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Cloud Algorithm-Driven Oximetry-Based Diagnosis of Obstructive Sleep Apnea in Symptomatic Habitually-Snoring Children.

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ABSTRACT

The ability of a cloud-driven Bluetooth oximetry-based algorithm to diagnose obstructive sleep apnea (OSA) was examined in habitually snoring children concurrently undergoing overnight polysomnography. Children clinically referred for overnight in-laboratory polysomnographic evaluation for suspected OSAS were simultaneously hooked with a Bluetooth oximeter linked to a smartphone. PSG findings were scored and the apnea hypopnea index (AHI_{PSG}) was tabulated while oximetry data yielded an estimated AHI_{OXI} using a validated algorithm. The accuracy of the oximeter in identifying correctly patients with OSAS in general, or with mild (AHI1-5events/hr), moderate (5-10events/hr) or severe OSAS (>10 events/hr) was examined in 432 subjects (6.5±3.2 years) with 343 having AHI_{PSG}>1event/hr. The accuracies of AHI_{OXI} were consistently >79% for all levels of OSAS severity, and specificity was particularly favorable for AHI≥10 events/hr (92.7%). Using the criterion of AHI_{PSG} >1event/hr, only 4.7% of false negative cases emerged, from which only 0.6% of cases showed moderate or severe OSAS. Overnight oximetry processed via Bluetooth technology by a cloud-based machine learning-derived algorithm can reliably diagnose OSAS in children with clinical symptoms suggestive of the disease. This approach provides virtually limitless scalability and should alleviate the substantial difficulties in accessing pediatric sleep laboratories while markedly reducing the costs of OSAS diagnosis.

Introduction

Obstructive sleep apnea-hypopnea syndrome (OSAS) has emerged in the last decades as a highly prevalent disease in children all over the world, and is estimated to affect 2-5% of all children. However, the cardinal symptom of OSAS in children is habitual snoring which affects a much higher proportion of children (range 6-25%). Furthermore, pediatric OSAS has been consistently associated with increased risk for major end-organ adverse consequences affecting neurocognitive, behavioral, cardiovascular and metabolic systems, ultimately resulting in overall health and quality of life declines, as well as increased healthcare costs (1-4). Based on current guidelines, nocturnal polysomnography (PSG) in an accredited sleep laboratory is considered as the gold-standard approach to diagnose OSAS in children (1,5,6). However, the scarcity of pediatric sleep laboratories around the world, the elevated costs of PSG and their labor intensive non-scalable characteristics, and the obvious inconvenience to both parents and children have led to the unfortunate reality that only a minute proportion of symptomatic habitually-snoring children are objectively evaluated before undergoing adenotonsillectomy (AT), the first line of therapy (7,8).

In an effort to overcome these problems and expand the accessibility and objectivity of OSAS diagnosis, many alternative methodologies have been developed, ranging from questionnaires to simplified multichannel studies or even exploration of diagnostic biomarker panels (9-13). Nocturnal oximetry was initially proposed as a screening tool for OSAS in symptomatic children (11,13), and this approach has gained increasing popularity despite exhibiting favorable specificity yet limited sensitivity, while also being marred by inter-scorer reliability issues particularly at the low end of OSAS severity, as well as scalability concerns (11). To overcome these issues, several investigative groups including ours have proposed a variety of automated

procedures that circumvent the subjectivity of oximetry recording interpretation (14-30). In this context, we have recently reported on the application of machine-learning procedures in the analysis of nocturnal oximetry recordings among children referred for clinical evaluation of suspected OSAS, and the derivation and validation of a diagnostic algorithm in a very large cohort of >4000 children (31). Here, we furthered our quest for a scorer-independent scalable diagnostic approach of pediatric OSAS by exploring and comparing the diagnostic performance of a Bluetooth enabled oximeter coupled to a smartphone for data transmission and derivation of the estimated apnea-hypopnea using a cloud-based algorithm when tested concurrent with a PSG study in the laboratory.

