



Clinical Application of the Multicomponent Grading System for Sleep Apnea Classification and Incident Cardiovascular Mortality

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Abstract

Objective To evaluate the clinical utility of the Baveno classification in predicting incident cardiovascular mortality after five years of follow-up in a clinic-based cohort of patients with obstructive sleep apnea (OSA).

Materials and Methods We evaluated the reproducibility of the Baveno classification using data from the Santiago Obstructive Sleep Apnea (SantOSA) study. The groups were labeled Baveno A (minor symptoms and comorbidities), B (severe symptoms and minor comorbidities), C (minor symptoms and severe comorbidities), and D (severe symptoms and comorbidities). Within-group comparisons were performed using analysis of variance (ANOVA) and post hoc tests. The associations between groups and incident cardiovascular mortality were determined through the Mantel-Cox and Cox proportional hazard ratios (HRs) adjusted by covariables.

Results A total of 1,300 OSA patients were included (Baveno A: 27.7%; B: 28%; C: 16.8%; and D: 27.5%). The follow-up was of 5.4 years. Compared to Baveno A, the fully-adjusted risk of cardiovascular mortality with Baveno B presented an HR of 1.38 (95% confidence interval [95%CI]: 0.14–13.5; $p = 0.78$); with Baveno C, it was of 1.71 (95%CI: 0.18–16.2; $p = 0.63$); and, with Baveno D, of 1.04 (95%CI: 0.12–9.2; $p = 0.98$). We found no interactions involving Baveno group, sex and OSA severity.

Discussion Among OSA patients, the Baveno classification can describe different subgroups. However, its utility in identifying incident cardiovascular mortality is unclear. Long-term follow-up studies and the inclusion of demographic variables in

Keywords

- ▶ obstructive sleep apnea
- ▶ cardiovascular
- ▶ hypoxia
- ▶ latino
- ▶ precision medicine

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the classification could improve its ability to detect a high-risk phenotype associated with cardiovascular mortality.

Conclusion The Baveno classification serves as a valuable method for categorizing varying groups of patients afflicted with OSA. Nevertheless, its precision in identifying occurrence of cardiovascular mortality is still unclear.

Introduction

Obstructive sleep apnea (OSA) is a heterogeneous disease with a variety of phenotypes and prognoses.¹ Continuous positive airway pressure (CPAP) is the primary therapy for airway obstruction during the night.^{2,3} Clinical trials⁴ have reported an unclear benefit of CPAP in preventing major cardiovascular events, and long-term cohort studies⁵ and per-protocol analyses⁶ of clinical trials have reported that CPAP is effective among the OSA population, with good compliance and long follow-up. This inconsistency in results could be due to the inadequate characterization of the OSA population.^{7,8} Moreover, the definition of OSA is based on the frequency of respiratory events; using the respiratory disturbance index (RDI), there is a potential risk of inconsistent results.^{9,10}

In recent years, different approaches have been proposed to redefine OSA according to the various OSA-related phenotypes.¹ Some of the approaches use the severity of sleepiness-related symptoms,^{11–13} while others use the burden of comorbidities.^{14,15} Physiologically-driven measures include nocturnal hypoxemia and autonomic response.^{16,17} In 2018, a group of European experts from the European Respiratory Society (ERS), the European Sleep Research Society (ERSR), and the Alpine Sleep Summer School (ASSS) published a novel method of OSA phenotyping that involved applying a multicomponent grading system for sleep apnea, called the Baveno classification.^{18,19} In brief, this classification was developed for patients with moderate to severe OSA and it includes different domains, such as sleepiness and comorbidities in four categories: A, B, C, and D.^{18,19}

Although the proposed classification may be relevant to the clinical practice, it is pertinent to assess its ability to identify a population with an increased risk of a major cardiovascular event, especially cardiovascular mortality. In addition, this classification was evaluated using the data included in the European Sleep Apnea Database (ESADA).¹⁹ Therefore, the reproducibility of the Baveno classification's in different populations is relevant to define the applicability of the results.

In the present study, we evaluated the reproducibility of the Baveno classification using a clinic-based cohort of patients with moderate to severe sleep apnea in Chile (-Hispanic/Latino sample), identifying the four categories proposed by Baveno and their associations with incident cardiovascular mortality.

