10.3 vs. 50.2 ± 11.8, p < 0.001 and; 41.7 ± 11.5 vs. 47.6 ± 9.3, p < 0.001, respectively) (Table 3).

Table 2. PCS-36 and MCS-36 model summaries

Model	F statistic	p	Adjusted R^2
PCS-36	12.164	P < 0.001	0.348
MCS-36	9.955	P < 0.001	0.221

Correlations and univariate analysis

Univariate analysis was performed to determine the strength, direction and significance of correlations between PCS-36/MCS-36 scores and demographic (age, gender), clinical (BMI, ESS, FCI, CCI), sleep quality (MOS-SS scores) and sleep study (AHI/REI, time with a SaO_2 < 90%, ODI, minSaO_2) variables (Table 4). Mean PCS-36 was significantly higher in males vs. females (45.6 ± 9.7 vs. 36.7 ± 9.1 years, p < 0.001) and displayed a significant negative correlation with age (rho –0.177, p < 0.05), BMI (rho –0.340, p < 0.001), ESS (rho –0.136, p < 0.05), time with a SaO_2 < 90% (rho –0.181, p < 0.05), FCI (rho –0.445, p < 0.001), CCI (rho –0.264, p < 0.001), "sleep disturbance" (rho –0.292. p < 0.001), "awakening with breathlessness/headache" (rho –0.307, p < 0.001) and "somnolence" (rho –0.186, p < 0.05). PCS-36 also had a significant positive correlation with "sleep adequacy" (rho 0.153, p < 0.05) and "sleep quantity" (rho 0.144, p < 0.05). Mean MCS-36 was also significantly higher in

Table 3. PCS-36 model variables, coefficients and significances

PCS-36 model variables	Beta coefficients (SE)	Standardized beta coefficients	P
Male gender*	4.760 (1.399)	0.194	0.001
Age	–0.097 (0.056)	–0.105	0.084
BMI*	–0.298 (0.096)	–0.189	0.002
ESS	–0.058 (0.126)	–0.030	0.645
Time with SaO_2 < 90%	0.011 (0.025)	0.026	0.428
FCI*	–2.158 (0.499)	–0.269	< 0.001
CCI	–0.682 (0.840)	–0.048	0.418
Sleep disturbance	–0.032 (0.028)	–0.071	0.246
Awakening with breathlessness/headache*	–0.049 (0.019)	–0.155	0.011
Sleep adequacy	0.031 (0.021)	0.092	0.143
Somnolence	–0.019 (0.028)	–0.047	0.498
Sleep quantity	–0.382 (0.399)	–0.056	0.339

*statistical significance; SE — standard error

males vs. females (43.0 ± 11.4 vs. 37.7 ± 10.9 years, p = 0.001) and showed a significant negative correlation with ESS (rho –0.149, p < 0.05), FCI (rho –0.201, p < 0.05), "sleep disturbance" (rho –0.342, p < 0.001), "snoring" (rho –0.125, p < 0.05), "awakening with breathlessness/headache" (rho –0.382, p < 0.001) and "somnolence" (rho –0.305, p < 0.001). MCS-36 also showed a significant positive correlation with "sleep adequacy" (rho 0.237, p < 0.001). For all other variables, correlations were non-significant (p > 0.1).

Prediction of health-related quality of life

All demographic, clinical, sleep study and sleep quality variables with a significant correlation (p < 0.05) with the PCS-36/MCS-36 scores were force-entered into multiple linear regression models, in which PCS-36 and MCS-36 were defined as the dependent variables.

PCS-36

The combinations of the included variables significantly predicted PCS-36 (F = 12.164, p < 0.001). According to the adjusted R^2 value, the model could explain approximately 35% of PCS-36 variance (Table 2). PCS-36 was predicted by male gender (p = 0.001), BMI (p = 0.002), FCI (p < 0.001) and "awakening with breathlessness/headache" (p = 0.011). According to the standardized beta coefficients, FCI was the most important quantitative predictor of PCS-36 (–0.269), followed by male gender (0.194), BMI (–0.189) and "awakening with breathlessness/headache" (–0.155) (Table 3).

MCS-36

The combinations of the included variables significantly predicted MCS-36 (F = 9.955, p < 0.001), while approximately 22% of MCS-36 variance could be explained by the model (Table 2). MCS-36 was predicted by "sleep disturbance" (p = 0.005) and "awakening with breathlessness/headache" (p < 0.001), the latter also being its most important quantitative predictor (Table 4).