Patients and Methods

Subjects

Consecutive, otherwise healthy, habitually snoring symptomatic children (≥ 3 nights per week) aged 2-15 years who were referred for suspected OSAS were recruited from Beijing Children's Hospital, Capital Medical University between June 1st, 2017 and June 1st, 2018. All participants underwent an overnight polysomnographic (PSG) evaluation while concurrently wearing a commercially and readily available Bluetooth oximeter linked to an Android smartphone via a custom designed application (Serenium Inc, Palo Alto, CA). Written informed consent and assent were obtained from parents and children, respectively (for children >7 years of age). The study was approved by the Ethics Committee of Beijing Children's Hospital affiliated to Capital Medical University (Protocol #2017-151), and received also approval for processing of the de-identified oximetry recordings by the University of Chicago Human Subject Committee (Protocol #IRB14-1241).

Exclusion criteria

Children who were known as suffering from congenital heart disease, systemic or pulmonary hypertension, diabetes mellitus, dyslipidemia, or those with craniofacial anomalies, neuromuscular disease, or defined genetic syndromes were excluded. In addition, children with any known acute or chronic illness, or who received previous treatment for OSAS were also excluded. Children with recordings from either PSG or Bluetooth oximeter lasting less than 3 hours were also excluded.

Anthropometry

All children were weighed on a calibrated scale and their weights were recorded to nearest 0.1

kg. Height (H, to 0.1cm) was measured with a stadiometer. The body mass index (BMI) and BMI z score were calculated using Chinese normative datasets (32). The definition of obesity in our study was BMI z score ≥ 1.65.

Polysomnography (PSG)

Children were monitored during the PSG using a digital acquisition system (Compumedics E; Compumedics, Melbourne, Australia; or ALICE 5; Philips Respironics, Amsterdam, Netherlands). No coffee, tea, cola-containing products or sedative hypnotics were taken before sleep. Total sleep time was more than 7.5 hours. PSG monitoring included the following parameters: EEG from four leads (C3/A2, C4/A1, O1/A2, O2/A3), bilateral electro-oculogram, electromyogram of mentalis activity and bilateral anterior tibialis, chest and abdominal movements, ECG, arterial oxyhemoglobin saturation and plethysmographic signal by pulse oximetry, air flow thermistor and nasal pressure cannula, snoring sensor and body position. Sleep data were scored manually by experienced pediatric PSG technicians according to the scoring manual published by American Academy of Sleep Medicine (AASM) (33). Oxygen desaturation index (ODI) was defined as the number of ≥ 3% arterial oxygen desaturations per hour of sleep. The definition of arousal was based on the AASM Guidelines. The diagnosis of children with OSAS was defined by the presence of an obstructive apnea-hypopnea index (AHI_{PSG}) ≥1 per hour of TST according to the most frequent clinical practice as described in the 2012 American Academy of Pediatrics consensus guideline for the diagnosis and management of childhood OSAS (1). Primary snoring was defined as AHI <1 events/h. Mild OSAS was defined as AHI_{PSG} ≥1 and AHI_{PSG} <5 events/h, moderate OSAS was defined as AHI_{PSG} ≥5 events/h, and severe OSAS was defined as AHI_{PSG} ≥10events/h.

Oximetry Data Processing: Oximetry signals from the Bluetooth oximeter were transferred via the smartphone to the cloud and were all rounded to the second decimal place. Artifacts were then automatically removed according to the method proposed by Magalang et al (34). Signals were then automatically processed with the algorithm previously developed and validated (31), which consisted of a multi-layer perceptron (MLP) model with the ability to automatically estimate AHI. MLP constitutes an artificial neural network that is typically arranged in three layers of mathematical units called neurons: input, hidden, and output (31), and Matlab R2016b was used to implement feature extraction and classification stages. Accordingly, an estimate of the AHI was computed (AHI_{OXI}), and compared with AHI_{PSG}.

Statistical Analyses

IBM SPSS Statistics version 20 software (Chicago, IL) was used, and data are presented as means and standard deviations. Intra-class correlation coefficient (ICC) was used to directly assess the agreement between the AHI_{PSG} and AHI_{OXI}, as well as Bland-Altman and Cohen's κ (36). In addition, the diagnostic performance for three cutoff (AHI = 1, 5 and 10 events/h) was assessed by means of sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), and accuracy. Plotting of the LR values was performed using a freely available web-based calculator developed by Shwartz A (http://araw.mede.uic.edu/cgi-bin/testcalc.pl?DT=&Dt=&dT=&dt=&2x2=Compute). For comparisons of continuous variables across clinical groupings, Kruskal–Wallis (non-parametric) or Mann-Whitney tests were used as appropriate. For comparisons of discrete variables, a $\chi 2$ test was used. A p-value < 0.05 was considered as indicative of statistical significance.

