Health Technology Assessment in India (HTAIn)

सर्वे सन्तु निरामयाः।

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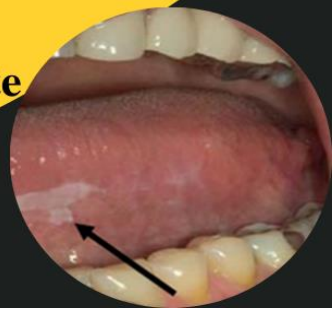
Health Technology Assessment of Strategies for Oral Cancer Screening in India 2022

Health Technology Assessment (HTA) Resource Hub
(Funded by Department of Health Research, Ministry of Health & Family Welfare, Government of India)
Department of Public Health
Kalyan Singh Super Specialty Cancer Institute
Lucknow, Uttar Pradesh (India)



Health Technology Assessment of Strategies for Oral Cancer Screening in India

2022

Supervised by:

Dr. Ayush Lohiya

Dr. Manish Kumar Singh

Compiled by:

Dr. Dahy Sulaiman

Dr. Pooja Dwivedi

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(Funded by Department of Health Research, Ministry of Health & Family Welfare, Government of India)

Department of Public Health
Kalyan Singh Super Specialty Cancer Institute
Lucknow, Uttar Pradesh (India)

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List of Abbreviations

ANM	Auxiliary Nurse Midwives
ASHA	Accredited Social Health Activists
ASR	Age-Standardized Rate
AWW	Anganwadi worker
BHW	Basic health worker
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CHC	Community Health Centre
CI	Confidence Interval
CLI	Chemiluminescent Illumination
COE	Conventional Oral Examination
DSA	Deterministic Sensitivity Analysis
FHW	Frontline Health Worker
GATS	Global Adult Tobacco Survey
GDP	Gross Domestic Product
GLOBOCAN	The Global Cancer Observatory: CANCER TODAY
HR	High Risk
HTA	Health Technology Assessment
IARC	International Agency for Research on Cancer
ICER	Incremental Cost-Effectiveness Ratio
INR	Indian Rupee
LBD	Light based detection
MHW	Male Health Worker
MSE	Mouth Self Examination
NFHS	National Family and Health Survey
NCD	Non-communicable diseases
NHM	National Health Mission
NMB	Net Monetary Benefit
NPCDCS	National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke
NSS	National Sample Survey

OC	Oral Cytology
OOPE	Out of Pocket Expenditure
OPD	Outpatient Department
OPMD	Oral potentially malignant disorder
OSCC	Oral Squamous Cell Carcinoma
PBCR	Population-Based Cancer Registries
PHC	Primary Health Centre
PMD	Potentially malignant disorder
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-adjusted life years
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies 2
RCT	Randomized Control Trial
SROC	Summary Receiver Operating Characteristic
TBS	Toluidine Blue Staining
TNM	Tumour Node Metastasis
UPHC	Urban Primary Health Centre
USD	United States dollars
VEOS	Visual Examination by Oral Surgeons
VETDN	Visual Examination by trained dental nurses
WHO	World Health Organization
WTP	Willingness to pay

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Executive Summary

The burden of oral cancer is highest in the WHO South-East Asia region. India ranks fourth in oral cancer burden among the population older than 30 years, both in incidence (21.3) and mortality (11.8). Two-thirds of the new cancers in India are diagnosed at an advanced stage. Oral cancer in advanced stages has poor survival. The reported five-year survival of oral cancer patients in India is around 50%, much lower than in most developed countries. Early detection and evaluation of oral precancers facilitate diagnosing oral cancers early, thereby reducing the oral cancer burden. The WHO recommended various non-invasive techniques for oral screening, are conventional oral examination (COE), toluidine blue staining (TBS), oral cytology (OC), light-based detection (LBD) screening devices like immune fluorescence, & chemiluminescent illumination (CLI), and blood & saliva analysis. Health technology assessment (HTA) aims to facilitate the process of transparent and evidence-informed decision-making in the field of health. This HTA study aimed to compare the clinical and cost-effectiveness of various commonly used oral cancer screening techniques in the Indian context.

