



Symptoms of Daytime Sleepiness and Sleep Apnea in Liver Cirrhosis Patients

Al Enezi Abdullah,* Fares AL-Jahdali,* Anwar E. Ahmed,** Nahid Shirbini,*** AL-Harbi Abdullah,*** Baharoon Salim,*** Yosra Z. Ali,** Aljumah Abdulrahman,**** Mohd Khan,* Abdullah Khaleid,**** AL-Jahdali Hamdan***

* College of Medicine. King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.

** College of Public Health and Health Informatics. King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.

*** Department of Medicine, Pulmonary Division, and Sleep Disorders Center. King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.

**** Departments of Hepatobiliary Surgery and Liver Transplantation. King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.

ABSTRACT

Background/propose. Sleep disturbance and excessive daytime sleepiness (EDS) have been reported in patients with hepatic cirrhosis with no hepatic encephalopathy (HE). The objective of this study was to evaluate daytime sleepiness and risk of obstructive sleep apnea (OSA) among liver cirrhosis patients. **Material and methods.** A cross-sectional study was conducted at King Abdulaziz Medical City (KAMC)-Riyadh over a period of six months, using a structured questionnaire that investigated: 1) Sleep patterns and daytime sleepiness using the Epworth Sleeping Scale (ESS), and 2) The risk for sleep apnea using the Berlin Questionnaire (BQ). We enrolled patients with a confirmed diagnosis of liver cirrhosis who were being followed at the hepatology and pre-liver transplant clinics. Results. We enrolled 200 patients with liver cirrhosis, 57.5% of whom were male. The mean age was 60 (\pm SD 12.2). The reported prevalence of EDS, OSA, and both EDS and OSA were 29.5%, 42.9%, and 13.6%, respectively. The prevalence of EDS was higher in patients with Hepatitis-C and patients with DM, who experienced short sleep duration. We did not find any association between the severity of liver disease and EDS or OSA as measured by Child-Pugh scores (CPS). Conclusions. The risk of OSA and EDS is high among liver cirrhosis patients. Those patients with cirrhosis secondary to Hepatitis C are at higher risk of EDS and OSA. Both EDS and OSA affect patients designated as CPS Class A more frequently than patients designated as CPS Class B.

Key words. Liver cirrhosis. Insomnia. Sleep disturbances. Sleep apnea. Excessive daytime sleepiness. Hepatitis C. Hepatitis B. Child-Pugh scores. CPS.

INTRODUCTION

Obstructive sleep apnea (OSA) is a common disorder that affects 4-24% of males, 2-9% of females, and exceeds 30-50% in obese individuals.¹⁻⁵ OSA is characterized by recurrent upper-airway collapse during sleep, resulting in recurrent oxygen desaturations, increased sleep arousal, fragmentation of sleep, and excessive daytime somnolence.⁶ Chronic intermittent hypoxia sequentially may cause hepatic ischemia-reperfusion injury.⁷⁻¹³ The pathophysiology of sleep disturbances in cirrhosis remains unclear.¹⁴ Although clinical reports vary, one possible explanation for sleep dysfunction in patients is a disruption in melatonin circadian rhythms.¹⁵ Studies reported elimination of OSA after ascites treatment, raising the pos-

sibility of the mechanical effect of ascites on diaphragmatic movement and reduction of the lung volume as a cause of OSA. Another possibility is due to upper airway edema in liver cirrhosis patients.^{16,17} Hypocapnia secondary to hormonal and chemical change in liver cirrhosis may cause sleep apnea, although this is considered controversial.¹⁸ Excessive day time sleepiness (EDS) appears to be attributable to a dysfunction of the neural circuit responsible for the maintenance of wakefulness and sleep states. High levels of ammonia can reduce serotonin and noradrenaline levels in the central nervous system, resulting in low alertness and attention-associated sleep complaints, including difficulty falling asleep and EDS.^{14,19,20} Studies in patients with compensated cirrhosis have illustrated that alterations in melatonin, cortisol, and ghrelin

secretion rhythms are the reasons for poor sleep architecture; however, this requires further study in cirrhotic patients with concomitant OSA.^{14,20,21} Sleep disturbance, including sleep apnea, is playing a major role in impairment of the quality of life in patients with cirrhosis and in the worsening of cirrhosis.^{16,22,23} Frequently, sequences of sleep disturbance are overlooked, and multiple other factors are blamed, such as fatigue, HE, and the underlying etiology of liver disease.^{23,24} Studies show OSA is associated with elevated alanine aminotransferase levels and a trend toward histologic evidence of progressive liver disease.^{7-10,13,25-29} OSA is also associated with markedly increased mortality and morbidity due to the metabolic and cardiovascular risks.³⁰⁻³³ While OSA is an important sleep disorder that can coexist with liver cirrhosis, treatment with continuous positive airway pressure (CPAP) improves quality of life and prevents worsening of liver cirrhosis.^{34,35}

There are few studies assessing the sleep patterns in patients with liver cirrhosis without overt HE.^{15,36}

This study aimed to estimate the risk of OSA, as evaluated by the Berlin questionnaires (BQ),³⁷ the presence of EDS assessed by the Epworth sleepiness scale (ESS),³⁸ among liver cirrhosis patients without overt HE. Also, we recognized the need to study the association between severity of liver cirrhosis as assessed by Child-Pugh Scores (CPS) and the risk of OSA.