Results

A total of 432 children completed the study out of 435 who were approached and agreed to participate. The reasons for inability to complete the study was related to intolerance by the 3 very young children (ages, 2,2.5, and 3 years) of the PSG equipment which led to them spending most of the recording time awake or without appropriate PSG recording montage. Table 1 provides the demographic and anthropometric characteristics of the cohort as well as their PSG findings.

Figure 1 displays the Bland-Altman plot comparing the AHI_{PSG} of the subjects with their corresponding and AHI_{OXI} estimation from the oximeter data concurrently acquired during their PSG testing. In addition, a low mean positive difference (slight AHI underestimation by the algorithm) is apparent, with 95% confidence intervals within [-40.5, 35.3] which reflects the dispersion that occurs when AHI_{PSG} values are very high indicative of extremely severe OSAS. In addition, a high ICC is reached (0.317).

Table 2 and Figure 2 shows the confusion matrix comparing the classification derived from the AHI_{PSG} with the classification achieved by the cloud based algorithm based on oximetry alone, i.e., AHI_{OXI}. Accordingly, Cohen's κ was 0.339. Table 2 also displays sensitivity, specificity, LR+, and LR- for the AHI = 1, 5, and 10 events/hr cutoffs, derived from the confusion matrix, and Figure 3 displays the receiver operator curves for each of these cut-off values. AHI_{OXI} showed increasing degrees of diagnostic ability as the cutoff increased and became <90% specific at AHI cutoff of 10. Accuracies remained above 79% at all cut-off levels with LR+ displaying optimal performance for AHI of 5 or higher.

Discussion

This study shows that a previously developed and validated neural network machine-learning algorithm based on overnight oximetry recordings (31) can be readily and accurately implemented as a readily scalable operator-independent diagnostic tool for the diagnosis of OSAS in symptomatic children referred for evaluation of OSAS.

Before we discuss the clinical implications of current findings, several methodological issues deserve mention. First, only a single commercially available oximeter model was employed for the present study, and displays industry standard accuracy. In this context, awareness to the potential imprecision of the oximeter being selected and employed during implementation of the approach used in the present study is obviously of great importance (37). Similarly, the potential imprecisions introduced by the finger probe being selected should also be accounted for in materials and supplies selection (38). However, we should also remark that the heterogeneity of the oximeters and their intrinsic performances was also incorporated in the process of derivation and validation of the cloud-based algorithm, and included 13 different pediatric sleep centers around the world using vastly different oximeters and oximeter data sampling frequencies (31). Furthermore, the oximeters used in the PSG and the wearable Bluetooth oximeter were also different in this study, but achieved concordance in the scored and automatically detected 3% oxygen desaturation indices, respectively (r^2: 0.35; data not shown). Secondly, while we attribute the designation of "gold standard" to the PSG, there can be considerable night-to-night variability, particularly in sleep architecture, embedded in the test (39-41), which may lead to substantial imprecision in the diagnostic decision, particularly at the low end of OSAS severity (41,42). Although not immediately relevant to this study since both PSG and Bluetooth oximetry were implemented concurrently, we should point out that this issue has arisen, albeit

inconsistently in oximetry recordings in children, prompting the recommendation that if a single night yields a negative result in a patient with a high pre-test probability, then addition of 2 more nights of oximetry recordings should lead to a more reliable clinical decision. (43,44). Such approach would obviously be highly feasible with ambulatory oximetry, but impossible with PSG, such that if the accuracies of oximetry-based approaches were virtually indistinguishable from PSG, there would be inherent advantages at using oximetry in this context.