Materials and Methods

Study Design

We conducted an observational study following the Strengthening the Reporting of Observational Studies in

Epidemiology (STROBE) statement's current recommendation²⁰ using the data from the Santiago Obstructive Sleep Apnea (SantOSA) study.²¹ In brief, SantOSA is a prospective, clinic-based study of the consequences of OSA among patients referred for clinical evaluation of OSA in a tertiary center located in the metropolitan region of Santiago, Chile.

The SantOSA study²¹ was registered in 2019 (ISRCTN62293645), and it was approved by the Review Board of Clínica Las Condes, Santiago. All of the patients signed the informed consent document prior to their incorporation; the cohort was established in 2009, and it included adults aged ≥ 18 years. To date, a total of 2,008 participants have been included, and they all have participated in a baseline sleep study using a home sleep apnea test (HSAT) from 2009 to 2019. In the present study, 535 records were excluded due to non-OSA status ($RDI < 5$ events/h), and 173 were excluded due to incomplete data. After the inclusion/exclusion criteria were applied, 1,300 subjects were included in the subsequent analysis.

Clinical Data

All participants were clinically evaluated in terms of socio-demographic characteristics, lifestyle habits (tobacco and alcohol use), comorbidities (hypertension [HTN], diabetes mellitus [DM], dyslipidemia [DLP], coronary heart disease [CHD], stroke, and chronic obstructive pulmonary disease [COPD]), and medications. In fact, 166 subjects (10.7%) reported the use of benzodiazepines. Regarding anthropometric variables, weight and height were measured after the subjects had fasted overnight and were wearing only underwear. The body mass index (BMI; kg/m^2) was calculated, and the neck circumference was measured using a plastic tape measure at the level of the cricoid.

Sleep Assessment

At baseline, a self-reported sleep symptom questionnaire was applied to evaluate the participants' sleep schedule, degree of daytime sleepiness, snoring intensity, witnessed apnea, insomnia, episodes of nocturnal suffocation, and morning headache.²² In addition, we collected data from the Spanish versions of the Epworth Sleepiness Scale (ESS).^{23–25}

To conduct the HSAT, we used a validated type-3 sleep test (using the Embletta Multi Parameter Recorder, Natus Medical, Inc., Middleton, WI, United States), including nasal pressure assessment (measuring airflow), thoracic and abdominal inductance plethysmography, body position assessment, audio assessment via a microphone, and pulse oximetry. The device presented rates of 92.4% of sensitivity

and of 85.7% of specificity in quantifying AHI when compared to polysomnography (PSG) in patients with suspected OSA syndrome.²⁶ The HSAT was performed once at the beginning of the study; in the case of repeated HSAT, we included the first diagnostic test.

The HSAT analysis was performed manually, according to current guidelines, by a respiratory disease specialist (JJ) blinded to the clinical history.^{9,10,27} We included the following variables of the HSAT for analysis: 1) the RDI, defined as apneas or hypopneas associated with 3% oxygen desaturation per hour; 2) the mean oxygen saturation (SpO₂); 3) the minimum SpO₂; 4) the total time with oxyhemoglobin saturation lower than 90% (T90%); and 5) oxygen desaturation index (ODI) \geq 3%. The definition of OSA was RDI \geq 5 events/h, and moderate to severe OSA (msOSA) was determined by RDI \geq 15 events/h.¹⁰

For the present analysis, we included all participants with an RDI \geq 5 events/h and complete data. The criteria used to allocate patients into the Baveno groups were similar to those used in the studies by Randerath et al.,^{18,28} including the following domains: 1) symptoms—we included the total score on the ESS, particularly those $>$ 10 points, excessive daytime sleepiness (EDS), insomnia, and hypersomnia (defined as total sleep time $>$ 10 hours/night and self-report of severe [frequent drowsy driving] and very severe [always falling asleep] excessive sleepiness during the day); and 2) comorbidities—we included data from self-reports and medical reports at baseline. Additionally, blood pressure was measured with a standard mercury sphygmomanometer on the left arm after 10 minutes of rest.²⁹ The major comorbidities were stroke, CHD, uncontrolled HTN (\geq 140/90 mm Hg upon evaluation), and DM. Moreover, we excluded all participants with missing values or those who were lost to follow-up.

Outcomes

Our primary outcome was defined as incident cardiovascular mortality after follow-up. In particular, deaths reportedly of cardiovascular causes followed the criteria of the 9th Revision of the International Classification of Diseases (ICD-9), which are available in **►Supplementary Appendix 1**. A secondary analysis included the association with all-cause mortality. We could assess both mortality and follow-up data since the sleep study was assigned through consultation at the Chilean National Register of Mortality database (www.registrocivil.cl).