MATERIAL AND METHODS

This was a cross-sectional study conducted at King Abdulaziz Medical City (KAMC)-Riyadh over a period of six months, between January 2012 and July 2012. The Institutional Review Board (IRB) at King Abdullah International Medical Research Center (KAIMRC), Riyadh, approved this study.

Data collection was carried out by personal professional interviews using structured sleep questionnaires. These questionnaires were adopted from validated international questionnaires, validated in the Arabic language, and used previously among hemodialysis patients and general Saudi population, this including Berlin Questionnaires (BQ) to estimate the risk for sleep apnea, Epworth Sleepiness Scale (ESS) to assess EDS and International Classification of Sleep Disorders-2 (ICSD-2), which defines insomnia.³⁹⁻⁴³ We enrolled all stable patients with a confirmed diagnosis of liver cirrhosis who were being followed at the hepatology and pre-liver transplant clinics. We excluded patients with chronic pulmonary diseases, congestive heart failure, and patients with hepatic encephalopathy.

The consultant hepatologist identified all patients with a confirmed diagnosis of liver cirrhosis, and classified them according to the severity of the liver cirrhosis based

on the CPS.⁴⁴ The diagnosis of liver cirrhosis was based on liver radiological studies, liver biopsy when available, and compatible clinical data as per the diagnosis of the hepatologist who referred the case for study. The patients who agreed to participate were introduced by the primary physician to the study co-investigator, who interviewed the patients, obtained the consent, and reviewed all the questionnaires with the participant.

We used the Arabic version of the BQ to assess the presence of risk of OSA among participants, since the Arabic BQ is a reliable and valid scale in screening patients for OSA risk among Arabic-speaking nations.⁴⁵ The BQ consisted of 10 items related to sleep apnea risk that include: snoring behavior, wake time, sleepiness or fatigue, history of obesity or hypertension, and body mass index (BMI). According to BMI values, respondents were classified as underweight (< 18.5); normal weight (18.5-24.9); overweight (25-29.9); and obese (> 30). Participants were classified as having a high risk of OSA if there were two or more categories where the score was positive. Participants were classified as low risk of OSA if there was only one or no category where the score was positive.^{37,46} We also used the ESS Arabic version to assess EDS.⁴⁷ A score of 11 or more (i.e., ESS > 11) is considered EDS. We also used the International Classification of Sleep Disorders-2 (ICSD-2), which defines insomnia as difficulty in falling asleep, waking up too early, frequent awakening with difficulty in falling asleep again, and secondary daytime impairment related to nighttime sleep difficulties.⁴⁸ In addition, we gathered demographic data and information pertinent to liver cirrhosis such as the underlying cause of liver cirrhosis, and the severity of liver cirrhosis based on CPS.^{44,49} We collected data on neck size as measured in cm, large neck size classified as having (≥ 38 cm for female and ≥ 40 cm for male) and small neck size classified as having (< 38 cm for female and < 40 for male).

Statistical analysis

The collected data were transferred and analyzed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

- Univariate analysis. The mean and standard deviation was used to summarize age. Percentages were used to summarize the demographic and clinical characteristics such as gender, marital status, occupation, smoking status, depression, EDS, and OSA (Table 1).
- Bivariate analysis. χ^2 tests were used to test the associations between the demographic/clinical characteristics across EDS, OSA, and both EDS and OSA in patients with liver cirrhosis (Table 2).
- Multivariate analysis. Multivariate logistic regression models were used to determine the association be-

Table 1. Demographic/clinical characteristics of patients with liver cirrhosis.

Characteristics	Levels	n (%)
Neck size	Female	85 (42.5)
	Male	115 (57.5)
Illiterate	Yes	69 (34.5)
	No	131 (65.5)
Employed	Yes	22 (11.0)
	No	178 (89.0)
Smoking	Yes	159 (79.5)
	No	41 (20.5)
Coffee Intake	Yes	58 (29.0)
	No	142 (71.0)
Depression	Yes	59 (29.5)
	No	141 (70.5)
DM	Yes	62 (31.0)
	No	138 (69.0)
Age	< 60	84 (42.0)
	≥ 60	116 (58.0)
Cause of liver cirrhosis	B	38 (19.4)
	C	118 (60.2)
	Others	40 (20.4)
CTP	A	80 (40.0)
	B	84 (42.0)
	C	36 (18.0)
Hours of sleep/night	≤ 5	86 (43.0)
	6-8	80 (40.0)
	> 8	34 (17.0)
Insomnia	Present	84 (42.0)
	Absent	116 (58.0)
Neck size	Small	140 (70.0)
	Large	60 (30.0)
EDS	No	141 (70.5)
	Yes	59 (29.5)
OSA	Low	113 (57.1)
	High	85 (42.9)
EDS and OSA	No	171 (86.4)
	Yes	27 (13.6)

tween demographic and clinical characteristics and the presence EDS, OSA, and both EDS and OSA in patients with liver cirrhosis (Table 3). P values ($P < 0.05$) were considered significant.