Overall, the accuracy of the portable oximeter-cloud based algorithm dyad exceeded 79%for AHI estimates of 1 to 10 events/hour, and displayed the anticipated progressive declines in sensitivity with increasing AHI cutoff values to higher specificity at an AHI cutoff of 5 events/hr (Table 2). Thus, and as previously inferred during the process of developing the algorithm, optimal benefits of this automated methodological approach to diagnose OSAS in habitually snoring children (31) is achieved with AHI≥5 events/hr. This cutoff value not only corresponds to a virtually universally agreed upon equipoise criterion for surgical adenotonsillectomy, but is also associated with an upward inflexion in morbidity risks in children with OSAS (46-48). Of note however, adoption of the AHI 1 event/hr cutoff would lead to relatively high rate of false positives, which would then be treated even if their AHI_{PSG} would have been <1 events/hr. Conversely, the false negative rate of our approach was small, as illustrated by the fact that using the criterion of AHI_{PSG} >1event/hr, only 4.7% of false negative cases emerged, from which only 0.6% of cases would be in the moderate or severe OSAS category. Notwithstanding, the relatively small proportion of children that would be missed using oximetry-based diagnostics might be further reduced by repeating the oximetry-based test for one or more additional consecutive nights (44), an issue that clearly deserves further exploration in future studies. Furthermore, repeating the test within weeks or months if the child's symptoms were to persist

would be much more readily achievable than repeating PSG. Thus, the clinical management options and algorithms offered by the PSG, whereby the AHI serves as one of the major parameters guiding clinical intervention, would be indistinguishably afforded by the AHI_{OXI}, albeit at a fraction of the cost and effort.

As alluded previously, the overall scarcity and labor- and financially-onerous nature of PSG has prompted exploration of multiple other suitable diagnostic alternative approaches ranging from questionnaires to ambulatory PSG or to simplified multichannel recordings (49). However, some of such approaches, e.g., respiratory polygraphy, are becoming increasingly accepted as a surrogate diagnostic test in children, despite their reduced accuracy at the low end of OSAS severity spectrum (50), a limitation that has prompted a lack of endorsement by the Academy of Sleep Medicine (51). In the present study, our findings clearly show that automated analysis of nocturnal oximetry provides a useful approach to the diagnosis of OSAS among high pre-test symptomatic children being referred for evaluation of suspected OSAS. Indeed, and according to the protocol proposed in our previous study which as mentioned above proposed a cutoff of AHI≥5 events/hr (31), OSAS would have been discarded in 38 children, most of them with AHI_{PSG}<5/events/hr. We should also remark that several of these children would potentially require treatment anyway due to concurrent SDB-related morbidity. In addition, 184 subjects would be referred for treatment, with 96.7% showing mild OSAS. Such approach would clearly reduce the need of conventional PSG, a finding that is coherent with our previous results (31), whereby 77.8% children with moderate-to-severe OSAS based on PSG would be identified as such by oximetry coupled to a mobile phone app interfaced with a cloud-based algorithm. Our findings are also in close agreement with the approach and conclusions from a recent study by Papadakis *et al* (52), in which oximetry approaches consisting of a ODI3%>3.5 successfully

post-surgical intervention outcomes.

In summary, this study provides initial confirmatory demonstration that diagnostic precision can be readily achieved via a portable oximeter linked via a smartphone to a cloud-based automated analytic algorithm. This approach offers not only valid alternative to standard PSG in the context of childhood OSAS, but also shows that it is a highly scalable, i.e., is incorporates the ability to seamlessly continue to deliver the desired service, in this case oximetry-based diagnostics, in the context of increasing demands in order to meet a user need without requiring additional expert personnel (current rate-limiting factor), and therefore should serve as a remarkably affordable option. Therefore, integrated collection of ambulatory nocturnal oximetry signals and their automated processing by well validated algorithms as the one employed herein, should lead to accurate and widely implementable diagnostic tools for childhood OSAS, thereby enabling timely objective evaluation and treatment with the attendant downstream benefits of reduced morbidity. Inasmuch as the current findings are promising, expanded implementation of the current system to the domiciliary venues and its real life performance in the clinical setting will need to be critically investigated and confirmed.

