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"Assessing Diagnostic Accuracy & Cost Effectiveness Of Level I & Level III for Diagnosis Of Obstructive Sleep Apnea In India: Health Technology Assessment"

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Abstract

E Objective: Obstructive sleep apnea (OSA) is the most common and the severe form of sleep breathing disorder (OSA). In India, prevalence ranges from 8% to 19% and associated with comorbidities (diabetes, higher BMI), which are also increasingly prevalent in India. Increasing prevalence of OSA and its awareness results in higher demand of diagnostic screening through sleep studies or polysomnography (PSG), which are resource and cost intensive. It is often undiagnosed in India, specifically in rural settings where 70% of total population lives. This study aims to assess the cost-effectiveness of Level I(PSG) and Level III (portable-device) diagnostic tests to diagnose OSA for Indian population.

Methods: A decision-analytical model was built in the Excel, comparing Level I, Level III and no screening using 1-year time horizon with a healthcare perspective in India. For the diagnostic accuracy, meta-analysis was performed via a bivariate mixed effect. Binary regression model used to estimate summary diagnostic accuracy parameters using Revman 5.3 and STATA 14. Studies were included from 2006 to 2019 and associated protocol was published in PROSEPRO database (CRD42018110619).

Results: This study showed incremental cost-effectiveness analysis of OSA screening through Level III could save INR 559,888.63 (USD 1,08,03,050.48) per QALY gained.

Conclusion: Diagnosis of OSA with portable Level III is a feasible and acceptable alternative in rural populations. In addition, screening is very cost-effective with the level III study. Though there is limited data on OSA diagnosis in rural India, there is a need to implement systems and policies to address this issue.

Keywords: Obstructive sleep apnea, portable-diagnosis device, polysomnography, quality of life, cost-effectiveness.

1. INTRODUCTION

Sleep-disordered breathing (SDB) is a spectrum of disorders characterized by a series of abnormal respiratory pattern in which partial or complete cessation of breathing occurs several times during sleep (1). Obstructive sleep apnea (OSA) is most common and severe form of SDB (1). Despite its high prevalence, it is an under-recognized health problem (1). It affects both gender, and prevalence increases with age, with a peak between 55 to 66 years. However, it is estimated that 82% men and 92% women with moderate to severe sleep apnea have not been diagnosed globally (2). The prevalence of

confirmed OSA in rural population is 3.73%, comparable to other non-communicable diseases such as diabetes (3% to 8.3%) (3). It also leads to various comorbidities, especially cardiovascular diseases, obesity and diabetes. Recent evidence reports that 53.7% of the population with OSA had a BMI>/=25 kg/m2 , considered obese as per the Asian standards (4),which is more prominent in the urban population. These comorbidities are associated as risk factors for COVID 19, which again is a severe respiratory disease. In a recent meta-analysis it is found that there is 2.93 times higher risk for COVID-19 hospitalization in patient with OSA (5). Moreover, it is also seen that patients with OSA have difficulty to concentrate on tasks and find themselves falling asleep at work while watching TV, or even driving, which can lead to accidents (6). Additionally, OSA can lead to neurologic complications, including memory problems, depression, and headaches (7). These non-specific symptoms are reasons for undiagnosed or inaccurately diagnosed OSA in large sections of the population.

Despite its high prevalence, it is under-recognized health problem, especially in resource-limited contexts (1). It is often undiagnosed, especially in rural areas where 70% of India's population resides. Estimates suggest, that OSA affects nearly 8% to 19% in India (8-12), with 7% to 14% males and 11% to 12.9% females (11,12). In India, 90% of the population remains undiagnosed (10).

However, the increasing prevalence of OSA and greater awareness about associated health risks appears in high demand for testing for sleep studies (13). Level I sleep study, or PSG, is the gold standard required to make a diagnosis of OSA, which involves overnight testing in a sleep laboratory in the presence of a health care professional (1).