RESULTS

We enrolled 200 patients with liver cirrhosis, 57.5% were male, the mean age was 60 (\pm SD 12.2), and other sample characteristics are shown in table 1. Hepatitis C was the most common cause of liver cirrhosis, 118 (60.2%). EDS was reported by 59/200 (29.5%) (95% confidence limit: 23.3%-36.3%). High risk for OSA was reported by 85/198 (42.9%) (95% confidence limit:

35.9%-50.1%). The presence of both EDS and OSA was reported by 27/198 (13.6%) (95% confidence limit: 9.2%-19.2%). The bivariate analysis in table 2 shows patients with liver cirrhosis due to hepatitis C were significantly more likely to report EDS symptoms (36.4%) than hepatitis B patients (10.5%), or other factors (20.4%) ($P = 0.009$). EDS was reported more in the non-illiterate than in the illiterate (36.6% *vs.* 15.9%, $P = 0.002$). EDS was more frequent among liver cirrhosis patients with insomnia than among those without it (46.4% *vs.* 17.2%, $P = 0.001$). EDS was reported more in liver cirrhosis patients with large neck size (≥ 38 cm for female and ≥ 40 for male) compared to liver cirrhosis patients with small neck size (< 38 cm for female and < 40 for male) (40% *vs.* 25%, $P = 0.033$).

High risk for OSA was reported more in liver cirrhosis patients with large neck size than liver cirrhosis patients with small neck size (55.9% *vs.* 37.4%, $P = 0.016$). Liver cirrhosis patients with short sleep duration were more likely to report high risk for OSA than patients who reported sleeping 6-8 h and more than 8 h (52.9% *vs.* 35.4% and 35.3%, respectively, $P = 0.048$). Liver cirrhosis patients with DM were significantly more likely to report high risk for OSA than those without DM (57.4% *vs.* 36.5%, $P = 0.006$).

The presence of both EDS and high risk for OSA were reported more in liver cirrhosis patients with large neck size than liver cirrhosis patients with small neck size (22% *vs.* 10.1%, $P = 0.025$). The presence of both EDS and high risk for OSA were associated with insomnia (19.3% *vs.* 9.6%, $P = 0.049$). The presence of both EDS and high risk for OSA was noted more frequently in the non-illiterate than in the illiterate (18.5% *vs.* 4.4%, $P = 0.006$).

In multivariate models (Table 3), insomnia (adjusted odds ratio [aOR] = 4.1; 95% CI: 1.770-9.595) and other causes of liver cirrhosis (aOR = 4.6; 95% CI: 1.090-19.178) were associated with the presence of EDS. The adjusted odds of EDS decreased by 70% in illiterate (aOR = 0.3; 95% CI: 0.127-0.792) as compared to non-illiterate. Compared with having no diabetes, those with diabetes had greater odds of high risk for OSA (aOR = 3.6; 95% CI: 1.691-7.520). Compared with CPS Class A, CPS Class B had 60% less odds of high risk for OSA (aOR = 0.40; 95% CI: 0.172-0.764). The odds of OSA were 3.1 times high in liver cirrhosis patients with short sleep duration (aOR = 3.1; 95% CI: 1.147-8.240). Liver cirrhosis patients with CPS Class B were 70% less likely to report both EDS and high risk for OSA compared with liver cirrhosis patients with CPS Class A (aOR = 0.30; 95% CI: 0.098-0.908). Lack of formal education was associated with less presence of both EDS and high risk for OSA (aOR = 0.10; 95% CI: 0.031-0.569).

Table 2. Characteristics Factors associated with EDS, OSA, or EDS and OSA in patients with liver cirrhosis.