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	All Participants (n=432)	Primary Snoring AHI_{PSG}≤1 event/hr (n = 89)	OSAS AHI_{PSG}>1 event/hr (n = 343)	OSAS AHI_{PSG}>5 events/hr (n = 171)	p value
Age, years	6.3 ± 2.5	6.5 ± 2.4	6.3 ± 2.6	6.4 ± 2.5	
Male, %	65.3 %	62.8%	69.4 %	64.5 %	
BMI (% obese)	17.8 ± 4.5 (26.3)	16.6 ± 3.9 (23.2)	18.3 ± 4.7 (26.7)	19.2 ± 5.4 (33.1%)*	*-p<0.01 vs. all other
Total Sleep Time (min)	474.1± 54.4	460.4± 72.2	478.1± 47.8	471.7± 48.4	
Sleep efficiency (%)	83.5 ± 8.6	83.7 ± 8.9	83.5 ± 8.6	82.2 ± 8.8	
AHI, events/ h (median; IQR)	10.0 ± 21.3 (3; 8.1))	0.5 ± 0.3 (0.5; 0.5)	11.4 ± 23.3 (4.5, 9.6)	22.3 ± 29.6 (12.2; 16.4)	**p<0.0001 vs. primary snoring
ODI3%, events/ h	6.7 ± 16.2	0.2 ± 0.7	8.3 ± 17.7	14.8 ± 21.4	** p<0.0001 vs. primary snoring
SpO_2 nadir, (range)	89.8 ± 7.2	94.3 ± 2.0	88.6 ± 7.6	85.2 ± 9.0	** p<0.0001 vs. primary snoring

Table 1 Demographic, anthropometric and polysomnographic characteristics of 432 symptomatic habitually snoring Chinese children undergoing overnight polysomnography and concurrent Bluetooth oximetry for suspected obstructive sleep apnea

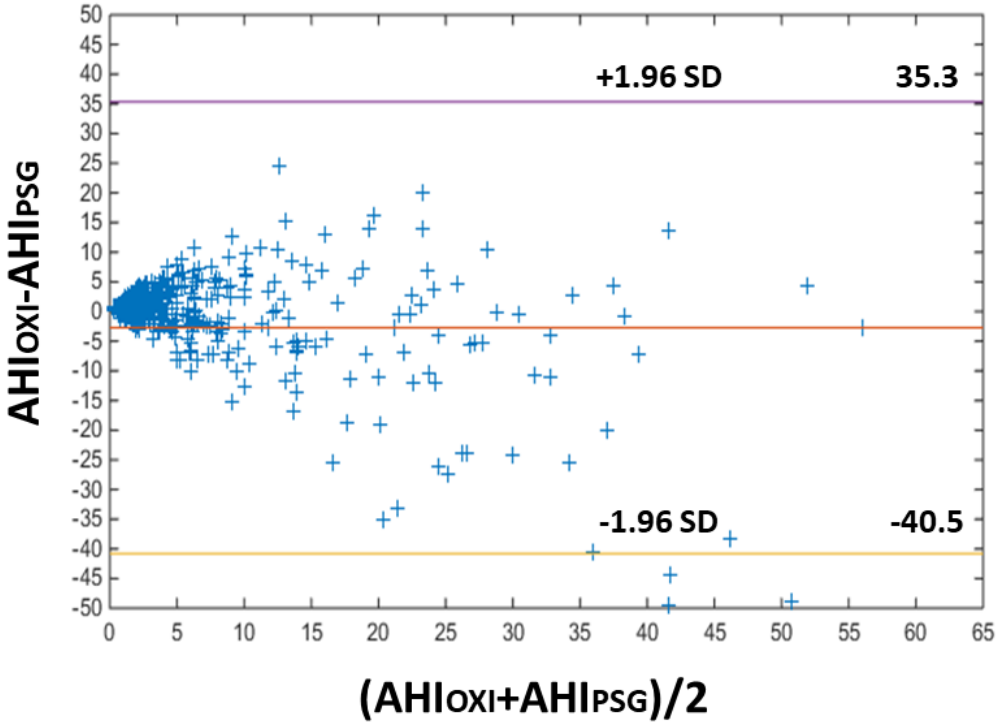
Table 2. Confusion matrix showing the classification agreement of Bluetooth oximeter cloud-based algorithm-calculated AHI estimate and the NPSG-derived AHI in 432 symptomatic habitually snoring Chinese children undergoing overnight polysomnography and concurrent Bluetooth oximetry for suspected obstructive sleep apnea.