Discussion

This study has demonstrated that FCI is independently associated with the physical, but not the mental aspect of HRQL in OSA patients, while sleep quality influences both. Importantly, FCI is the most important quantitative determinant of the physical aspect of HRQL in OSA as compared to the other clinical, demographic and sleep quality predictors. In addition, FCI is more robust than CCI in assessing the effect of comorbidities on HRQL.

Although several studies have shown that multimorbidity exerts a negative impact on HRQL in OSA, only a few of them have employed structured comorbidity tools in their assessments. In the study by Martinez-Garcia et al, CCI was an independent predictor of several of SF-36 subscales but this effect was clear only in OSA patients > 65 years old [3]. A correlation between CCI and most SF-36 subscales in OSA has also been reported by other authors [1]. To the best of our knowledge, only one study has compared FCI and CCI as predictors of HRQL outcomes in OSA patients.

Table 4. MCS-36 model-1 variables, coefficients and significance

MCS-36 model variables	Beta coefficients (SE)	Standardized beta coefficients	p
Male gender	1.490 (1.632)	0.056	0.362
ESS	0.034 (0.151)	0.016	0.821
FCI	–0.765 (0.524)	–0.086	0.145
Sleep disturbance*	–0.094 (0.033)	–0.187	0.005
Snoring	0.006 (0.027)	0.014	0.810
Awakening with breathlessness/head-ache*	–0.086 (0.023)	–0.244	< 0.001
Sleep adequacy	0.027 (0.023)	0.072	0.242
Somnolence	–0.061 (0.033)	–0.136	0.066

*statistical significance; SE — standard error

Thus, in a study of 250 OSA patients, Levine and Weaver observed that both FCI and CCI predicted "physical functioning", PCS-36 and MCS-36 scores, although FCI explained a higher percentage of the above outcomes' variance; however, in this study, FCI and CCI were considered in separate regression models and thus were not directly compared [2]. By entering FCI and CCI in the same model, our study demonstrated that FCI predicted only PCS-36 scores, while neither PCS-36 nor MCS-36 were influenced by CCI. Importantly, among other PCS-36 predictors, FCI exerted the most significant quantitative effect. These findings can be explained by the fact that FCI was designed with the SF-36 "physical functioning" subscale as the outcome variable. In addition, FCI had a wider range of score distribution than CCI, given that several variables that may impact on HRQL (e.g. obesity, osteoporosis, spine disease, depression, gastric reflux etc.) are included in FCI [6], but not in CCI [5].

The detrimental effects of impaired sleep quality on HRQL of patients with OSA has been suggested by several other studies. Lee et al have also shown that "sleep problems index II" is independently associated with both PCS-36 and MCS-36 scores in a cohort of 793 patients with OSA [25]. Other authors have also demonstrated an association between difficulties in initiating and maintaining sleep and impaired HRQL in OSA patients [26] and in large-scale population studies [27]. Likewise, our study has observed an association between HRQL and the "awakening with breathlessness/headache" and "sleep disturbance" MOS-SS subscales, the former being specifically pertinent to complaints commonly reported by OSA patients [28].

The detrimental effect of obesity mainly on the physical aspect of HRQL scores in OSA has also been demonstrated by several authors [2, 4, 25]. In the present study obesity exerts a negative effect on PCS-36 scores via the effect of two independent variables: first, the FCI score which increases by one point in obese patients (BMI > 30kg/m^2); second, the BMI which is negatively correlated with PCS-36 scores, suggesting a poorer physical aspect of HRQL for more obese patients. In addition, this study demonstrated that male as opposed to female gender is associated with a better physical aspect of HRQL in agreement with previous reports [29,30].

In contrast to some [25, 27, 31, 32] but not all [1, 26] studies, neither AHI/REI nor the indices of sleep desaturation were correlated with impaired HRQL in our cohort of OSA patients. On the other hand, by using a simple-count (tier) comorbidity tool which incorporated most of the FCI diseases/disorders, Ruel et al. demonstrated a significant association between OSA severity and multimorbidity; moreover, the co-existence of ≥ 3 comorbidities in patients with moderate-to-severe OSA was associated with a greater reduction in HRQL [4]. It is possible that the severity of sleep-disordered breathing in our study might indirectly impair HRQL by inducing sleep fragmentation and reducing sleep quality (e.g. "sleep disturbance") or influencing symptoms and health perception in patients with various comorbidities, e.g. obesity, asthma or heart failure [33–36].