Characteristics	EDS			OSA			EDS and OSA		
	No	Yes	P	Low	High	P	No	Yes	P
	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Gender									
Female	58 (68.2)	27 (31.8)	0.546	43 (51.2)	41 (48.8)	0.151	72 (85.7)	12 (14.3)	0.819
Male	83 (72.2)	32 (27.8)		70 (61.4)	44 (38.6)		99 (86.8)	15 (13.2)	
Illiterate									
Yes	58 (84.1)	11 (15.9)	0.002*	40 (58.8)	28 (41.2)	0.719	65 (95.6)	3 (4.4)	0.006*
No	83 (63.4)	48 (36.6)		73 (56.2)	57 (43.8)		106 (81.5)	24 (18.5)	
Employed									
Yes	17 (77.3)	5 (22.7)	0.460	14 (63.6)	8 (36.4)	0.509	19 (86.4)	3 (13.6)	1.000
No	124 (69.7)	54 (30.3)		99 (56.3)	77 (43.8)		152 (86.4)	24 (13.6)	
Smoking									
Yes	116 (73)	43 (27)	0.134	86 (54.4)	72 (45.6)	0.136	136 (86.1)	22 (13.9)	0.815
No	25 (61)	16 (39)		27 (67.5)	13 (32.5)		35 (87.5)	5 (12.5)	
Coffee Intake									
Yes	39 (67.2)	19 (32.8)	0.518	31 (53.4)	27 (46.6)	0.507	49 (84.5)	9 (15.5)	0.620
No	102 (71.8)	40 (28.2)		82 (58.6)	58 (41.4)		122 (87.1)	18 (12.9)	
Depression									
Yes	45 (76.3)	14 (23.7)	0.247	32 (55.2)	26 (44.8)	0.728	48 (82.8)	10 (17.2)	0.341
No	96 (68.1)	45 (31.9)		81 (57.9)	59 (42.1)		123 (87.9)	17 (12.1)	
DM									
Yes	49 (79)	13 (21)	0.076	26 (42.6)	35 (57.4)	0.006*	52 (85.2)	9 (14.8)	0.760
No	92 (66.7)	46 (33.3)		87 (63.5)	50 (36.5)		119 (86.9)	18 (13.1)	
Age									
< 60	63 (75)	21 (25)	0.235	46 (55.4)	37 (44.6)	0.690	72 (86.7)	11 (13.3)	0.894
60	78 (67.2)	38 (32.8)		67 (58.3)	48 (41.7)		99 (86.1)	16 (13.9)	
Cause of liver cirrhosis									
B	34 (89.5)	4 (10.5)	0.009*	24 (63.2)	14 (36.8)	0.574	35 (92.1)	3 (7.9)	0.276
C	75 (63.6)	43 (36.4)		67 (57.3)	50 (42.7)		101 (86.3)	16 (13.7)	
Others	29 (72.5)	11 (27.5)		20 (51.3)	19 (48.7)		31 (79.5)	8 (20.5)	
CTP									
A	50 (62.5)	30 (37.5)	0.127	40 (50)	40 (50)	0.203	64 (80)	16 (20)	0.091
B	64 (76.2)	20 (23.8)		53 (63.9)	30 (36.1)		76 (91.6)	7 (8.4)	
C	27 (75)	9 (25)		20 (57.1)	15 (42.9)		31 (88.6)	4 (11.4)	
Hours of Sleep/night									
5	60 (69.8)	26 (30.2)	0.435	40 (47.1)	45 (52.9)	0.048*	70 (82.4)	15 (17.6)	0.338
6-8	54 (67.5)	26 (32.5)		51 (64.6)	28 (35.4)		70 (88.6)	9 (11.4)	
> 8	27 (79.4)	7 (20.6)		22 (64.7)	12 (35.3)		31 (91.2)	3 (8.8)	
Insomnia									
Present	45 (53.6)	39 (46.4)	0.001*	45 (54.2)	38 (45.8)	0.491	67 (80.7)	16 (19.3)	0.049*
Absent	96 (82.8)	20 (17.2)		68 (59.1)	47 (40.9)		104 (90.4)	11 (9.6)	
Neck size**									
Small	105 (75)	35 (25)	0.033*	87 (62.6)	52 (37.4)	0.016*	125 (89.9)	14 (10.1)	0.025*
Large	36 (60)	24 (40)		26 (44.1)	33 (55.9)		46 (78)	13 (22)	

* χ^2 test is significant at $\alpha = 0.05$. ** Large neck size (≥ 38 cm for female and ≥ 40 for male) and small neck size (< 38 cm for female and < 40 for male).

DISCUSSION

This study was designed to predict the prevalence of EDS and high risk for OSA as determined in a series of patients diagnosed with liver cirrhosis. Our study confirms

that patients with cirrhosis frequently have EDS at 29.5%, high risk of OSA at 42%, and a combination of both symptoms at 13.6%. Previous studies reported prevalence of EDS between 18.5%-38% in patients with liver cirrhosis.⁵⁰⁻⁵³ Previously we reported the prevalence of EDS,

Table 3. Multivariate factors associated with EDS, OSA, or EDS and OSA in patients with liver cirrhosis.

Factors	EDS						OSA						EDS and OSA					
	B	SE	P	OR	95% C.I. for OR		B	SE	P	OR	95% C.I. for OR		B	SE	P	OR	95% C.I. for OR	
					Lower	Upper					Lower	Upper					Lower	Upper
Female	0.16	0.46	0.726	1.2	0.476	2.900	0.58	0.41	0.159	1.8	0.797	4.001	0.18	0.56	0.749	1.2	0.399	3.589
Illiterate	-1.15	0.47	0.014*	0.3	0.127	0.792	-0.42	0.39	0.281	0.7	0.302	1.416	-2.02	0.74	0.007*	0.1	0.031	0.569
Unemployed	-0.27	0.67	0.689	0.8	0.207	2.829	0.17	0.58	0.765	1.2	0.382	3.699	0.35	0.83	0.671	1.4	0.28	7.223
Smoke	-0.50	0.48	0.301	0.6	0.234	1.565	0.63	0.46	0.175	1.9	0.755	4.651	0.67	0.66	0.310	1.9	0.537	7.050
Coffee Intake	-0.13	0.41	0.758	0.9	0.394	1.971	0.19	0.37	0.613	1.2	0.586	2.474	-0.16	0.52	0.758	0.9	0.307	2.361
Depression	0.06	0.46	0.891	1.1	0.431	2.631	-0.13	0.39	0.746	0.9	0.41	1.893	0.52	0.57	0.356	1.7	0.556	5.101
DM	-0.16	0.44	0.713	0.9	0.363	2.001	1.27	0.38	0.001*	3.6	1.691	7.52	0.81	0.56	0.148	2.2	0.750	6.714
Age < 60	-0.55	0.43	0.200	0.6	0.251	1.336	0.10	0.39	0.793	1.1	0.516	2.381	-0.66	0.56	0.234	0.5	0.173	1.537
Cause of liver cirrhosis - C	1.14	0.62	0.069	3.1	0.917	10.575	0.23	0.45	0.615	1.3	0.516	3.059	0.37	0.77	0.628	1.5	0.32	6.605
Cause of liver cirrhosis - others	1.52	0.73	0.038*	4.6	1.09	19.178	0.55	0.54	0.305	1.7	0.606	4.959	1.56	0.90	0.083	4.8	0.818	27.592
CTP-B	-0.31	0.40	0.448	0.7	0.333	1.625	-1.01	0.38	0.008*	0.4	0.172	0.764	-1.21	0.57	0.033*	0.3	0.098	0.908
CTP-C	-0.29	0.53	0.588	0.8	0.266	2.117	-0.54	0.47	0.254	0.6	0.231	1.474	-1.01	0.72	0.159	0.4	0.089	1.488
Sleep duration 5 h	-0.15	0.58	0.801	0.9	0.276	2.703	1.12	0.50	0.026*	3.1	1.147	8.24	0.75	0.82	0.357	2.1	0.427	10.569
Sleep duration 6-8 hrs	0.27	0.58	0.643	1.3	0.420	4.070	0.14	0.50	0.773	1.2	0.437	3.047	0.44	0.85	0.606	1.6	0.293	8.194
Insomnia	1.42	0.43	0.001*	4.1	1.770	9.595	-0.31	0.40	0.433	0.7	0.336	1.596	0.71	0.58	0.215	2.0	0.660	6.318
Large neck size**	0.56	0.39	0.158	1.7	0.806	3.784	0.58	0.36	0.106	1.8	0.883	3.644	0.85	0.5	0.087	2.3	0.884	6.248
Constant	-1.67	0.92	0.071	0.2	-1.72	0.75	0.022	0.2					-3.31	1.3	0.011	0.0		