The clinical effectiveness study was conducted to assess the diagnostic accuracy of screening modalities (COE, TBS, OC, and CLI) by frontline health workers (FHW) for detecting premalignant lesions and oral cancer in apparently healthy individuals. A comprehensive search strategy was used to retrieve articles from PubMed, Scopus, Embase, Cochrane Library, and Google Scholar databases. The criteria for inclusion were: (1) population- apparently healthy individuals being screened for cancer or potentially malignant disorder (PMD) of the lip and oral cavity (2) intervention- screening by FHW with COE, TBS, OC, and CLI (3) comparator- evaluation by specialist/histopathological examination (4) outcome- sensitivity & specificity. The methodological quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool for the quality assessment of diagnostic accuracy studies. The pooled results were estimated using MetaDTA version 1.27. Subgroup analysis was performed to address the heterogeneity based on the prevalence of the disease and study location. The review identified no studies fitting the inclusion criteria for TBS, OC, and CLI. For COE, five articles were included in the review, where FHW conducted screening among apparently healthy individuals in a community setting. Included studies were conducted in South-East Asia, two in Kerala, India, and three in Sri Lanka. Diagnostic accuracy was estimated from these five studies with a total of 10,069 participants above the age of 20. Pooled sensitivity of oral screening by COE performed by an FHW on apparently healthy

individuals was 88.8% (95% CI: 71.6-96.1), whereas pooled specificity was 91.9% (95% CI: 78.3-97.3).

The cost-effectiveness study compared the oral cancer screening techniques COE, TBS, OC, and LBD at three, five, and ten years intervals of periodic screening check-ups versus no-screening. It was a model-based cost-effectiveness analysis for estimating the lifetime costs and health outcomes in a hypothetical cohort of one lakh men and women above 30 years of age using the societal perspective in India. The estimation was done for both the screened and unscreened groups. Two probabilistic Markov models were developed with a 1-year cycle length which runs for 70 cycles. Model A adopted a mass screening strategy versus no screening, whereas Model B adopted a high-risk screening strategy versus no screening. Model parameters included incidence of precancer, the stage-wise prevalence of oral cancer, annual probabilities of progression/regression, the proportion of individuals showing symptoms, sensitivity and specificity of screening strategies, age-specific all-cause mortality, probability of oral cancer deaths, and health utility values. For the no-screening group, the cohort followed the natural history of the progression of the disease and was diagnosed and treated based on their health-seeking behaviour. The costs included screening costs, treatment costs, and diagnosis costs. A combination of top-down and bottom-up costing approaches was undertaken using data from already published literature to estimate the cost of each screening test and stage-wise treatment of oral cancer. To assess the uncertainty in model parameter values, probabilistic sensitivity analysis (PSA) was undertaken. The following outcomes were measured: QALYs gained, ICER and deaths averted. Threshold analysis was done to assess the effect of the screening coverage level. A 3% discount rate was used for future costs and consequences.

The no-screening arm had the maximum number of new cases (5,673.59 cases). When comparing mass and high-risk (HR) screening strategies, mass screening with LBD three years had the least incident cases (3,271.68 cases). The no-screening arm had the maximum number of oral cancer deaths (1,180.45 deaths). Mass screening at three years intervals averted the maximum number of deaths. Among them, OC and LBD (459.76 deaths averted) averted the higher number of oral cancer deaths, followed by COE (451.69 deaths averted) and TBS (431.30 deaths averted). The no-screening arm incurred a lifetime cost of 21,34,93,287.27 INR. Among mass-screening and HR screening strategies, HR screening incurred less cost across all comparisons; thus, it was a cost-saving approach. The cost of screening was highest for OC three years (32,84,47,216.49 INR) and the least for COE ten years HR (1,39,87,824.13 INR)

among all the strategies. Likewise, the cost of treatment was highest for LBD five years (31,57,86,039.84 INR) and the least for COE ten years HR (16,79,44,813.34 INR) when compared to all strategies. Mass screening at an interval of three years with OC and LBD yielded maximum incremental QALYs (6,679.29), followed by COE (6,560.48) and TBS (6,258.09).