Level I sleep studies diagnosis presents itself with several limitations, which majorly includes necessity of performing the study in a sleep laboratory, requirement of technical expertise, high cost and long analyzing time needed by the operator (14). Additionally, patients finding time to visit, and labs being overwhelmed, results in delaying patient diagnosis, especially during COVID times, where respiratory precautions are necessary. Therefore, the alternative diagnostic approach includes using home based unsupervised portable PSG equipment (also known as, Level II and Level III sleep study). The perceived advantage of these home-based portable monitoring is time and resource efficiency with lower cost (1,15). As these devices are less expensive than Level I and widely available, they could potentially be an alternative point of care devices in the Indian public health setting.

Moreover, as per Indian Initiative on Obstructive Sleep Apnea (INOSA) guidelines, in the laboratory, PSA is not necessary for all patients suspected to have OSA. According to INOSA, a portable monitoring device with Level III or IV is adequate for diagnosis. This is acceptable in conjunction with comprehensive sleep evaluation and patients with a high pretest probability of moderate to severe OSA without comorbid sleep disorders or medical disorders (1). The Indian National health Policy 2017 states, "One important capacity with respect to introduction of new technologies and their uptake into public health programs is HTA, guided by considerations of scientific evidence, safety, cost effectiveness considerations and social values". Therefore, diagnostic accuracy of screening of these devices, cost-effectiveness, and accessibility are the major factors essential for effective uptake and implementation of a screening technique in the Indian public health system.

At present, neither the state or central health insurance in India cover the cost of sleep studies, thus it is mostly out of pocket expenditure (OOPS). Several studies are published regarding the importance and awareness of sleep in India (10-14, 16,17). However, the economic impact of available technologies in India is still not well established. Therefore, we undertook this Health Technology Assessment (HTA) of Level III compared with Level I from an Indian perspective.

2. Materials and Method:

2.1. Search strategy

We performed a systematic review of literature between 2006 to 2019, using a peer reviewed search strategy in Cochrane Database of Systematic reviews, and PubMed, following, Centre for Reviews and Dissemination's (CRD) for comparative study of Level I and Level III for clinical effectiveness. For economic studies,

NHS Economic Evaluation Database, Center for Review and Dissemination, and Cost Effectiveness Analysis (CEA) registry were searched. The search strategy includes keywords related to portable-monitoring device, PSG, OSA, SDB, diagnostic accuracy for clinical effectiveness. Whereas for cost-effectiveness strategies, keywords comprised of terms relating to economic evaluation, cost-effectiveness, costs, utility, and Quality of Life (QoL) were used.

2.2. Meta-analysis:

2.2.1. Selection of studies and data extraction

Title and abstracts were independently screened by three reviewers (AC, SJ, NR), to identify possible studies for inclusion. All studies comparing Level III with Level I sleep tests involving adults were included if they reported on diagnostic accuracy parameters. Patients, Intervention, Comparator, Outcomes and Study design (PICOS) criteria were followed to take decision on inclusion and exclusion of studies and Preferred Reporting Items in Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed for reporting the studies (18) (Figure 1).