Statistical Analysis

The extracted data were recollected in a Microsoft Excel (Microsoft Corp., Redmond, WA, United States) spreadsheet. The continuous variables were reported as mean and standard deviation (SD) values, and the numerical variables, as percentages. The Shapiro-Wilk test was used to examine data distribution. Differences between the Baveno groups were tested using analysis of variance (ANOVA) with Tukey post hoc pairwise comparisons for the numerical variables, and the Chi-squared test and odds ratios (ORs) with respective 95% confidence intervals (95% CIs) for the numerical variables.

The association between the Baveno group and incident cardiovascular mortality was evaluated using the Kaplan-Meier survival analysis, the log-rank test (Mantel-Cox), and the Cox proportional hazard ratio (HR). As covariables, we included cardiovascular confounders related to an increased risk of cardiovascular mortality (age, sex, BMI, CHD, and HTN). Additionally, differences in survival within Baveno groups were evaluated through pairwise comparisons using the Wilcoxon (Gehan) statistic. Finally, we conducted three exploratory analyses based on an interaction analysis of sex differences (men versus women), age, and OSA severity (msOSA).

Results

A total of 1,300 subjects were included in the subsequent analysis. The 4 Baveno groups were composed of 360 (27.7%) subjects in Baveno A, 364 (28%) in Baveno B, 218 (16.8%) in Baveno C, and 358 (27.5%) in Baveno D. The study flowchart is shown in **►Figure 1**.

A summary of the baseline characteristics and demographic data across groups is shown in **►Table 1**. Compared to Baveno A, groups C and D were older. We found a high prevalence of men across groups. The burden of comorbidities and increased cardiometabolic parameters (obesity, waist and neck circumferences, and uncontrolled HTN) were significant in Baveno C and D, and the prevalence of COPD (6.7%) in these groups was higher. Regarding sleep symptoms, the results showed that Baveno B and D presented a higher prevalence of witnessed apnea (of 73.68% and 78.21% respectively), along with sleepiness evaluated through the ESS, with median scores of 11 (interquartile range [IQR]: 9.0 to 14.0) and 11 (IQR: 9 to 15) respectively. Additionally, the Baveno B and D groups presented a higher prevalence of severe snoring, EDS, and insomnia.

Burden of Sleep-Related Symptoms

Regarding the HSAT, a total of 903 (69.5%) subjects presented msOSA: Baveno A – 62.5%; Baveno B – 65.9%; Baveno C – 71.5%; and Baveno D – 78.7%. The median (IQR) RDI was of 18.8 (11.7 to 29.8), 21 (12.1 to 36), 21.6 (12.6 to 38.5), and 32.4 (17 to 49) for Baveno A, B, C, and D respectively. Multiple comparisons showed differences that were not statistically significant between Baveno A and D and between Baveno B and D. (**►Figure 2**). Compared to Baveno A, both Baveno C and D reported severe hypoxemia according to T90% and ODI \geq 3%, and Baveno D showed the lowest nadir SpO₂. However, the RDI was higher in Baveno B and Baveno D.

Follow-up and Cardiovascular Mortality

The men follow-up of the entire cohort was of 65.11 years (\pm 39.2 years and 5.42 months). During follow-up, we observed 126 cases of all-cause mortality (9.6%) and 60 (4.4%) new cardiovascular mortality events. The unadjusted Kaplan-Meier survival analysis showed a Chi-squared of 15.8 with a *p*-value $<$ 0.01. Furthermore, the pairwise comparisons using Wilcoxon (Gehan) statistic showed that Baveno D presented a significant difference from Baveno A