Amongst the screening strategies, the HR scenario was cost-effective compared to the mass-screening strategy. When compared against the current willingness-to-pay (WTP), all the HR strategy scenarios were cost-effective compared to mass screening. The HR screening strategies COE at five and ten years' intervals; TBS and LBD at ten years' intervals dominated the no-screening arm. Among various screening strategies, COE in high-risk individuals at ten years was the most cost saving approach.

The threshold analysis demonstrated that when the screening coverage was below five per cent, high-risk strategies COE five and ten years, TBS, and LBD ten years were cost-saving. The sensitivity analysis revealed that at the WTP of INR 1,50,000, the high-risk screening strategies COE ten years, TBS ten years, COE five years, and LBD ten years had a 90% or higher probability of being cost-effective. The budget impact analysis showed that oral screening using COE for the high-risk population at a ten-year interval would cost 2,572 crores, which is only 0.03% of India's annual healthcare budget of 86,200.65 crores for the year (2022-2023).

Recommendations of the study:

- Conventional oral examination by trained frontline health workers had high sensitivity and specificity for oral screening. The prevalence of oral cancer, PMD and the study site did not affect the high sensitivity and specificity. COE after training FHW could be considered for screening oral cancer and potentially malignant disorders, especially in low-middle income countries.
- The screening was better than the no-screening approach in terms of reducing the oral cancer burden and cost-effectiveness in the Indian context. The high-risk approach was more cost-effective than the mass and high-risk screening strategies. It will lead to a decrease in the requirement of resources for treating and managing oral cancer and the associated economic burden. The high-risk screening using COE at ten years was the most cost-saving strategy among all the screening strategies. Hence, high-risk screening using COE at ten years should be considered for oral cancer screening in a resource-constrained country like India.

Chapter 1 Introduction

1.1 Background

Oral cancer is malignant neoplasia on the lip or oral cavity (1). It has different levels of differentiation and a propensity for lymph node metastasis (2). About 96% of all oral cancers are carcinomas, and the remaining 4% are sarcomas (2). It is also estimated that nine of every ten oral malignancies are squamous cell carcinomas (2). It is a disease of increasing age, with 95% of the patients older than 40 (2). The clinical staging of oral cancer given in the World Health Organization (WHO) Classification of Tumours (2) is given below:

TNM (Tumour Node Metastasis) staging of oral cancer:

T- Primary tumour

TX	Primary tumours cannot be assessed
T0	No evidence of a primary tumour
Tis	Carcinoma in situ
T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but not more than 4 cm in the greatest dimension
T3	Tumour more than 4 cm in greatest dimension
T4a (lip)	Tumour invades through cortical bone, inferior alveolar nerve, the floor of mouth, or skin (chin or nose)
T4a (oral cavity)	Tumour invades through cortical bone, into deep/extrinsic muscle of the tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of the face
T4b (lip and oral cavity)	Tumour invades masticator space, pterygoid plates, or skull base; or encases internal carotid artery

N - Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in the greatest dimension
N2	Metastasis as specified in N2a, 2b, 2c below
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in the greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in the greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in the greatest dimension

M -Distant Metastasis

M0	No distant metastasis
M1	Distant metastasis

Stage grouping of oral cancers:

Stage0	Tis N0 M0
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T1, T2 N1 M0 OR T3 N0, N1 M0
Stage IVA	T1, T2, T3 N2 M0
Stage IVB	T4a N0, N1, N2
Stage IVC	Any T Any N M1

1.2 Disease burden

Globally the number of new cases of lip and oral cavity cancer is estimated to be 377,713, with an age-standardised rate (ASR) incidence of 4.1 in 2020 (3). In the same year, deaths due to lip and oral cavity cancer were 177, 757 with an ASR mortality of 1.9 (3). The burden of oral cancer is highest in the WHO South-East Asia region, with an ASR incidence and mortality of 8.0 and 4.5, respectively (3).