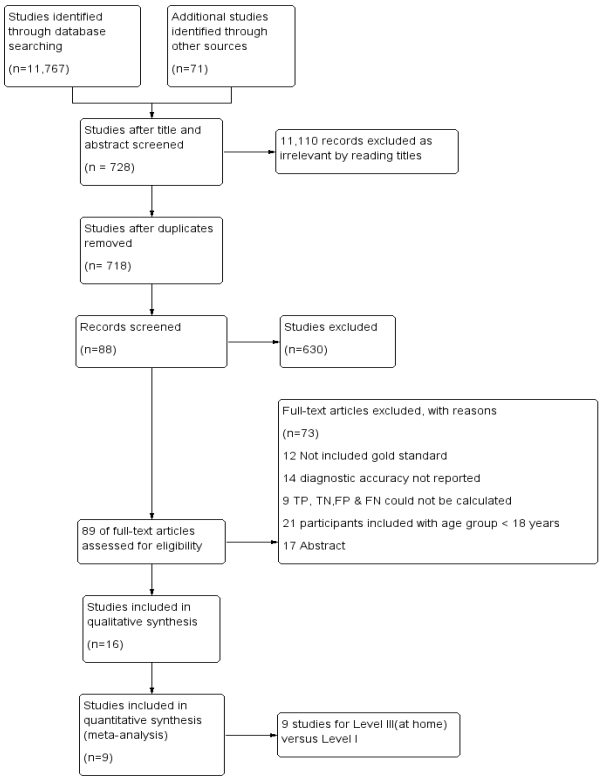

Figure 1 *Selection of studies for inclusion in meta-analysis for sleep studies' diagnostic characteristics*

Three reviewers (AC, SJ & BS) extracted the data independently from included studies using a excel based tool with the details of the author, year of publication and diagnostic accuracy parameters. Diagnostic accuracy parameters included true positive (TP), true negative (TN), false positive (FP), false negative (FN), sensitivity (SN), specificity (SP), positive and negative likelihood ratio. In case of any disagreement, we approached third reviewer (NR) for resolution.

2.2.2. Quality assessment:

We used Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool, to check the quality of the included studies. QUADAS-2 assesses bias and applicability, i.e., internal validity and external validity respectively, in multiple domains, which are: i. flow and timing, ii. reference-standard test, iii. Index tests, and iv. patient selection (19).

2.2.3. Statistical analysis:

Studies reported Level III test performed at different AHI severity levels, we analyze the diagnostic accuracy parameters in all studies to determine the ranges of SN and SP. A meta-analysis is performed using a bivariate mixed-effects binary regression model. The model estimates variation between the studies in diagnostic accuracy in terms of SN and SP through random effects using the Review manager version 5.3 software from Cochrane. However, this software has the limitation of not calculating pooled data, therefore pooled diagnostic analysis was estimated using STATA 14 and for generating summary ROC curves. This model requires the primary parameters of TP, FP, TN, and FN, in case such parameters were not reported in the included studies directly, where possible, we calculated these from the data provided in the study.

2.3. Economic evaluation:

2.3.1. Cost-effectiveness analysis:

A decision model was developed from a healthcare perspective with a time horizon of one year, to estimate the cost-effectiveness of a portable monitoring device. Health outcomes are expressed in terms of quality-adjusted life years (QALY). Cost and benefits are discounted at a rate of 3% per annum (20). We searched for incidence and prevalence data in the locally

published literature on Level III and Level I sleep studies. Pooled diagnostic accuracy data was taken from the meta-analysis result section, which is part of this study. We surveyed the Indian market to take the cost range for Level I and Level III sleep studies. For the analysis, we averaged the cost used to elicit the unit costs of Level I and Level III diagnostics. If required cost was converted to 2021 Indian Rupees using the web-based tool CCEMG-EPPI-Centre Cost Converter'v1.5(21). Results are reported as incremental cost (Indian rupee [INR]) per QALY gained. According to guidelines for HTA in India, to evaluate cost-efficiency we used a threshold of per capita gross domestic product (GDP)(22). We have also demonstrate cost in terms of International US Dollars using Purchasing Power Parity (PPP) conversion from World Economic Outlook.

To ascertain the price at which the Incremental cost-effectiveness ratio (ICER) value was below per capita GDP, A threshold analysis was undertaken. The threshold was justified based on economic evaluations conducted in India (23) and Indian HTA guidelines (22). Model Input parameters are reported in Table 1.

2.3.2. Cost Monetary Benefit analysis:

A Cost Monetary benefit (CMB) analysis was also done performed for the two diagnostics devices. CMB analysis was carried out using the model input parameters.

This HTA was registered in International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42018110619, https://www.crd.york.ac.uk/prospero).

3. Results

3.1. Meta-analysis

An initial literature search provided 11,838 citations. After full-text screening, we included nine full-text studies for comparing Level III and Level I sleep study, including 1694 patients (Figure 1) for meta-analysis. We included patients with suspected OSA for analysis. The studies included for the meta-analysis were conducted across the United States, Spain, Brazil, Canada, Iceland, and Japan. Study characteristics of included studies are reported in Table 1.