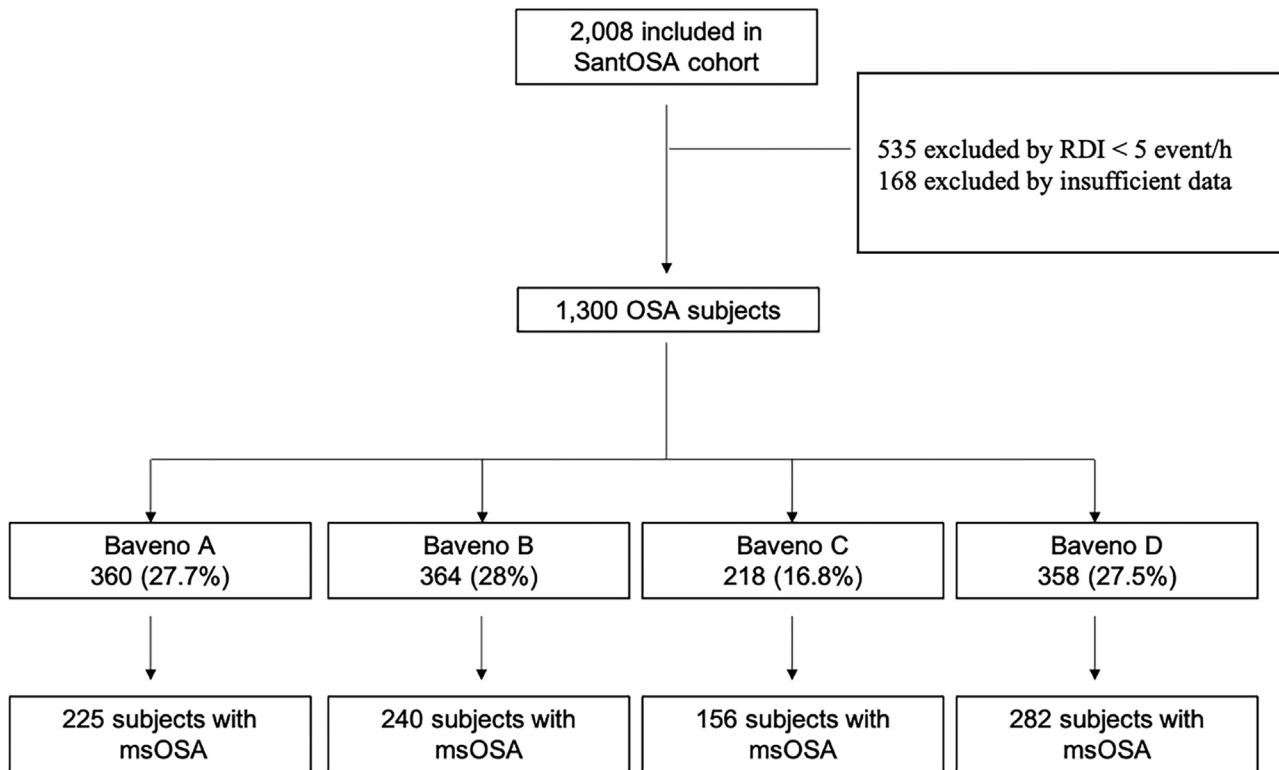


Fig. 1 Study flowchart. Abbreviations: OSA, obstructive sleep apnea; msOSA, moderate to severe OSA.