In terms of incidence and mortality, oral cancer is the second and third most cancer in India (3). It is also estimated that in India, there are 2 to 2.5 million oral cancer patients at any given time, with about 0.7% million new cases diagnosed yearly and nearly half dying yearly (4). Two-thirds of the new cancers are diagnosed at an advanced stage (4). More than 60% of these affected patients are in the age group between 35 and 65 years of age (4).

1.3 Risk factors of oral cancer

The main risk factors for developing oral cancer are tobacco in its different available forms and alcohol use (1, 5, and 6). Tobacco use, including smokeless tobacco and betel quid chewing, excessive alcohol use, poor oral hygiene, and long-term viral infections, including the human papillomavirus, are all risk factors for oral cancer (7, 5, and 6).

Tobacco

Tobacco accounts for nearly 1.35 million deaths in India yearly (8). India is the second-largest consumer and producer of tobacco (8). A variety of tobacco products are available at very minimal prices in the country (8). According to the Global Adult Tobacco Survey India (GATS) 2016-17, almost 267 million adults in India (29% of all adults) are users of tobacco (8). The most common tobacco use in India is smokeless tobacco products like khaini, gutkha, betel quid with tobacco, and zarda (8). Almost 13% chew tobacco in the form of paan (betel leaf, areca nut, tobacco, slaked lime, and flavouring agents) or gutkha (4). Close to 15% are addicted to chewing and smoking habits (4). Only about 1-3% use tobacco in the form of snuff (4). Smoking forms of tobacco used are beedi, cigarette, and hookah (8). It is estimated that 80-85% of tobacco is consumed for smoking, either as beedis or cigarettes (4). Previous literature indicates that cigarette smoking is associated with a 1·9–3·6 times increase in the risk of oral cancer and that chewing tobacco is associated with a relative risk of 4·7–12·8 (9-12). It leads to disease and related economic burdens, like social and economic costs (8). The total economic costs contributed by tobacco use from all diseases in India in 2017-18 for persons aged 35 years and above amounted to INR 177,341 crore (USD 27.5 billion) (8).

Alcohol

Alcohol is a risk factor along with tobacco for oral cancer (1, 4, 6, and 7). It is estimated that the average consumption of above 30 ml of alcohol per day increases the risk of oral cancer linearly with the quantity of alcohol consumed (4). The International Agency for Research on Cancer (IARC) monograph on alcohol as a risk factor lists various ways it predisposes to oral cancer (13). Alcohol has a high calorific value, because of which appetite in heavy drinkers is reduced. (13). Ethyl alcohol also increases the permeability of oral mucosa (13). It has a solvent action on the keratinocyte membrane, thereby allowing the passage of carcinogens into proliferating cells where they may exert a mutagenic action (13). It leads to nutritional deficiency, which in turn is a risk factor for oral cancers (13). Compared with non-users, alcohol users are 3.6 times more likely, tobacco users are 5.8 times more likely, and users of both alcohol and tobacco are 19 times more likely to have oral cancer (4).

1.4 Survival of oral cancer patients in India

In India, the reported five-year survival of oral cancer patients is around 50%, much lower than in most developed countries. According to a retrospective study by Thavarool et al. in Kerala, India, they wanted to see improved survival among oral cancer patients undergoing surgery between June 2009 to June 2013. In the study, two hundred and twenty patients were included and analysed (136 males). The majority (51.1%) had tongue cancer, of which 75 patients (34.1%) had T4 tumours. The median disease-free survival duration was 48.2 months. Five-year survival in stage I patients was 86.5%; in stage II patients was 72.0%; in stage III patients was 62.0%; and in stage IV, it was 60.0%. Thus, overall survival and disease-free survival are better in patients with early stages of cancer than those with node involvement and advanced stages (14).