Table 1: *Characteristics of included studies in meta-analysis to determine diagnostic characteristics of OSA diagnostic tests*

Author_Year	Country	Study Population (Numbers)	Portable monitor device name and number of channels	Outcome Measure
Ayappa_2008(24)	United states	102	Ares & 4	AE, DA & TF
Danzi-Soares_2011(25)	Brazil	102	Stardust II & 4	DA
Driver_2011 (26)	Canada	80	Medibyte & 4	DA & TF
Garcia_Diaz_2007 (27)	Spain	65	Apnoescreen II& 4	AE, DA & TF
Gjevre_2011 (28)	Canada	47	Embletta & 4	AE, DA & TF
Hernandez_2007 (29)	Spain	88	Respiratory Polygraph & 4	DA
NG_2010 (30)	Hong Kong	90	Embleta & 4	DA & TF
Santos-Silva_2009 (31)	Brazil	82	Stardust II & 4	AE, DA & TF
Yin_2006 (32)	Japan	40	Stardust II & 4	DA

AE=Adverse events, DA= Diagnostic accuracy, TF = technical failures

Analysis was done for different apnea-hypopnea index (AHI) cut-offs used to measure the severity of OSA at 95% CI. Diagnostic characteristics for mild OSA (AHI>/=5 hour to <15 hour) revealed a SN of 0.89 [CI:0.86, 0.92] and SP of 0.71 [CI:0.59,0.81] (Figure 3A). For moderate OSA (AHI>/=15hour to <30hour), SN of 0.79 [CI:0.72, 0.84] and SP of 0.87 [CI:0.77, 0.94] (Figure 3B). Lastly, for severe OSA (AHI>/=30hr) 0.45 [CI:NA] (Figure 3C). All pooled analysis was done on STATA version 14, however, for the severe disease, we calculated values manually, as two studies reported false positive of zero, leading to default errors in STATA.

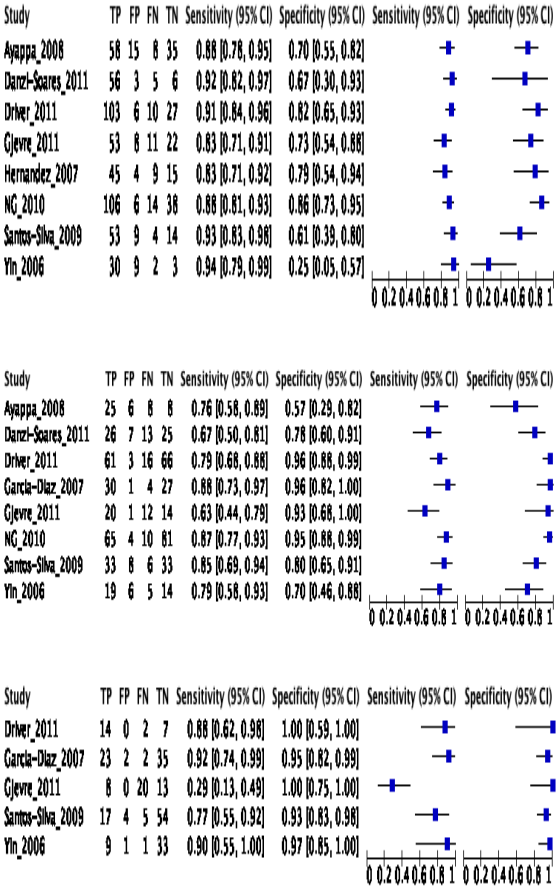

Figure 3 *(A) Forest plot for Mild- (AHI>/=5hr to <15 hr) (B) Forest plot for Moderate - (AHI>/=15hr to <30hr) (C) Forest plot for Severe (AHI>/=30hr). *AHI – apnea hypopnea index.*

Most studies showed a low risk of bias (Figure 2 & Figure 3). The majority of studies described the tests, number of patients, recruitment methods, and attrition. The "green" color showed there is "low risk" of bias in the included studies, while "yellow" means the bias in "unclear". At last, if the color reflects "red" demonstrate that the studies included have "high risk" of bias.