Table 1 Baseline characteristics within Baveno groups

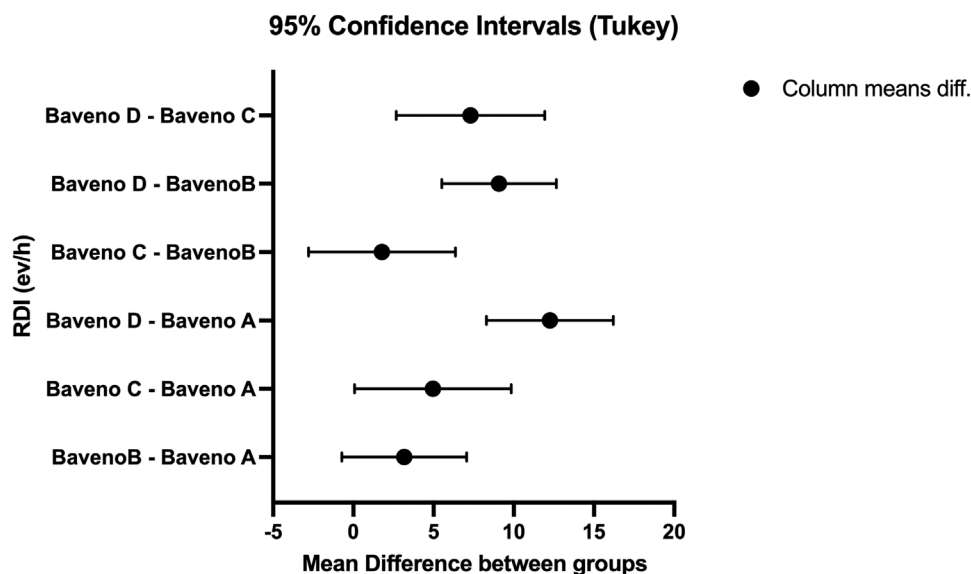
	Baveno A (n = 360)	Baveno B (n = 364)	Baveno C (n = 218)	Baveno D (n = 358)
Age (year), median [IQR]	51 [40-61]	52 [42-61]	60 [50-70]	59 [48-67]
Gender (Male, %)	85%	77.5%	83.1%	77.9%
		Comorbidities		
HTN, (%)	26.3%	31.7%	59.3%	63.1%
D.M. (%)	0%	0%	29.9%	37.9%
Dyslipidemia, (%)	24.5%	23.7%	34.5%	37.6%
COPD, (%)	2.5%	1.9%	2.8%	6.7%
CHD, (%)	0	0	22%	20%
Depression, (%)	5.3%	12.9%	11.9%	18.6%
Anti-HTN medication, (%)	24.5%	29.5%	54.9%	56.2%
Glycemic medication, (%)	0%	0%	33.5%	42%
		Tobacco History		
nonsmoker, (%)	49.8%	47.6%	44.9%	47.2%
current smoker, (%)	28.7%	30.8%	30.1%	35.6%
former smoker, (%)	21.5%	21.7%	25%	17.2%
		Alcohol. history		
non-OH, (%)	20.6%	23.9%	33.4%	33.3%
occasionally, (%)	65.8%	62.4%	54.7%	55.8%
frequent, (%)	13.6%	13.7%	11.9%	10.9%
		Sleep Symptoms		

(Continued)

Table 1 (Continued)

	Baveno A (n = 360)	Baveno B (n = 364)	Baveno C (n = 218)	Baveno D (n = 358)
ESS (points), median [IQR]	5.0 [3.0-7.0]	11 [9.0-14.0]	5.0 [3.0-7.0]	11 [9-15]
Witnesses Apnea, (%)	58%	73.68%	68.22%	78.21%
ESD, (%)	0	19%	0	19.9%
Severe Snoring, (%)	86.11%	92.3%	87.1%	94.1%
Insomnia, (%)	0%	41.5%	0%	47.4%
		Physical evaluation		
Neck circumference (cm), median [IQR]	41 [39-43]	41 [39-44]	42.5 [40.8-45]	43 [40-46]
Waist circumference (cm), median [IQR]	102 [97-108]	104 [98-111]	107 [100-114]	110 [103-117]
BMI (Kg/m ²), median [IQR]	28.7 [26.6-31.3]	29.4 [26.8-32.8]	30.3 [27.5-33.6]	31.9 [28.9-35.6]
BP systolic (mmHg), median [IQR]	120 [110-121]	120 [110-125]	130 [120-140]	130 [120-140]
BP diastolic (mmHg), median [IQR]	80 [70-80]	80 [70-80]	90 [80-90]	90 [80-90]
		Home Sleep Apnea Test		
RDI (events/h), median [IQR]	18.8 (11.7-29.8)	21 (12.1-36)	21.6 (12.6-38.5)	32 (17.6-49.2)
mean SpO ₂ (%), median [IQR]	92.8 (91.4-94.0)	92.9 (91.3-94.2)	92.4 (90.9-93.5)	91.8 (89.9-93.5)
T90% (%), median [IQR]	3.05 (0.6-12.8)	3.5 (0.95-13.2)	6.1 (1.7-22.8)	12.5 (2.5-36.4)
ODI-3% (events/h), median [IQR]	17 (8.9-27.1)	17.3 (10.2-33)	19.6 (11.7-36)	28 (14.8-47.3)
Nadir SpO ₂ (%), median [IQR]	82 (77-86)	82 (76-85.5)	81 (75.5-85)	78 (70-83.5)
Time (min), median [IQR]	451 (400-500)	456 (402-500)	466 (411-522)	474 (412-523)
msOSA (RDI > 15 events/h)	62.5%	65.7%	68%	79.6%

Abbreviation list: HTN: Arterial hypertension, D.M: diabetes mellitus, COPD: chronic obstructive pulmonary disease, OH: Alcohol, ESS: Epworth sleepiness scale, ESD: Excessive sleepiness during the day, BMI: Body mass index, BP: Blood pressure, RDI: Respiratory disturbance index, T90%: Time under 90% of SpO₂, ODI: Oxygen desaturation index, msOSA: Moderate to severe Obstructive Sleep Apnea. Highlights: Statistically significant compared to Baveno A.