Although numerous studies have demonstrated a relationship between EDS and HRQL scores [25–27, 31, 32, 37–39], in the present study neither "somnolence" nor ESS scores were included in the PCS-36/MCS-36 predictors. However, the vast majority of the patients (75%) had an ESS ≤ 12 with only 36.4% of them presenting with EDS (ESS > 10), while percentages between 40% and 53% have been reported by some tertiary

centers [25, 37, 40, 41]. This finding may indicate an increasing awareness of sleep problems among healthcare providers and users leading to earlier referral and a higher diversity of sleep complaints.

This study has several limitations. First, neither of the two comorbidity tools we used displayed an association with MCS-36. Thus, the effect of comorbidities on the mental aspect of HRQL could not be defined by this study. However, by virtue of its own design, FCI is limited to the prediction of the physical aspect of HRQL. Likewise, Fortin et al observed a significant negative correlation between FCI and PCS-36, but no correlation with MCS-36 in primary care patients [11]. On the other hand, Levine and Weaver reported a correlation between MCS-36 and FCI in patients with OSA, as well as between MCS-36 and CCI, although the latter was much weaker [2]. Second, polygraphy rather than polysomnography was used for OSA diagnosis in some included patients, although the number of patients who underwent polygraphy is relatively small (15.7%). Nevertheless, it is unlikely that in-lab attended studies might yield grossly different results in terms of disease severity and diagnostic efficacy as compared to polysomnography, especially regarding patients with a high OSA suspicion [42]. Third, the efficacies of our models in the prediction of the HRQL are rather limited, accounting for 35% and 22% of PCS-36 and MCS-36 variances, respectively. It is possible that other variables, not considered here e.g. depression, might also exert a significant impact on HRQL in OSA patients [25].

Despite the abovementioned limitations, the findings of this study have some clinical merit. Multimorbidity, as assessed by FCI, is a very important determinant of the physical aspect of HRQL in OSA but does not exert any effect on its mental counterpart; sleep quality however affects both. In addition, FCI is more robust that CCI in assessing the impact of comorbidities on HRQL in OSA.

Conflict of interest

None to declared.