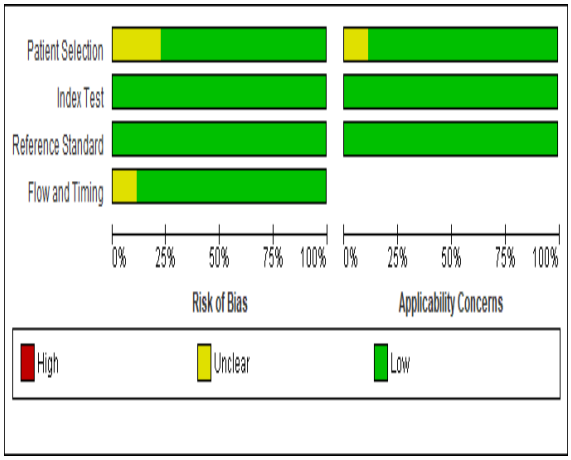

Figure 3 *Quality appraisal of included studies for the meta-analysis for diagnostic characteristics for Obstructive Sleep apnea using the QUADAS-2 tool*

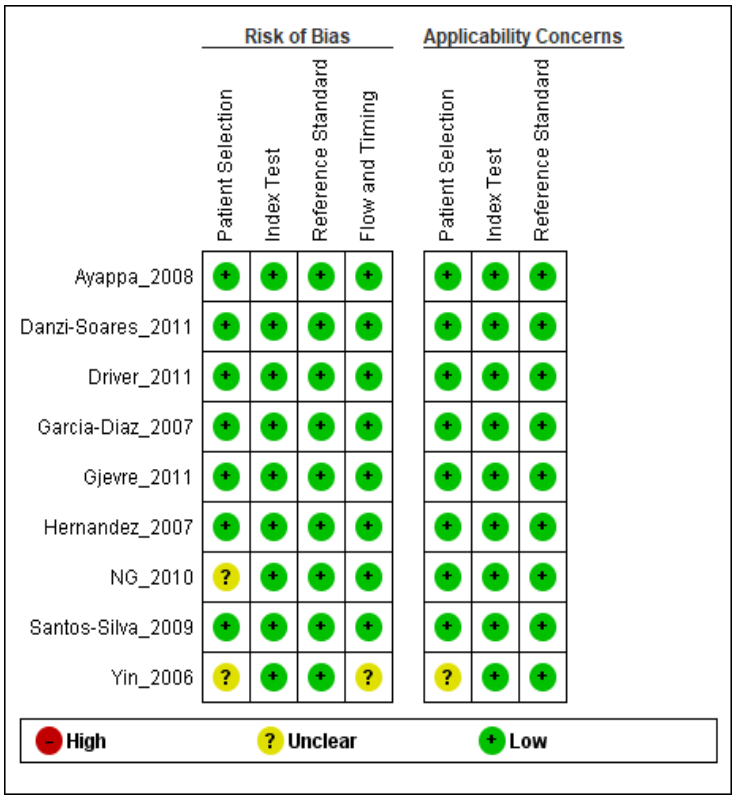

Figure 2 *Quality appraisal for individual studies included for meta-analysis*

3.2 Economic Analysis

3.2.1. Cost-Effectiveness Analysis

Cost-effectiveness analysis was carried out to calculate incremental cost per QALY gained for the model input parameters described in Table 2. We calculated incremental cost-effectiveness ratios (ICERs) for three comparators. First was no screening, second Level I polysomnography,

and third-Level III portable-device. ICER is the primary endpoint of cost-effectiveness analysis, which is defined as follows:

ICER=Incremental cost/incremental benefit

$= (Cost_{level\ III} - Cost_{no\ screening}) / (Benefit_{level\ III} - Benefit_{no\ screening})$ *(for level III versus no screening)*

$= (Cost_{level\ I} - Cost_{no\ screening}) / (Benefit_{level\ III} - Benefit_{no\ screening})$ *(for level I versus no screening)*

Table 2 *Model Inputs for cost effectiveness analysis and cost monetary benefit analysis for diagnostic tests for OSA, (costing per year, 2021).*

Description	Values			Distribution	Source
CEA inputs	Base value	Min	Max		
Decision Tree					
Prevalence	0.016	-	-		(12)
Probability of positive OSA result after level III (at home) test is a true positive (SN)	0.79	-	-	Gamma	Meta-analysis
Probability of negative OSA result after level III (at home) test is true negative (SP)	0.87	-	-	Gamma	Meta-analysis
Probability of positive OSA result after level III (at lab) test is a true positive (SN)	0.96	-	-	Gamma	Meta-analysis
Probability of negative OSA result after level III (at lab) test is true negative (SP)	0.98	-	-	Gamma	Meta-analysis
Patient getting CPAP	0.147	0.147	0.30		Expert Opinion
Probability from OSA to CVD	0.49	-	-		(24)
Probability from OSA to Diabetes	0.3	-	-		(24)

OSA into deaths	0.063	-	-		(24)
Time Horizon	1 year	-	-		Expert Opinion
Discount Rate	3%	-	-		HTAIn
Willingness to Pay	INR 96000 (USD 18,52,320)	-	-		HTAIn
Utility					
EQ 5D Utility Value for CPAP					
CPAP	0.55	-	-		
No CPAP	0.32	-	-		Calculated from Tan et al. 2008 (33)
CVD without CPAP per person	0.746	-	-		(34)
CVD without CPAP per person	0.884	-	-		(35)
Annual Cost per person					
Total cost of sleep specialist	INR 1,350 (USD 26,048.25)	INR 200 (USD 3,859)	INR 2,500 (USD 48,237.5)		Indian Market Survey & Expert opinion
Total cost of level I study (split night) per patient	INR 23,000 (USD 4,43,785)	INR 18,000 (USD 3,47,310)	INR 28,000 (USD 5,40,260)		Indian Market Survey & Expert opinion
Total cost of level III (at home) study per patient	INR 3,500 (USD 67,532.5)	INR 2,000 (USD 38,590)	INR 5,000 (USD 96,475)		Indian Market Survey & Expert opinion
CPAP Manually per patient	INR 20,000 (USD 3,85,900)	INR 15,000 (USD 289425)	INR 25,000 (USD 4,82,375)	Gamma	Indian Market Survey & Expert opinion

CPAP Automatic per patient	INR 47,500 (USD 9,16,512.5)	INR 25,000 (USD 4,82,375)	INR 70,000 (USD 13,50,650)	Gamma	Indian Market Survey & Expert opinion
CPAP Treatment	INR 1,22,640 (USD 23,66,338.8)	-	-		Indian Market Survey & Expert opinion
Diabetes Treatment	INR 55,000 (USD 10,61,225)	INR 35,000 (USD 6,75,325)	INR 75,000 (USD 14,47,125)		Expert Opinion
CVD Treatment	INR 13,99,300 (USD 2,69,99,493.5)	-	-		Expert opinion
CMB inputs					
Total population (P)	135.26 Crore	NA	NA	NA	World Bank, 2018
Total number of Community Health Center (CHC) in India (T_{CHCs})	5,396	NA	NA	NA	Health Management Information System (HMIS) Data
Time taken by device for a single test	7 hours	6 hours	8 hours	NA	Expert consultation
Apparent lifetime for a single device (LT)	7 years	6	8	NA	Expert & Biomedical consultation
Total number of tests during the life span of a device	1,848	NA	NA	NA	Calculation: T_{Test}*LT
Average Cost of level III portable device ($C_{level\ III}$)	INR 80,000 (USD 15,43,600)	INR 60,000 (USD 11,57,700)	INR 10000 (USD 1,92,950)	NA	Market Survey
Cost of level I polysomnography ($C_{level\ I}$)	INR 21.5 Lakh (USD 41,48,425)	INR 18 Lakh (USD 34,73,100)	INR 25 Lakh (USD 48,23,750)	NA	Market Survey