**Fig. 2** Multiple comparison and mean differences across different Baveno groups.

($p=0.044$) and B ($p=0.002$). Additionally, Baveno B also presented differences from Baveno C ($p=0.022$) and D ($p=0.002$). Baveno A and C exhibited significant differences from Baveno D ($p=0.044$) and B ($p=0.022$) respectively (► **Supplementary Table S1** and ► **Figure 3**).

The summary of the Cox proportional hazard model is shown in ► **Table 2**. Compared to Baveno A (reference group), the unadjusted HR for Baveno C was of 6.1 (95%CI: 3.4 to 12.5) for all-cause mortality, and of 22.2 (95%CI: 2.9 to 170) for cardiovascular mortality ($p < 0.001$); for Baveno D, HR = 4.3

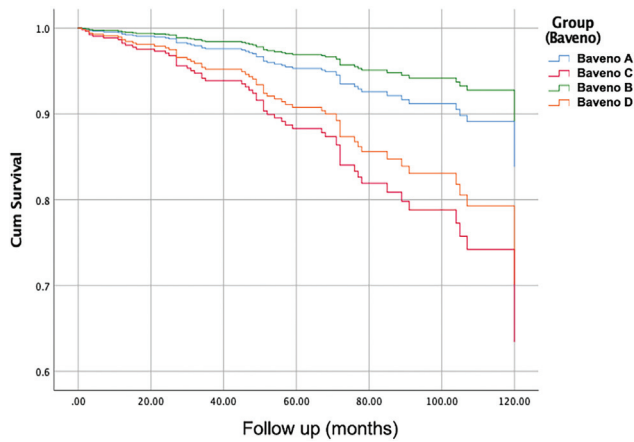


Fig. 3 Unadjusted survival analysis of different Baveno groups and cardiovascular mortality.

(95%CI: 1.01 to 2.85) and 14.3 (95%CI: 1.9 to 105) for all-cause and cardiovascular mortality respectively. However, after adjusting for demographic covariables, these differences were not significant.

The interaction analysis by sex showed nonsignificant interactions involving the risks of all-cause mortality and cardiovascular mortality and sex (interaction $p = 0.99$), age (interaction $p = 0.43$) and msOSA (interaction $p = 0.99$).

Discussion

The main findings of the present research are as follows: 1) the multicomponent grading system for sleep apnea can identify four different groups with different risks of cardio-

vascular outcomes and hypoxic load at baseline; 2) although the Baveno classification identifies populations with an increased burden of metabolic and sleep-related symptoms, the ability to identify OSA patients with an increased risk of cardiovascular mortality is unclear, mainly due to other covariables not included in the model.

In recent years, many approaches to identify subgroups of OSA patients with different prognoses have been reported in the literature.^{1,8,22,30} Most of these studies focused on the stratification of two principal components: the burden of comorbidities and the symptom phenotypes.¹⁰⁻¹⁵ In this scenario, the Baveno classification is a tool to easily identify subjects with different risks and select personalized interventions. In a previous study on the associations between the Baveno classification and cardiovascular response after CPAP therapy, Randerath et al.,²⁸ using data from the ESADA, reported changes in sleepiness and blood pressure parameters after 24 to 36 months, with significant changes in the Baveno B, C, and D groups. Additionally, this effect was not associated with RDI at baseline. In the present study, we found groups similar to those in the study by Randerath et al.²⁸ However, the association with cardiovascular mortality is unclear. Although the original purpose was clear, we could not provide robust data about the associations of different Baveno stages with all-cause and cardiovascular mortalities. Moreover, our findings suggest that demographic characteristics not included in the classification explain the differences between the unadjusted and adjusted analysis.

