

**Text S1. Description of the methodology used for inclusion criteria of both the training and validation cohorts, the neuroradiological and sleep studies conducted, and the statistical methods used for both the multiple logistic regression model and for the conditional inference trees model.**

**A) Brain and spinal magnetic resonance imaging (MRI) protocol**

MRI data were acquired using a 1.5 T scanner (MAGNETOM Symphony or Vision models, Siemens, Erlangen, Germany). In all patients, sagittal, transversal, and coronal conventional spin-echo T1-weighted, T2-weighted, and fast-FLAIR sequences were obtained. Cranial and brain measurements were assessed using a midsagittal T1-weighted MRI of the skull. Spinal measurements were assessed using sagittal T2-weighted MRI of the cervical spinal cord. For all brain and spinal MRI morphometric analysis, representative images of the MRI scans were exported to a compatible image file format and analyzed using the public domain Image J software version 1.43 (National Institutes of Health, USA). From the digitalized images, a reduced version of the more comprehensive craniometric parameters, previously used and published by our group, were evaluated (**Fig. 1**).<sup>1-3</sup>

The definition and description of these morphometrics measurements used in Figure 1 were;

***Linear and planimetric parameters:*** (1) *Diameter FM*: distance between basion and opisthion margins of the FM (*McRae line*) (C); (2) *Cerebellar TD respect to the McRae line* (C); (3) *Clivus length*: the distance between the top of the dorsum sellae and the basion (C); (4) *Suboccipocium length*: measured from the center of the internal occipital protuberance to the opisthion (C); (5) *Tentorium length*: measured from its anterior middle (posterior to the vein of Galen) to the internal occipital protuberance (D); (6) *Basal line* (BL): Line extending posteriorly from the upper cortical of the hard palate (D); (7) *Cerebellar TD respect to BL*: the degree of TD evaluated by measuring the distance to the most caudal aspect of the tonsils on a line running perpendicular to BL (D); (8) *Pons length*: distance between the BL and the upper part of the pons at the junction between the midbrain and pons (D); (9) *Fastigium length*: distance between the BL and fastigium (highest point in the roof of the fourth ventricle of the brain) (D); (10) *The osseous area of the posterior cranial fossa (PCF)*: was estimated from a polygon bound by the following edges: occipital bone (basioccipital portion of the clivus and supraoccipital portion of the occipital bone to the insertion of the tentorium), basisphenoid and a line from the upper basisphenoid to the internal occipital protuberance (a) (E); (11) *Total PCF area* was estimated from a single MRI sagittal slice and

the surface delimited by the following boundaries: tentorium, supraoccipital portion of the occipital bone, FM, and clivus (**a + b**) (E);

**Angular measurements (F,G)::** (12) *Basal angle*: the angle formed by a line from the basion to the posterior clinoid processes and a second line drawn from the posterior clinoid processes to the nasion (F); (13) *Wackenheim angle*: formed by a line drawn along the clivus prolonged downwards to meet a line tangential to the posterior aspect of the odontoid process (asterisk in G). (14) *Basilar impression respect to the Chamberlain line* (line drawn from the posterior margin of the hard palate to the opisthion): distance in mm from the top of the odontoid process and this line (values can be negative-below the Chamberlain line-or positive-above the Chamberlain line) (G). (15) *Odontoid angle*: formed by a horizontal line along the base of C2 body and another bisecting the odontoid process (asterisk in F); (16) *Tentorium-occipital angle*: formed by the tentorium and supraoccipital. (**H, I**)

**Syringomyelia and spinal measurements:** (**c**, arrow) *Syringomyelia superior limit*: higher superior vertebra of the syrinx cavity was detectable (H); (**d**, arrow) *Syringomyelia inferior limit*: lower inferior vertebral of the syrinx cavity was detectable (I); *Syringomyelia length*: distance between superior and inferior limit. (**e**) *Syringomyelia antero-posterior (AP) diameter*: maximal AP diameter of the cavity in millimeters (H); (**f**) *Spinal cord diameter*: maximal diameter of the cord in the same slice that maximal diameter of the cavity in millimeters (H); (**g**) *Maximum spinal canal diameter*, measured at the same level than e and f (H). *Syringo-cord ratio*: Syringomyelia diameter divided by spinal cord diameter multiplied by 100; *Spinal cord-canal ratio*: spinal cord diameter divided by canal diameter multiplied by 100.