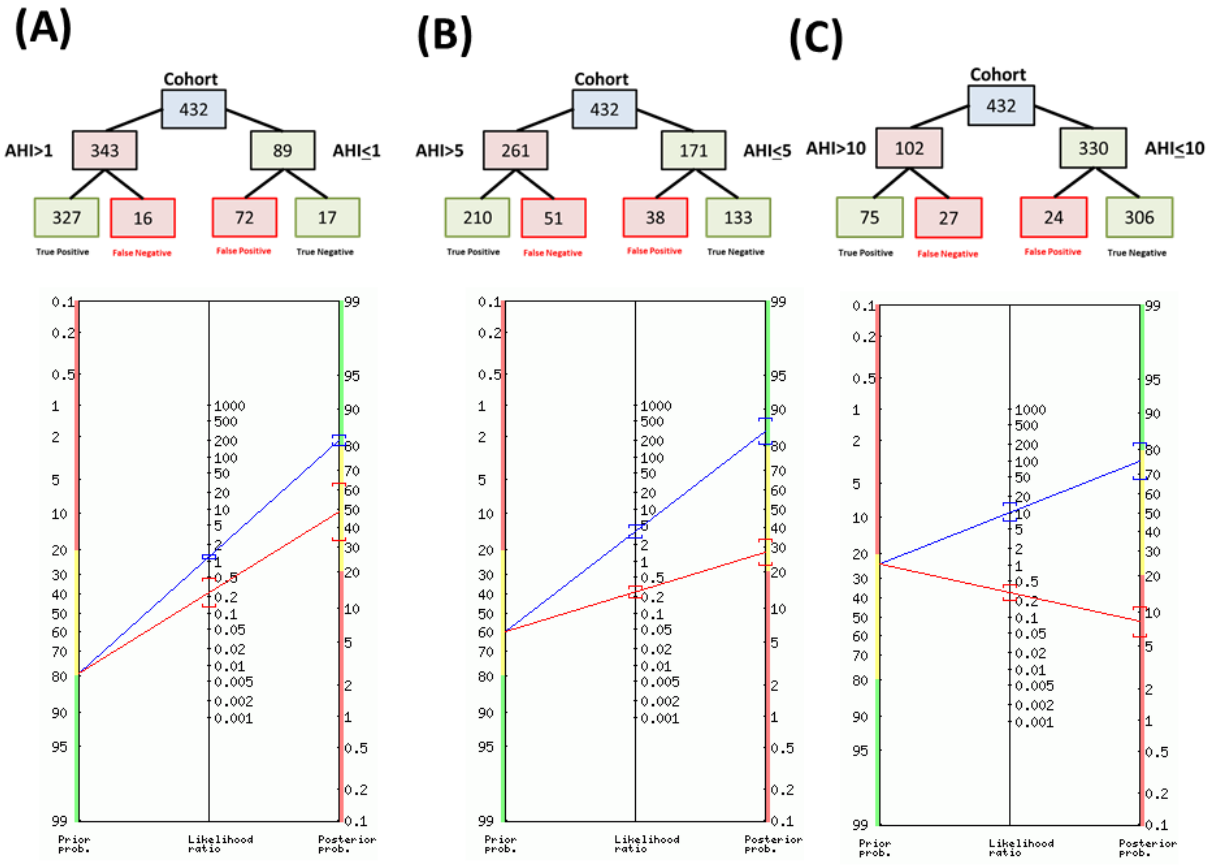
		AHI_{OXI}				
		<1 event/hr	**1 to 5 events/h**	**5 to 10 events/h**	**≥ 10 events/h**	**N PSG**
AHI_{PSG}	**<1 e/h**	17	66	4	2	89
	1 to 5 e/h	14	113	41	4	172
	5 to 10 e/h	2	22	27	18	69
	>= 10 e/h	0	14	13	75	102
	N OXI	33	215	85	99	**432**
	Cohen's κ= 0.339					
		Sensitivity	**Specificity**	**Accuracy**	**LR+**	**LR-**
	AHI=1	95.3	19.1	79.6	1.18	0.25
	AHI=5	77. 8	80.5	79.4	3.99	0.27
	AHI=10	73.5	92.7	88.2	10.07	0.29