NA: Not Applicable

Outcome in terms of effect for this study was QALY. The average annual per-patient costs and the outcome was calculated and are shown in Table 3. For level I polysomnography compared with no screening, the incremental cost for screening and treatment to gain one

QALY was INR 4,006.15 (USD 77,298.67). However, if screening was done using Level III portable devices, the net saving would be INR 559,888.63 (USD 1,08,03,051.12) per QALY gained (Table 3). The ICER graph has also been plotted (Figure 5), which shows that without screening, then the cost of OSA treatment is higher with less gained in QALY, as compared to the ones after screening with the other two screening methods i.e., Level III and Level I. Moreover, the graph indicates that if level III is implemented as a screening tool for OSA, there would be no significant changes in QALY gained as compared to Level III polysomnography.

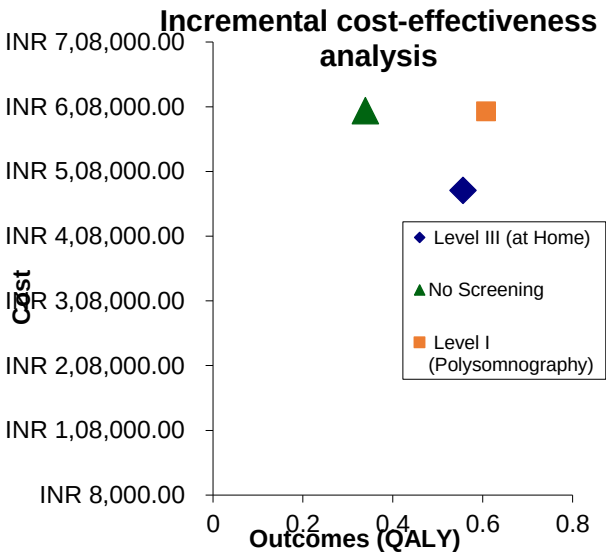

Figure 5 *Deterministic sensitivity analysis: for Cost effectiveness ratio (ICER) of diagnostic test cost vs. QALYs gained.*

Table 3 *Average annual per patient costs for level I and III diagnostic tests, and outcome measure QALY (Result for ICER):*

	Expected cost, INR (USD)	Expected outcome (QALY)	Incremental cost, ΔINR(USD)	Incremental effect (ΔQALY)	ICER, INR/QALY (USD/QALY)
No Screening	601,879.92 (1,16,13,273.06)	0.338530016		NA	
Level I (PSG)	600,804.72 (1,15,92,527.07)	0.606916371	1,075.20 (20,745.98)	0.268386356	4,006.15 (77298.95)
Level III (at Home)	478,985.14 (92,42,018.28)	0.556108264	121,819.59 (23,50,508.80)	0.217578248	-559,888.63 (1,08,03,050.48)

NA: Not applicable

Cost-effectiveness analysis demonstrates which alternative provides maximum benefit in terms of cost per QALY gained. We also performed a cost monetary benefit analysis to examine the potential cost per test if Level III gets implemented in the Community Health Center (CHC) in India. The analysis is shown in Table 4. As per the analysis, the average cost per test for a level III portable device will be approximately INR 48.70 (USD 939.67), ranging from INR 43.29 (USD 835.28) to INR 54.11 (1,044.05), whereas the average cost per test for level I will be approximately INR1,163.41(USD 22,447.99), ranging from INR 974.00 (USD 18, 793) to INR 1,352.81 (USD 26,102.47).