Hydrocephalus was defined by an Evans index  $\geq 0.30$ , which was calculated by dividing the maximum bifrontal distance in the axial MRI slice by the maximum inner diameter of the skull at the same level of measurement.<sup>4</sup> The presence of basilar impression (BI) was defined as a projection of the axis odontoid process at least 3 mm above the Chamberline line and/or violation the McRae line.<sup>5</sup> In both cohorts, we subclassified patients according to the criteria used in the most recent literature.<sup>2, 6-8</sup> All patients presented classical CM-1, but for the purposes of this study they were subclassified into 2 groups: CM type 1, with a TD  $\geq 3$  mm below the FM and an obex located above the level of the FM, and CM type 1.5, with a TD  $\geq 3$  mm and the obex located below the level of the FM (**Fig. 1**). A more detailed explanation of this classification may be found in our previous work.<sup>2, 3, 6</sup>

## **B) Post-hoc logistic regression analysis with an RDI cutoff of 5**

**Methodology and results of logistic regression post-hoc analysis:** Despite our primary endpoint was the detection of patients with an RDI >10, we conducted an additional MLR post-hoc analysis using the lower traditional cutoff of 5 that corresponds to a mild sleep disturbance according to the American Academy of Sleep Medicine Task Force (AASM).<sup>9</sup> For this analysis, the outcome variable was described as an RDI >5. For this model, the absence of a clinically significant sleep disorder (RDI <5) was coded as 0 and coded as 1 when the RDI was >5. For this analysis, we used the same methodology described in the supervised machine learning approaches section. In brief, the same preselected input variables chosen for an RDI <sup>10</sup> (Supplemental data Tables S2 and S3). Risk factors in a continuous scale for the preselected RDI of 5 were individually tested by univariate analysis. All variables with p <0.25 in the univariate analysis were then entered in a MLR analysis.<sup>10</sup> Variables that were not statistically significant at p <0.05 were eliminated, and a new model was generated without them.

**Results:** Using a cutoff of 5, the prevalence of SRBD in our training cohort was 50%, and the three variables that showed statistical significance in MLR were age, sex, and BMI (Table S4). However, when using an RDI  $\geq$ 10 or an RDI  $\geq$ 15, BMI, clivus length, and the Chiari type were lost as statistically significant predictors. In addition, for a cutoff of 5, the accuracy of the model was reduced to 0.71, sensitivity to 0.78, and specificity to 0.64 compared with the model with a cutoff of 10 (Table 2).

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**Table S2.** Demographic and clinical data in the Chiari malformation patients with a different AHI cut off (<10 and ≥10).

	AHI cut off		<i>p</i>
	AHI <10 (n=60)	AHI ≥10 (n=30)	
Female sex	43 (71.7%)	15 (50.0%)	0.043 <sup>†</sup>
Age in years	39.3±11.6 [18-65]	47.4±12.8 [19-68]	0.004 <sup>†</sup>
BMI (kg/m <sup>2</sup> )	25.0±4.2 [14.5-37.7]	27.4±3.9 [19.1-37.7]	0.010 <sup>†</sup>
ESS	5.0 [0-16]	4.0 [0-12]	0.249
ESS > 11	17 (19.4%)	3 (10.0%)	0.057
Chiari 1	48 (80%)	22 (73.3%)	0.473
Chiari 1.5	12 (20%)	8 (26.7%)	0.473
<b>Associated problems</b>			
Syringomyelia	28 (46.7%)	15 (50.0%)	0.765
Hydrocephalus	7 (11.7%)	10 (33.3%)	0.013 <sup>†</sup>
Retroflexed odontoid	12 (20.0%)	5 (16.7%)	0.703
Basilar invagination	5 (8.3%)	5 (16.7%)	0.781
<b>Clinical symptoms</b>			
Headache	49 (81.7%)	23 (76.7%)	0.576
Sensory abnormalities	32 (53.3%)	18 (60.0%)	0.549
Reflex abnormalities	26 (43.3%)	12 (40.0%)	0.763
Motor abnormalities	16 (26.7%)	9 (30.0%)	0.739
Cranial motor nerve abnormalities (VII, IX, X, XI, and XII cranial nerves)	12 (20.0%)	8 (26.7%)	0.473

Results are expressed as N (%). Variables that followed a normal distribution are presented as mean ± standard deviation and minimum and maximum values [min-max]. Data that did not follow a normal distribution are presented as median and minimum and maximum values [min-max].<sup>†</sup>Statistically significant differences between different cut-offs for AHI,  $p \leq 0.05$ . BMI, Body Mass Index; ESS, Epworth Sleepiness Scale; AHI, apnea-hypopnea index.

**Table S3.** MRI morphometry measurements in the total cohort of patients with Chiari malformation (training group) and in the subgroups with different SRBD cut-off (RDI<10 and RDI ≥10).