* χ^2 test is significant at $\alpha = 0.05$. ** Large neck size (≥ 38 cm for female and ≥ 40 for male) and small neck size (< 38 cm for female and < 40 for male).

high risk for OSA, or both among hemodialysis Saudi patients³⁹ and healthy Saudis using the same questionnaires, ESS and BQ.^{41,43} The prevalence of EDS, OSA, or both among healthy studies was 20.5%, 31.9%, and 7.9 respectively.⁴³ When we compared the prevalence of EDS, high risk for OSA, or both to healthy Saudis, the prevalence for all variables was higher than among those with liver cirrhosis. Furthermore, risk for OSA in this study was much lower than the risk for OSA reported among Saudi dialysis patients which was 70.9%.³⁹ Pulixi, *et al.* used the ESS as a measurement for EDS and the BQ to estimate risk for sleep apnea, and found ESD at 5%, risk for OSA at 25% and both at 8%.⁵⁴ The age of the participants in our study is much higher than the study reported by Pulixi, *et al.* among nonalcoholic fatty liver disease at 60 ± 12 vs. 51.8 ± 12 respectively, and the weight was similar: the mean was 27.7.54 The increasing age and obesity, among others, are major risks for OSA and other sleep disorders.^{55,56} In our study, almost one-third of our patients were obese $> 35\%$, and almost 50% of the participants were 60 years or older, which partially explains the higher prevalence in our study. Also 43% of our patient reported short sleep duration less than 5 h which may contribute to EDS. The etiologies of sleep problems in cirrhotic patients are likely multi-factorial, and include enlarged abdominal diameter due to ascites compromising lung volume and upper airway edema, in addition to other hormonal changes and comorbid conditions such as obesity, DM, and changes in the autonomic nervous activities.^{16,17,36,57,58}

The association between liver cirrhosis severity or its underlying cause and sleep apnea is controversial, partially due to the small number of studies.

Ogata, *et al.*³⁶ reported an association between severe liver cirrhosis CPS-C compared to CPS-A and B, and they attribute this to changes in the autonomic nervous activities. Other studies also reported an association between liver disease severity and OSA.^{17,50,54,59} Studies reported that OSA is related to disease severity, more in CPS-C than in A.^{16,17,36,59} In our study there is no statistical difference between the severity of liver cirrhosis and OSA and both (EDS and OSA), all at $P < 0.05$. This is probably so because our patients had other comorbid conditions such as obesity where the prevalence was 33.9% and being older in age, in this study population. We did not adjust for obesity because it is one of the criteria used in BQ to classify participants as being at high risk for OSA, but DM was one of the independent risk factors for sleep apnea. Even if the risk of OSA was linked to BMI, the association of high risk for OSAS and EDS with liver damage was independent of the BMI and of the other major clinical confounders, such as age, gender, the presence of hyperglycemia, and ALT levels.¹² The relationship between high risk for OSA and liver damage is independent of advanced liver

disease, or presence of other co-morbidities such as obesity, insulin resistance, or hyperglycemia.¹² Indeed, ALT levels and other noninvasive biomarkers, which were correlated with OSA in previous studies as indices of liver damage,¹¹ are insufficient as accurate biomarkers of the severity of liver disease.⁶⁰

We found that hepatitis C infection was the most common cause of liver cirrhosis in our study population and similar to other studies, it was, from a statistical perspective, significantly associated with EDS and sleep disturbances. To the best of our knowledge this is the only study from the region which reports the association between liver cirrhosis and EDS and OSA. The number is reasonably large, and included 200 patients using validated questionnaires and personal interviews that document the association between liver disease and OSA. This is extremely significant, as the OSA by itself is a highly documented cause of the worsening of liver cirrhosis and a risk factor for further liver injury and increased liver enzymes, independent of other risk factors.^{8-10,12,13,23,25,61} Furthermore, identification and treatment of OSA may ameliorate the progression of liver injury and progression to cirrhosis.^{34,35} Knowing the negative impact of OSA in liver cirrhosis patients and the benefit of identifying and treating patients at risk for OSA is crucial for physicians taking care of these patients. There are several limitations to our study:

- It was based on questionnaires which are less specific than formal polysomnographic studies.
- We did not correlate with the criteria of other laboratories, and
- We did not use non-liver cirrhosis as a control group.