Another study was done by Lohia et al. in a tertiary cancer care hospital in northern India to see survival trends in oral cavity cancer patients treated with surgery and adjuvant radiotherapy (15). The study included patients with oral cavity cancers treated with surgery and received adjuvant radiotherapy between November 2012 and November 2016. A total of 167 patients with oral cavity cancer were treated during the study period, out of which 112 were included. The age of the included patients varied from 31 to 90 years. The most common age group was 51–70 years (70%), followed distantly by those ≤50 years (18%) and ≥70 years (13%) (14). The most common sites encountered were the tongue (39%) and buccal mucosa (34%). They reported five-year survival for stage I at 100.0%, stage II at 85%, stage III at 43%, and stage IV at 42% (15). They stated that the lack of follow-up for most patients not only leads to late

detection of recurrences but is also the reason for the lack of actual survival and treatment data from our country (15). Their study showed that establishing regular follow-up and careful maintenance of records could help recognise the treatment's impact on patient survival (15).

Thus, from previously published literature on the survival of oral cancer patients in India, it can be concluded that oral cancer in advanced stages has poor survival compared to early stages making an early diagnosis the need of the hour. Early detection and evaluation of oral precancers will be useful in preventing invasive oral cancer before regional node metastasis. It will help reduce the high burden related to oral cancer.

1.5 Prevention

Primordial prevention of oral cancer can come from measures aimed at reducing the need to produce and consume tobacco products and alcohol. Our country needs to take adequate measures to curb the underlying threat and mitigate the economic burden caused by these risk factors. Early detection and treatment of precancerous lesions reduce cancer-specific morbidity and mortality (16). Therefore, screening has a role to play in the prevention and control of oral cancer.

1.5.1 Screening of oral cancer in India

For the prevention and control of the rising burden of non-communicable diseases (NCD) in India, the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular diseases & Stroke (NPCDCS) was launched in 2010 by the Government of India under the National Health Mission (NHM) with a focus on strengthening infrastructure, human resource development, health promotion, early diagnosis, management, and referral (17,18). One of the objectives of this program includes opportunistic screening at all levels in the health care delivery system from sub-centre and above for early detection of common NCDs, including oral cancer (17,18). The existing infrastructure and workforce envisaged can be utilised for the early detection of cases, diagnosis, treatment, training, and monitoring of the program (17,18). Population above 30 years and above is to be screened under this initiative for oral cancer through opportunistic and/or camp approaches at various levels of health facilities and in urban slums of large cities (17, 18). According to this program, auxiliary nurse midwives (ANM) must be trained to screen at the sub-centre level (17, 18). The screening conducted by NCD nurses, ANMs, or Male Health Workers (MHW) by oral visual examination is recommended every five-year (17,18). The suspected cases from the screening are to be referred to the district hospital and tertiary cancer care facilities (17,18).

1.5.2 Screening modalities

Evidence suggests early detection is crucial in reducing mortality in oral cancer patients (19). In the case of oral cancer, screening plays a pivotal role in the early examination of the occurrence of the disease. Numerous techniques, such as physical and histopathological examination, staining, biopsy, spectroscopic and radiological techniques, are routinely used to detect oral cancer. WHO recommends various strategies for screening and diagnosing oral cancer (20). Various non-invasive commonly used techniques for oral cancer screening are conventional oral examination (COE), Toluidine Blue Staining (TBS), Oral cytology (OC), Light-based screening devices like immune fluorescence, and chemiluminescent illumination (CLI), and Blood and saliva analysis.

Conventional Oral Examination

Visual examination of the oral cavity is carried out in adequate lighting to look for any abnormality (premalignant lesion or oral cancer) by trained personnel (20, 21, 22).

Toluidine Blue Staining

It is a vital staining test used to identify premalignant lesions. The test is performed by applying the toluidine blue dye on the suspected area and identifying the precancerous area that gets stained. Toluidine blue dye is a basic thiazine metachromatic dye with a high affinity for acidic tissue components, thereby staining tissues rich in DNA and RNA. It has found wide applications both as vital staining in living tissues and as a special stain owing to its metachromatic property (20, 22, 23).

Oral cytology

It is an exfoliative cytological technique. This screening test involves scraping off the superficial (epithelial) surface from the suspected area of the oral cavity for microscopic examination. It is a simple, non-invasive technique with good acceptability (20, 24).