The association of age and cardiovascular mortality is one of the most studied, and age is an independent risk factor for major cardiovascular events.³¹ Our results showed an

Table 2 Summary of the association between cardiovascular mortality and Baveno groups

	All-cause mortality		CV mortality	
Model 1 (HR, 95%-CI) ‡				
Baveno A	REF	p-value	REF	p-value
Baveno B	0.8 (0.3 - 2.0)	0.74	3.2 (0.3-28.7)	0.29
Baveno C	6.1 (3.4 - 12.5)	<0.001	22.2 (2.9-170)	<0.01
Baveno D	4.3 (1.01 - 2.85)	<0.001	14.3 (1.9-105)	<0.01
Model 2 (HR, 95%-CI) &				
Baveno A	REF	p-value	REF	p-value
Baveno B	0.46 (0.2 - 1.15)	0.07	1.3 (0.14-13.0)	0.80
Baveno C	1.97 (0.9 - 4.18)	0.09	6.7 (0.8-52)	0.06
Baveno D	1.57 (0.7-3.20)	0.21	3.7 (0.5-28)	0.20
Model 3 (HR, 95%-CI) \$				
Baveno A	REF	p-value	REF	p-value
Baveno B	0.54 (0.21 - 1.41)	0.69	1.38 (0.14-13.5)	0.78
Baveno C	0.84 (0.34 - 4.18)	0.20	1.71 (0.18-16.2)	0.63
Baveno D	0.76 (0.33-1.74)	0.51	1.04 (0.12-9.2)	0.97

values expressed as Hazard ratios, REF: Reference

‡: Model 1: Unadjusted Analysis

&: Model 2: Cox proportional hazard model adjusted by age, sex, BMI

\$: Model 3: Model 2 + Hypertension + Diabetes Mellitus + Coronary heart disease at baseline

average age ranging from 50 to 60 years across Baveno stages. We believe that this variable should improve the accurate selection of OSA patients with increased cardiovascular risk.

Second, in recent years, the novel concept of severe hypoxemia during the night as a measure to identify the population with worse outcomes has been another relevant issue in OSA phenotyping.^{32,33} The findings of the present study suggest that oximetric parameters, such as T90% and ODI \geq 3%, are higher in the Baveno C and D groups. Previous research has strongly suggested that severe hypoxemia is a marker of worse results: Azarbarzin et al.¹⁷ published the sleep apnea-specific hypoxic burden (SASHB), a continuous variable that includes the “area under the curve of desaturation” from baseline saturation related to a respiratory event. The SASHB was tested with samples derived from two separate population-based cohorts in the United States (the sleep health heart study [SHHS] and the osteoporotic fractures in men [MrOS] sleep study), and the primary results indicated an independent association involving the SASHB, all-cause mortality, and cardiovascular mortality in the SHHS and MrOS cohorts.¹⁷

Moreover, these findings were independent of OSA severity according to the RDI, and they suggest that nocturnal hypoxemia is a relevant component in the diagnosis and stratification of OSA phenotypes. In a previous study,³⁴ using cluster analysis including 780 msOSA patients, we showed that severe hypoxemia (defined as high T90%, high frequency of ODI \geq 3%, and lowest nadir SpO₂) was independently associated with all-cause mortality, cardiovascular comorbidities, and cancer-related outcomes beyond the RDI.

Limitations

The main limitations of the present study are related to its design. First, we enrolled a single-center study, with a cohort from a tertiary center located in the metropolitan region of Santiago, Chile. Therefore, our patients' culture and incomes might be different from those of patients from other cities and countries. Moreover, although our dataset included a compressive evaluation of sleep-related symptoms, the data on cardiovascular comorbidities were restricted to self-reports, and we might have missed information about other cardiovascular comorbidities, such as arrhythmias and heart failure. Second, although we reported an average follow-up of 5.4 years, only 6.6% of the sample experienced a cardiovascular event; as a potential explanation, we suggest that the combination of the age at baseline in this sample and the high incidence chronic cardiovascular disease (HTN and DM) might have contributed to the number of events.

Moreover, previous studies on cardiovascular mortality, such as those by Marin et al.,³⁵ and Azarbarzin et al.,¹⁷ showed that the number of events increased in 5 to 10 years of follow-up, including a 30-year prospective cohort study⁵ with a median follow-up of 14 years. Finally, we could not provide accurate data about CPAP adherence during the follow-up and, therefore, about the potential efficacy of CPAP across different Baveno stages. Per-protocol meta-analyses of randomized controlled clinical trials^{6,36–38} have reported that, among msOSA patients with good com-

pliance with CPAP therapy, the efficacy of CPAP is higher. Future studies exploring the efficacy of CPAP in the correct OSA phenotype should be performed.

Conflict of Interests

The authors have no conflict of interests to declare.

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