References

1. Gülbay BE, Acican T, Onen ZP, et al. Health-related quality of life in patients with sleep-related breathing disorders: relationship with nocturnal parameters, daytime symptoms and comorbid diseases. Respiration. 2008; 75(4): 393–401, doi: 10.1159/000104865, indexed in Pubmed: 17596681.
2. Levine CG, Weaver EM. Functional comorbidity index in sleep apnea. Otolaryngol Head Neck Surg. 2014; 150(3): 494–500, doi: 10.1177/0194599813518164, indexed in Pubmed: 24395621.
3. Martínez-García MA, Soler-Cataluña JJ, Román-Sánchez P, et al. Obstructive sleep apnea has little impact on quality of life in the elderly. Sleep Med. 2009; 10(1): 104–111, doi: 10.1016/j.sleep.2007.11.009, indexed in Pubmed: 18207454.
4. Ruel G, Martin SA, Lévesque JF, et al. Association between multimorbidity and undiagnosed obstructive sleep apnea severity and their impact on quality of life in men over 40 years old. Glob Health Epidemiol Genom. 2018; 3: e10, doi: 10.1017/gheg.2018.9, indexed in Pubmed: 30263134.
5. Charlson M, Pompei P, Ales K, et al. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. Journal of Chronic Diseases. 1987; 40(5): 373–383, doi: 10.1016/0021-9681(87)90171-8.
6. Groll DL, To T, Bombardier C, et al. The development of a comorbidity index with physical function as the outcome. J Clin Epidemiol. 2005; 58(6): 595–602, doi: 10.1016/j.jclinepi.2004.10.018, indexed in Pubmed: 15878473.
7. Groll DL, Heyland DK, Caeser M, et al. Assessment of long-term physical function in acute respiratory distress syndrome (ARDS) patients: comparison of the Charlson Comorbidity Index and the Functional Comorbidity Index. Am J Phys Med Rehabil. 2006; 85(7): 574–581, doi: 10.1097/01.phm.0000223220.91914.61, indexed in Pubmed: 16788388.
8. Levine C, Davis G, Weaver E. Functional Comorbidity Index in chronic rhinosinusitis. International Forum of Allergy & Rhinology. 2015; 6(1): 52–57, doi: 10.1002/alr.21620.
9. Tessier A, Finch L, Daskalopoulou SS, et al. Validation of the Charlson Comorbidity Index for predicting functional outcome of stroke. Arch Phys Med Rehabil. 2008; 89(7): 1276–1283, doi: 10.1016/j.apmr.2007.11.049, indexed in Pubmed: 18586129.
10. Gabbe BJ, Harrison JE, Lyons RA, et al. Victorian Orthopaedic Trauma Outcomes Registry. Comparison of measures of comorbidity for predicting disability 12-months post-injury. BMC Health Serv Res. 2013; 13: 30, doi: 10.1186/1472-6963-13-30, indexed in Pubmed: 23351376.
11. Fortin M, Hudon C, Dubois MF, et al. Comparative assessment of three different indices of multimorbidity for studies on health-related quality of life. Health Qual Life Outcomes. 2005; 3: 74, doi: 10.1186/1477-7525-3-74, indexed in Pubmed: 16305743.
12. Fan E, Gifford JM, Chandolu S, et al. The functional comorbidity index had high inter-rater reliability in patients with acute lung injury. BMC Anesthesiol. 2012; 12: 21, doi: 10.1186/1471-2253-12-21, indexed in Pubmed: 22974239.
13. Johns, MW. Sleepiness in different situations measured by the Epworth iness Scale. Sleep. 1994; 17(8): 703–10.
14. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992; 30(6): 473–83.
15. Hays RD, Steward AL. Sleep measures. In: Measuring functioning and well-being: the Medical Outcomes Study. 1992: 235–259.
16. Ware J, Gandek B, Kosinski M, et al. The equivalence of SF-36 summary health scores estimated using standard and country-specific algorithms in 10 countries. Journal of Clinical Epidemiology. 1998; 51(11): 1167–1170, doi: 10.1016/s0895-4356(98)00108-5.
17. Ware JE, Kosinski M. SF-36 physical and mental health summary scales. Lincoln, Rhode Island: Quality Metric 2001.
18. Kontodimopoulos N, Pappa E, Niakas D, et al. Validity of SF-12 summary scores in a Greek general population. Health Qual Life Outcomes. 2007; 5: 55, doi: 10.1186/1477-7525-5-55, indexed in Pubmed: 17900374.
19. Pappa E, Kontodimopoulos N, Niakas D. Validating and norming of the Greek SF-36 Health Survey. Qual Life Res. 2005; 14(5): 1433–1438, doi: 10.1007/s11136-004-6014-y, indexed in Pubmed: 16047519.
20. Mpougia, ME. Discriminative power and reliability of the Medical OUtcomes Study Sleep Scale: a study on patients with sleep-disordered breathing. 2016.Master of Science. Democritus University of Thrace.
21. Iber C, Ancoli-Israel S, Chesson A, et al. The AASM manual for the scoring of sleep and associated events. 2007.
22. Berry RB, Budhiraja R, Gottlieb DJ, et al. American Academy of Sleep Medicine. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and

Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2012; 8(5): 597–619, doi: 10.5664/jcsm.2172, indexed in Pubmed: 23066376.
23. Simonds AK, Backer WD. ERS Handbook of Respiratory Sleep Medicine. European Respiratory Society 2012.
24. Janssens JP, Borel JC, Pépin JL, et al. SomnoNIV Group. Nocturnal monitoring of home non-invasive ventilation: the contribution of simple tools such as pulse oximetry, capnography, built-in ventilator software and autonomic markers of sleep fragmentation. Thorax. 2011; 66(5): 438–445, doi: 10.1136/thx.2010.139782, indexed in Pubmed: 20971980.
25. Lee W, Lee SA, Ryu HUk, et al. Quality of life in patients with obstructive sleep apnea: Relationship with daytime sleepiness, sleep quality, depression, and apnea severity. Chron Respir Dis. 2016; 13(1): 33–39, doi: 10.1177/1479972315606312, indexed in Pubmed: 26396158.
26. Silva GE, An MW, Goodwin JL, et al. Longitudinal evaluation of sleep-disordered breathing and sleep symptoms with change in quality of life: the Sleep Heart Health Study (SHHS). Sleep. 2009; 32(8): 1049–1057, doi: 10.1093/sleep/32.8.1049, indexed in Pubmed: 19725256.
27. Baldwin CM, Griffith KA, Nieto FJ, et al. The association of sleep-disordered breathing and sleep symptoms with quality of life in the Sleep Heart Health Study. Sleep. 2001; 24(1): 96–105, doi: 10.1093/sleep/24.1.96, indexed in Pubmed: 11204058.
28. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. Journal of Clinical Sleep Medicine. 2009; 05(03): 263–276, doi: 10.5664/jcsm.27497.
29. Appleton SL, Vakulin A, McEvoy RD, et al. Undiagnosed obstructive sleep apnea is independently associated with reductions in quality of life in middle-aged, but not elderly men of a population cohort. Sleep Breath. 2015; 19(4): 1309–1316, doi: 10.1007/s11325-015-1171-5, indexed in Pubmed: 25896898.
30. Tasbakan MS, Gunduz C, Pirildar S, et al. Quality of life in obstructive sleep apnea is related to female gender and comorbid insomnia. Sleep Breath. 2018; 22(4): 1013–1020, doi: 10.1007/s11325-018-1621-y, indexed in Pubmed: 29352360.
31. Lee HK, Park DH, Shin HS, et al. Relationship between quality of life and mood or depression in patients with severe obstructive sleep apnea syndrome. Chest. 2002; 122(3): 861–865, doi: 10.1378/chest.122.3.861, indexed in Pubmed: 12226024.
32. Kang JM, Kang SG, Cho SJ, et al. The quality of life of suspected obstructive sleep apnea patients is related to their subjective sleep quality rather than the apnea-hypopnea index. Sleep Breath. 2017; 21(2): 369–375, doi: 10.1007/s11325-016-1427-8, indexed in Pubmed: 27815846.
33. de Raaff CAL, Coblijn UK, de Klerk ESM, et al. Impact of obstructive sleep apnea on quality of life after laparoscopic Roux-en-Y gastric bypass. Surgeon. 2018; 16(3): 151–155, doi: 10.1016/j.surge.2017.04.003, indexed in Pubmed: 28549529.
34. Redeker NS, Jeon S, Muench U, et al. Insomnia symptoms and daytime function in stable heart failure. Sleep. 2010; 33(9): 1210–1216, doi: 10.1093/sleep/33.9.1210, indexed in Pubmed: 20857868.
35. Redeker NS, Muench U, Zucker MJ, et al. Sleep disordered breathing, daytime symptoms, and functional performance in stable heart failure. Sleep. 2010; 33(4): 551–560, doi: 10.1093/sleep/33.4.551, indexed in Pubmed: 20394325.
36. Teng YK, Chiang LC, Lue KH, et al. Poor sleep quality measured by polysomnography in non-obese asthmatic children with or without moderate to severe obstructive sleep apnea. Sleep Med. 2014; 15(9): 1062–1067, doi: 10.1016/j.sleep.2014.04.017, indexed in Pubmed: 25018024.
37. Vinnikov D, Blanc PD, Alilin A, et al. Fatigue and sleepiness determine respiratory quality of life among veterans evaluated for sleep apnea. Health Qual Life Outcomes. 2017; 15(1): 48, doi: 10.1186/s12955-017-0624-x, indexed in Pubmed: 28288646.
38. Stepnowsky C, Sarmiento KF, Bujanover S, et al. Comorbidities, health-related quality of life, and work productivity among people with obstructive sleep apnea with excessive sleepiness: findings from the 2016 US national health and wellness survey. J Clin Sleep Med. 2019; 15(2): 235–243, doi: 10.5664/jcsm.7624, indexed in Pubmed: 30736870.
39. Wanberg LJ, Rottapel RE, Reid ML, et al. Prevalence of sleepiness and associations with quality of life in patients with sleep apnea in an online cohort. J Clin Sleep Med. 2021; 17(12): 2363–2372, doi: 10.5664/jcsm.9436, indexed in Pubmed: 34170220.
40. Lee SA, Han SH, Ryu HUk. Anxiety and its relationship to quality of life independent of depression in patients with obstructive sleep apnea. J Psychosom Res. 2015; 79(1): 32–36, doi: 10.1016/j.jpsychores.2015.01.012, indexed in Pubmed: 25661543.
41. Ryu HS, Lee SA, Lee GH, et al. Subjective apnoea symptoms are associated with daytime sleepiness in patients with moderate and severe obstructive sleep apnoea: a retrospective study. Clin Otolaryngol. 2016; 41(4): 395–401, doi: 10.1111/coa.12659, indexed in Pubmed: 27086649.
42. Masa JF, Corral J, Pereira R, et al. Effectiveness of home respiratory polygraphy for the diagnosis of sleep apnoea and hypopnoea syndrome. Thorax. 2011; 66(7): 567–573, doi: 10.1136/thx.2010.152272, indexed in Pubmed: 21602541.