CONCLUSIONS

EDS and OSA are common in Saudi liver cirrhosis patients, and both affect patients with CPS Class A more than those with CPS Class B. Physicians should be aware of such association knowing that OSA has a deleterious effect on the liver. OSA should be considered in the differential diagnosis of deteriorating liver function and progressive liver cirrhosis. Controlled prospective studies are warranted in studying the effect of OSA on sleep in patients with cirrhosis.

ABBREVIATIONS

- **aOR**: adjusted odds ratio.
- **BQ**: berlin questionnaire.
- **CI**: confidence interval.
- **CPS**: child-Pugh scores.
- **DM**: diabetes mellitus.

- **EDS**: excessive daytime sleepiness.
- **ESS**: epworth sleepiness scale.
- **HE**: hepatic encephalopathy.
- **NAFLD**: nonalcoholic fatty liver disease.
- **OSA**: obstructive sleep apnea.

ACKNOWLEDGMENTS

We declare the absence of any conflicts of interest of each author, and any off-label or investigational use. This research is supported by King Abdullah International Medical Research Center (KAIMRC).

REFERENCES

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993; 328: 1230-5.
2. Lindberg E, Gislason T. Epidemiology of sleep-related obstructive breathing. *Sleep Med Rev* 2000; 4: 411-33.
3. Resta O, Foschino-Barbaro MP, Legari G, Talamo S, Bonfitto P, Palumbo A, Minenna A, et al. Sleep-related breathing disorders, loud snoring and excessive daytime sleepiness in obese subjects. *Int J Obes Relat Metab Disord* 2001; 25: 669-75.
4. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 2002; 165: 1217-39.
5. Hiestand DM, Britz P, Goldman M, Phillips B. Prevalence of symptoms and risk of sleep apnea in the US population: Results from the national sleep foundation sleep in America 2005 poll. *Chest* 2006; 130: 780-6.
6. Simon S, Collop N. Latest advances in sleep medicine: obstructive sleep apnea. *Chest* 2012; 142: 1645-51.
7. Sundaram SS, Sokol RJ, Capocelli KE, Pan Z, Sullivan JS, Robbins K, Halbower AC. Obstructive sleep apnea and hypoxemia are associated with advanced liver histology in pediatric nonalcoholic fatty liver disease. *J Pediatr* 2014; 164: 699-706 e1.
8. Mishra P, Nugent C, Afendy A, Bai C, Bhatia P, Afendy M, Fang Y, et al. Apnoeic-hypopnoeic episodes during obstructive sleep apnoea are associated with histological nonalcoholic steatohepatitis. *Liver Int* 2008; 28: 1080-6.
9. Tanne F, Gagnadoux F, Chazouilleres O, Fleury B, Wendum D, Lasnier E, Lebeau B, et al. Chronic liver injury during obstructive sleep apnea. *Hepatology* 2005; 41: 1290-6.
10. Tian JL, Zhang Y, Chen BY. Sleep apnea hypopnea syndrome and liver injury. *Chin Med J (Engl)* 2010; 123: 89-94.
11. Turkay C, Ozol D, Kasapoglu B, Kirbas I, Yildirim Z, Yigitoglu R. Influence of obstructive sleep apnea on fatty liver disease: role of chronic intermittent hypoxia. *Respir Care* 2012; 57: 244-9.
12. Byrne TJ, Parish JM, Somers V, Aqel BA, Rakela J. Evidence for liver injury in the setting of obstructive sleep apnea. *Ann Hepatol* 2012; 11: 228-31.
13. Petta S, Marrone O, Torres D, Buttacavoli M, Camma C, Di Marco V, Licata A, et al. Obstructive Sleep Apnea Is Associated with Liver Damage and Atherosclerosis in Patients with Non-Alcoholic Fatty Liver Disease. *PLoS One* 2015; 10: e0142210.
14. Montagnese S, Middleton B, Mani AR, Skene DJ, Morgan MY. On the origin and the consequences of circadian abnormali-