	Training cohort CM	RDI cut-off<10 (n=60)	RDI cut-off ≥10 (n=30)	<i>p</i>
<b>MRI parameters</b>				
Evans index	0.27 [0.12-0.40]	0.26 [0.22-0.40]	0.28 [0.19-0.39]	0.007 <sup>†</sup>
Tonsillar herniation Mc Rae (mm)	9.0 [3-30.0]	9.0 [3.0-30.0]	9.0 [3.0-29.0]	0.525
Tonsillar herniation basal line (mm)	9.0 [0.0-33.0]	11.0 [0-33.0]	8.0 [0.0-29.0]	0.073
Fastigium length (mm)	26.0 [4.0-40.0]	25.5 [4.0-40.0]	28.0 [10.0-36.0]	0.015 <sup>†</sup>
Pons length (mm)	41.0 [23.0-54.0]	40.5 [23.0-54.0]	43.0 [27.0-51.0]	0.004 <sup>†</sup>
Tentorium length (mm)	48.1±5.1 [31.0-59.0]	47.6±5.3 [31.0-59.0]	49.2±4.9 [40.0-59.0]	0.161
Suboccipucium length (mm)	40.2±5.0 [25.0-55.0]	40.1±5.3 [25.0-55.0]	40.4±4.2 [33.7-48.0]	0.774
Foramen Magnum AP diameter (mm)	36.0 [27.0-42.0]	36.0 [27.0-42.0]	36.0 [29.0-40.0]	0.219
Clivus length (mm)	40.0±4.6 [29.0-52.0]	39.3±4.4 [29.0-50.0]	41.5±4.6 [32.9-52.0]	0.028 <sup>†</sup>
Total PCF area (cm <sup>2</sup> )	31.6±4.3 [15.0-42.0]	31.0±4.3 [15.0-42.0]	32.2±4.1 [22.3-38.0]	0.424
Bone PCF area (cm <sup>2</sup> )	19.4±2.9 [10.0-26.0]	19.2±2.7 [10.0-26.0]	19.9±3.1 [12.4-25.0]	0.245
Basal angle (°)	118.0 [104.0-146.0]	119.0 [104.0-146.0]	116.5 [104.0-133.0]	0.174
Tentorium-occipital angle (°)	91.0 [68.0-117.0]	92.0 [68.0-117.0]	90.1 [71.0-107.0]	0.902
Wackenheim's angle (°)	146.5±11.3 [113.0-171.0]	144.4±10.5 [113.0-164.0]	150.2±12.1 [126.0-171.0]	0.028 <sup>†</sup>
Odontoid angle (°)	108.3±6.2 [104.0-113.0]	108.6±6.6 [94.0-122.0]	107.7±5.5 [99.0-118.0]	0.517
Basilar invagination (mm)	-0.1±4.3 [-8.0- 14.0]	-0.4±4.4 [-8.0- 14.0]	-0.9±3.8 [-8.0- 8.0]	0.158
<b>Syringomyelia</b>	43 (47.8%)	28 (46.7%)	15 (50.0%)	0.765
Syringomyelia medulla	2 (2.2%)	0 (0%)	2 (6.7%)	0.048
Syringomyelia superior limit	2.9 [0.0-11.0]	3.0 [1.0-6.0]	2.0 [0.0-11.0]	0.027 <sup>†</sup>
Syringomyelia inferior limit	11.4±2.8 [0.0-23]	11.3±4.4 [1.0-19.0]	11.4±6.9 [0.0-23.0]	0.997
Syringomyelia length (VB)	8.4 [0.0-22.0]	7.0 [0.0-17.0]	9.0 [0.0-22.0]	0.798
Syringomyelia AP diameter (mm)	3.8 [1.1-12.0]	3.8 [1.1-9.8]	3.6 [2.0-12.0]	0.810
Spinal cord diameter (mm)	8.0 [5.0-15.0]	8.0 [5.3-15.0]	7.6 [5.0-13.0]	0.936
Syringomyelia-cord ratio (%)	52.9±20.4 [20.3-92.3]	52.7±20.0 [20.3-85.7]	53.3±21.9 [25.0-92.3]	0.938
Spinal canal diameter (mm)	14.0 [11.0-25.0]	13.0 [11.0-25.0]	14.0 [11.7-16.0]	0.730
Spinal cord-canal ratio (%)	61.8±15.9 [33.0-95.3]	61.7±15.2 [33.0-95.3]	62.0±18.1 [31.3-92.2]	0.958

Variables that followed a normal distribution are presented as mean ± standard deviation and minimum and maximum values [min-max]. Data that did not follow a normal distribution are presented as median and minimum and maximum values [min-max]. <sup>†</sup>Statistical significance, *p* ≤ 0.05. AP, antero-posterior; PCF, posterior cranial fossa; VB, number of vertebral bodies between the superior and the inferior limit of the cavity.

**Table S4:** Multiple logistic regression predicting the probability of an RDI  $\geq 5$

<b>Variables</b>	<b>Coefficient</b>	<b>SE</b>	<b>Z</b>	<b>P</b>	<b>OR</b>	<b>95 % CI</b>
Intercept	-5.57	1.811	-3.08	0.0020	--	0 - 0.02
Age	0.05	0.022	2.50	0.0122	1.06	1.01 - 1.11
Sex (female)	-1.25	0.555	-2.26	0.0238	0.28	0.09 - 0.82
BMI	0.15	0.066	2.30	0.0213	1.17	1.03 – 1.34

SRBD, sleep-related breathing disorder; RDI, respiratory disturbance index; SE, standard error; Z, Z value; OR, odds ratio; CI, confidence interval; P: Statistical significance.