Table 4 *Cost per test for level III and level I.*

Parameter	Level III		Level I		Net Monetary Saving (Average INR[USD])
	Upper Range, INR (USD)	Lower Range INR (USD)	Upper Range INR (USD)	Lower Range INR (USD)	
Cost for device	80,000	1 lakh	18 lakh	25 lakh	20.7 lakh
	(15,43,600)	(1,92,950)	(34,73,100)	(48,23,750)	(39,94,065)

4. Discussion:

In a meta-analysis we identified that for severe OSA level III portable device shows poor specificity, through sensitivity to diagnose moderate OSA was 89% which is considered effective for a point of care device. Most cited inclusion criteria were the presence of suspected OSA based on patient-reported presentation/symptoms or clinical assessment. Our diagnostic accuracy findings were in line with published Indian and clinical American practice guidelines (1,4). The current INOSA guidelines also accepts the portable-device as useful, convenient, and time saving method of diagnosis (1).

For India, presently, there are no cost-effectiveness studies for Level III tests from a healthcare perspective. This study assessed the ICER for Level III comparing with Level I. Implementing portable-monitoring device in India could save approximately INR 559, 888.63 (USD 1,08,03,051.12) per QALY gained as compared to no screening and PSG. Calculations from the cost per test also demonstrated that it is evident that there will be huge substantial net monetary benefit i.e., INR 1114.71 (USD 21,508.33).

For new technologies such as Level III apart from diagnostic accuracy, its accessibility and large-scale procurement at state and central level, is yet to explore from the Indian context, along with surrounding additional resources, training capacity of the existing manpower to use the device.

Many studies do emphasize the role of awareness of the OSA among Indian population (13, 14). Frontline health workers are an important source of dissemination of OSA knowledge to the Indian population. Level III sleep studies as the first-line screening method, offers frontline workers, nurses and medical officers and opportunity to educate and helps in diagnosing rural population and mitigate the risks of OSA. A study conducted in south India showed technical adequacy of community health workers 86.4% about the need for sleep studies and how to connect the machines (11).

Currently, the availability of sleep studies at District hospital, community health center, or primary health center in most states is absent. A policy needs to be developed to implement OSA screening in India at public health center. Although physicians understand that good sleep is essential to patient health and well-being, often this issue glossed over in primary settings which is coupled with lack of manufacturing unit for these devices in India. Further, opportunistic screening with cardiovascular disease, obesity and diabetes could be performed by the clinicians.

For treatment, Level III devices scored well, for SN (the ability of a test those who have the disease correctly), SP (the ability of a test to correctly identify those who do not have the disease). Where, specificity increased, and sensitivity is decreased with increase in the disease severity. Additionally, it demonstrates cost-effectiveness as compared to PSG. Once the suspected patient is screened through a portable device, they could be referred to the district hospital for treatment. For OSA treatment the therapeutic use of Continuous Positive Airway Pressure (CPAP) or bilevel positive airway pressure (BiPAP). CPAP is the standard treatment option for OSA to manage with appropriate titration of the device.

We do acknowledge few limitations of this HTA. Meta-analysis included only English language studies, over the last decade, therefore relevant studies from other language were

excluded. Another, limitations is that we have not included split night sleep study analysis in this study due to lack of evidence and inclusion criteria have been limited to OSA disease only. Further, costing data may vary per region, and set up, and exact estimated may vary as only direct costs were included and other costs such as implementations cost, maintenance cost of such devices, training cost and capacity building costs and not considered.

5. Conclusion

This HTA study concluded that, Level III sleep studies with a high pretest probability of moderate to severe forms of condition without substantial complexities could be feasible point of care device at various centers in an Indian public health setting. However, Level I remain the standard for the diagnosis in patients having suspected with comorbid sleep apnea/disorder, or complex SDB in India. Moving forward, there is a need of real-world data and studies with longer time horizons and capture clinical effectiveness and cost data, that will eventually optimize cost effectiveness of a home base portable-monitoring device.

6. Ethical Approval:

Ethical approval was not required. Protocol was registered and published in the PROSPERO database (CRD42018110619). Available at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018110619

7. Conflict of Interest:

None

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