- ties in patients with cirrhosis. *Am J Gastroenterol* 2010; 105: 1773-81.
15. Tarter RE, Hegedus AM, Van Thiel DH, Schade RR, Gavaler JS, Starzl TE. Nonalcoholic cirrhosis associated with neuropsychological dysfunction in the absence of overt evidence of hepatic encephalopathy. *Gastroenterology* 1984; 86: 1421-7.
 16. Crespo J, Cifrian J, Pinto JA, Jimenez-Gomez A, Pons-Romeiro F. Sleep apnea obstructive syndrome: a new complication previously undescribed in cirrhotic patients with ascites. *Am J Gastroenterol* 2003; 98: 2815-6.
 17. Nikaina I, Pastaka C, Zachou K, Dalekos GN, Gourgoulanis K. Sleep apnoea syndrome and early stage cirrhosis: a pilot study. *Eur J Gastroenterol Hepatol* 2006; 18: 31-5.
 18. Javaheri S, Almoosa KF, Saleh K, Mendenhall CL. Hypocapnia is not a predictor of central sleep apnea in patients with cirrhosis. *Am J Respir Crit Care Med* 2005; 171: 908-11.
 19. Lozeva-Thomas V. Serotonin brain circuits with a focus on hepatic encephalopathy. *Metab Brain Dis* 2004; 19: 413-20.
 20. Ahabrach H, Piedrafita B, Ayad A, El Mili N, Errami M, Felipe V, Llansola M. Chronic hyperammonemia alters the circadian rhythms of corticosteroid hormone levels and of motor activity in rats. *J Neurosci Res* 2010; 88: 1605-14.
 21. Montagnese S, Middleton B, Mani AR, Skene DJ, Morgan MY. Sleep and circadian abnormalities in patients with cirrhosis: features of delayed sleep phase syndrome? *Metab Brain Dis* 2009; 24: 427-39.
 22. Marchesini G, Bianchi G, Amodio P, Salerno F, Merli M, Panella C, Loguercio C, et al., Italian Study Group for quality of life in c. Factors associated with poor health-related quality of life of patients with cirrhosis. *Gastroenterology* 2001; 120: 170-8.
 23. Bajaj JS, Thacker LR, Leszczyszyn D, Taylor SA, Heuman DM, Raman S, Sterling RK, et al. Effects of obstructive sleep apnea on sleep quality, cognition, and driving performance in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2015; 13: 390-7 e1.
 24. Newton JL, Jones DE, Henderson E, Kane L, Wilton K, Burt AD, Day CP. Fatigue in non-alcoholic fatty liver disease (NAFLD) is significant and associates with inactivity and excessive daytime sleepiness but not with liver disease severity or insulin resistance. *Gut* 2008; 57: 807-13.
 25. Kallwitz ER, Herdegen J, Madura J, Jakate S, Cotler SJ. Liver enzymes and histology in obese patients with obstructive sleep apnea. *J Clin Gastroenterol* 2007; 41: 918-21.
 26. Polotsky VY, Patil SP, Savransky V, Laffan A, Fonti S, Frame LA, Steele KE, et al. Obstructive sleep apnea, insulin resistance, and steatohepatitis in severe obesity. *Am J Respir Crit Care Med* 2009; 179: 228-34.
 27. Daltro C, Cotrim HP, Alves E, de Freitas LA, Araujo L, Boente L, Leal R, et al. Nonalcoholic fatty liver disease associated with obstructive sleep apnea: just a coincidence? *Obes Surg* 2010; 20: 1536-43.
 28. Aron-Wisnewsky J, Minville C, Tordjman J, Levy P, Bouillot JL, Basdevant A, Bedossa P, et al. Chronic intermittent hypoxia is a major trigger for non-alcoholic fatty liver disease in morbid obese. *J Hepatol* 2012; 56: 225-33.
 29. Verhulst SL, Jacobs S, Aerts L, Schrauwen N, Haentjens D, Rooman RP, Gaal LV, et al. Sleep-disordered breathing: a new risk factor of suspected fatty liver disease in overweight children and adolescents? *Sleep Breath* 2009; 13: 207-10.
 30. Drager LF, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: an emerging risk factor for atherosclerosis. *Chest* 2011; 140: 534-42.
 31. Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ, Stubbs R, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. *Sleep* 2008; 31: 1071-8.
 32. Coughlin SR, Mawdsley L, Mugarza JA, Calverley PM, Wilding JP. Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. *Eur Heart J* 2004; 25: 735-41.
 33. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005; 365: 1046-53.
 34. Shpirer I, Copel L, Broide E, Elizur A. Continuous positive airway pressure improves sleep apnea associated fatty liver. *Lung* 2010; 188: 301-7.
 35. Buttacavoli M, Gruttad'Auria CI, Olivo M, Virdone R, Castrogiovanni A, Mazza E, Marotta AM, et al. Liver Steatosis and Fibrosis in OSA patients After Long-term CPAP Treatment: A Preliminary Ultrasound Study. *Ultrasound Med Biol* 2016; 42: 104-9.
 36. Ogata T, Nomura M, Nakaya Y, Ito S. Evaluation of episodes of sleep apnea in patients with liver cirrhosis. *J Med Invest* 2006; 53: 159-66.
 37. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med* 1999; 131: 485-91.
 38. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; 14: 540-5.
 39. Al-Jahdali H. Prevalence of sleep apnea and excessive day time sleepiness in patients with end-stage renal disease on dialysis. *Saudi J Kidney Dis Transpl* 2012; 23: 251-61.
 40. Al-Jahdali HH, Khogeer HA, Al-Qadhi WA, Baharoon S, Tamim H, Al-Hejaili FF, et al. Insomnia in chronic renal patients on dialysis in Saudi Arabia. *J Circadian Rhythms* 2010; 8: 7.
 41. Bahammam AS, Al-Rajeh MS, Al-Ibrahim FS, Arafah MA, Sharif MM. Prevalence of symptoms and risk of sleep apnea in middle-aged Saudi women in primary care. *Saudi Med J* 2009; 30: 1572-6.
 42. BaHammam AS, Alrajeh MS, Al-Jahdali HH, BinSaeed AA. Prevalence of symptoms and risk of sleep apnea in middle-aged Saudi males in primary care. *Saudi Med J* 2008; 29: 423-6.
 43. Hind Alruwaili, Anwar Ahmed, Abdulhamid Fatani, Khalid Al-Otaibi, Sarah AL-Jahdali, Yosra Ali, Abdullah Al-Harbi, et al. Symptoms and risk for obstructive sleep apnea among sample of Saudi Arabian adults. *Sleep and Biological Rhythms* 2015; 13: 332-41.
 44. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; 60: 646-9.
 45. Saleh AB, Ahmad MA, Awadalla NJ. Development of Arabic version of Berlin questionnaire to identify obstructive sleep apnea at risk patients. *Ann Thorac Med* 2011; 6: 212-6.
 46. Netzer NC, Hoegel JJ, Loube D, Netzer CM, Hay B, Alvarez-Sala R, Strohl KP. Prevalence of symptoms and risk of sleep apnea in primary care. *Chest* 2003; 124: 1406-14.
 47. Anwar E. Ahmed AF, Abdullah Al-Harbi, Abdullah Al-Shimeri, Yosra Z. Ali, Salim Baharoon, Hamdan Al-Jahdali. Validation of the Arabic version of the Epworth Sleepiness Scale. *J Epidemiol Global Health* 2014. Available from: <http://dx.doi.org/10.1016/j.jegh.2014.04.004>
 48. AASM. International Classification of Sleep Disorders. Rochester, MN, American Academy of Sleep Medicine 1997.