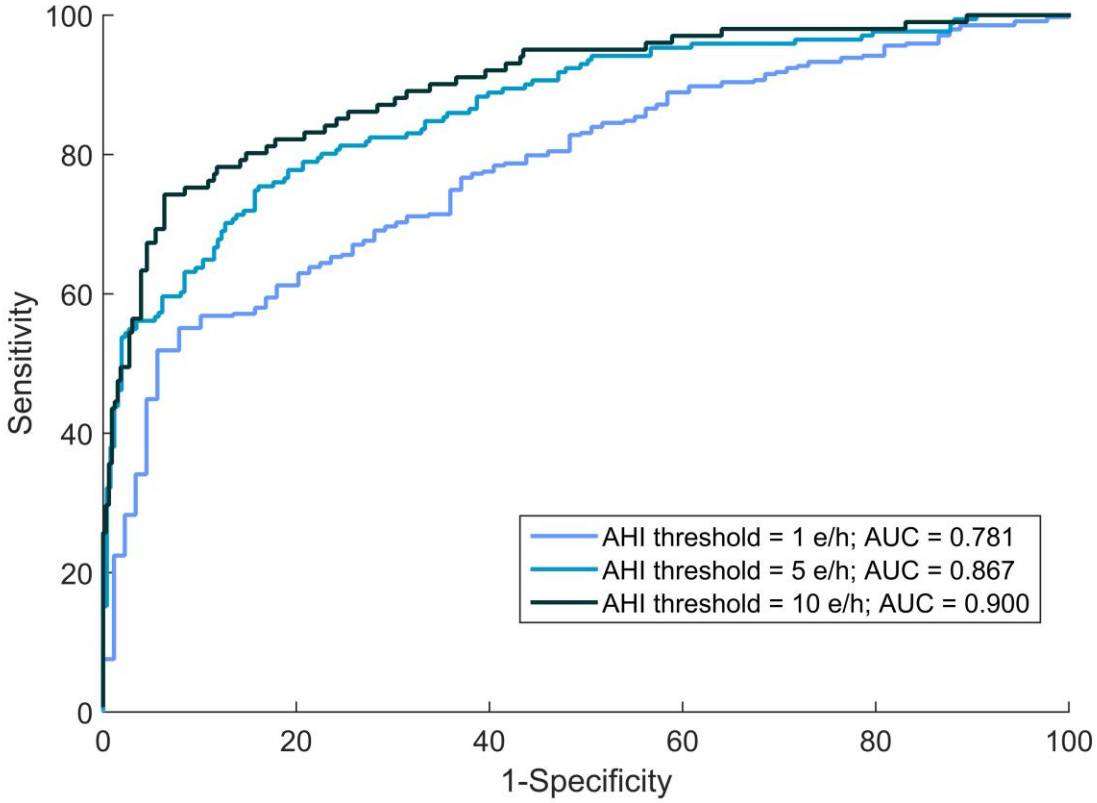
Figure 1. Bland-Altman plot comparing AHI_{PSG} with the estimated AHI_{OXI} from a portable Bluetooth oximeter using a cloud- based algorithm.

Figure 2. Schematic representation of AHI_{OXI} algorithm performance and corresponding likelihood ratios relative to AHI_{PSG}, when diagnostic cutoff values are set at 1 event/hr (panel A), 5 events/hr (panel B) or 10 events/hr (Panel C).

Figure 3. Receiver operator curves and corresponding AUC when diagnostic cutoff values are set at 1 event/hr, 5 events/hr or 10 events/hr


+1.96 SD
35.3
-1.96 SD
-40.5
AHIOXI-AHIPSG
(AHIOXI+AHIPSG)/2


(A)
Cohort
432
AHI>1
343
89
AHI≤1
327
16
72
17
True Positive
False Negative
False Positive
True Negative
(B)
Cohort
432
AHI>5
261
171
AHI≤5
210
51
38
133
True Positive
False Negative
False Positive
True Negative
(C)
Cohort
432
AHI>10
102
330
AHI≤10
75
27
24
306
True Positive
False Negative
False Positive
True Negative
Prior prob.
Likelihood ratio
Posterior prob.


100
80
60
40
20
0
Sensitivity
0
20
40
60
80
100
1-Specificity
AHI threshold = 1 e/h; AUC = 0.781
AHI threshold = 5 e/h; AUC = 0.867
AHI threshold = 10 e/h; AUC = 0.900