49. Suman A, Barnes DS, Zein NN, Levinthal GN, Connor JT, Carey WD. Predicting outcome after cardiac surgery in patients with cirrhosis: a comparison of Child-Pugh and MELD scores. *Clin Gastroenterol Hepatol* 2004; 2: 719-23.
50. Bernsmeier C, Weisskopf DM, Pflueger MO, Mosimann J, Campana B, Terracciano L, Beglinger C, et al. Sleep Disruption and Daytime Sleepiness Correlating with Disease Severity and Insulin Resistance in Non-Alcoholic Fatty Liver Disease: A Comparison with Healthy Controls. *PLoS One* 2015; 10: e0143293.
51. Samanta J, Dhiman RK, Khatri A, Thumbaru KK, Grover S, Duseja A, Chawla Y. Correlation between degree and quality of sleep disturbance and the level of neuropsychiatric impairment in patients with liver cirrhosis. *Metab Brain Dis* 2013; 28: 249-59.
52. Mostacci B, Ferlisi M, Baldi Antognini A, Sama C, Morelli C, Mondini S, Cirignotta F. Sleep disturbance and daytime sleepiness in patients with cirrhosis: a case control study. *Neurol Sci* 2008; 29: 237-40.
53. Lang CA, Conrad S, Garrett L, Battistutta D, Cooksley WG, Dunne MP, Macdonald GA. Symptom prevalence and clustering of symptoms in people living with chronic hepatitis C infection. *J Pain Symptom Manage* 2006; 31: 335-44.
54. Pulixi EA, Tobaldini E, Battezzati PM, D'Ingianna P, Borroni V, Fracanzani AL, Maggioni M, et al. Risk of obstructive sleep apnea with daytime sleepiness is associated with liver damage in non-morbidly obese patients with nonalcoholic fatty liver disease. *PLoS One* 2014; 9: e96349.
55. Berzigotti A, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Morillas R, Escorsell A, et al. Portal Hypertension Collaborative G. Obesity is an independent risk factor for clinical decompensation in patients with cirrhosis. *Hepatology* 2011; 54: 555-61.
56. Chung F, Abdullah HR, Liao P. STOP-Bang Questionnaire: A practical approach to screen for obstructive sleep apnea. *Chest* 2015.
57. De Cruz S, Espiritu JR, Zeidler M, Wang TS. Sleep disorders in chronic liver disease. *Semin Respir Crit Care Med* 2012; 33: 26-35.
58. Musso G, Olivetti C, Cassader M, Gambino R. Obstructive sleep apnea-hypopnea syndrome and nonalcoholic fatty liver disease: emerging evidence and mechanisms. *Semin Liver Dis* 2012; 32: 49-64.
59. Sockalingam S, Abbey SE, Alosaimi F, Novak M. A review of sleep disturbance in hepatitis C. *J Clin Gastroenterol* 2010; 44: 38-45.
60. Musso G, Cassader M, Olivetti C, Rosina F, Carbone G, Gambino R. Association of obstructive sleep apnoea with the presence and severity of non-alcoholic fatty liver disease. A systematic review and meta-analysis. *Obes Rev* 2013; 14: 417-31.
61. Benotti P, Wood GC, Argyropoulos G, Pack A, Keenan BT, Gao X, Gerhard G, et al. The impact of obstructive sleep apnea on nonalcoholic fatty liver disease in patients with severe obesity. *Obesity* (Silver Spring) 2016.

Correspondence and reprint request:

Hamdan AL-Jahdali, M.D., FRCPC, FCCP

Adjunct professor McGill University.

Professor of Medicine-Pulmonary.

King Saud University for Health Sciences. Head of Pulmonary

Division. Medical Director of Sleep Disorders Center.

King Abdulaziz Medical City, Riyadh, Saudi Arabia.

Tel.: +96612520088. Ext.: 17597, 17531

E-mail: Jahdali@gmail.com