Light-based detection

Newer diagnostic tools such as Velscope and ViziLite plus, Raman spectroscopy, and high-performance laser spectroscopy-laser-induced fluorescence also play a significant role in the early diagnosing of oral malignancies (4). The Velscope is based on the direct visualisation of tissue luminescence and the changes that occur when abnormal cells are present (4). The Velscope emits safe light into the oral cavity, which allows differentiating between normal and abnormal tissue (4). ViziLite Plus is another popular screening tool for the detection of oral cancers. It is a chemiluminescent illumination device. This technique uses chemiluminescent

light to visualise the oral cavity after rinsing the mouth with 1% acetic acid (20, 23). It highlights dysplastic white lesions as aceto-white regions (20, 25). As ViziLite Plus is passed over oral tissue treated with rinse solution, normal healthy tissue will absorb the light and appear dark, and abnormal tissues will appear white (4).

Blood and saliva analysis

Blood and saliva analysis are novel technologies at an early stage of development and evaluation (20). The saliva and blood tests are minimally invasive techniques. In these tests, blood or saliva samples are analysed and tested for biomarkers of premalignant disorders and oral cancer (21).

1.6 Health Technology Assessment

Health technology assessment (HTA) is a multidisciplinary process that uses systematic and explicit methods to evaluate the properties and effects of health technology (26). It aims at decision-making to promote an equitable, efficient, and high-quality health system which is the need of the hour. HTA is also used to identify gaps in previously existing technologies and generate suggestions for innovative technology development. It provides scope for innovation in the field of healthcare. HTA strives to answer critical issues about the deployment, need, and operation of new technology in the healthcare field (26, 27).

1.7 Rationale for conducting HTA for oral cancer screening techniques

In terms of incidence and mortality, oral cancer is the second and third most cancer in India (3). Most patients with oral cancer present at an advanced stage, requiring costly and aggressive combined modality treatment (28). The late diagnosis and treatment in advanced stages increase the burden on the individual and the government resources available for healthcare expenditure, i.e. it increases the economic burden associated with oral cancer. To combat the burden and improve the prognosis and quality of life of affected patients, there is a need to incorporate preventive measures for oral cancer. Screening helps identify oral cancers earlier and reduces oral cancer mortality (17, 18, and 29). Implementing aids such as decision trees and algorithms is crucial for evaluating the performance of screening modalities (29). Therefore, there is a need to measure the effect of commonly used screening modalities in terms of their clinical effectiveness and cost-effectiveness to generate evidence for the policy decision (29). Thus, this HTA study was undertaken to generate evidence and aid in policy decisions.

1.8 Aim

This health technology assessment study compares the clinical and cost-effectiveness of various commonly used oral cancer screening techniques.

1.9 Objectives

Primary objectives

1. To assess the diagnostic accuracy of commonly used screening modalities for oral cancer, i.e. conventional oral examination, toluidine blue staining, oral cytology, and chemiluminescent illumination.
2. To evaluate the cost-effectiveness of commonly used screening modalities, i.e. conventional oral examination, toluidine blue staining, oral cytology, and light-based detection for oral cancer screening.

Secondary objectives

1. To determine the most appropriate strategy between mass screening and high-risk strategy.
2. To determine the most cost-effective interval (out of three, five, and ten years) between periodic screening check-ups.

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Chapter 2 Clinical Effectiveness Review

2.1 Background

The previous chapter concluded that screening facilitates the identification of precancerous lesions, early changes of malignant transformation, and oral neoplasia in pre-invasive or early preclinical invasive stages. This chapter details the diagnostic accuracy of commonly used screening strategies for oral cancer screening.

Most countries with a high burden of oral cancer are from the developing world. Developing countries have a scarcity of trained healthcare professionals (1, 2). This scarcity is even more evident in rural areas (1, 2). According to the report titled 'The health workforce in India' by World Health Organization (WHO), the ratio of urban to rural density of dental professionals was 9.9. In other words, there is a ten times difference in dentists per person in urban compared to rural areas (1). The same report states that India has an exceedingly low density of dentists at 2.4 per lakh population (1). It indicates the substantial number of unserved national populations for oral health and cancer screening (1).

Frontline health workers (FHW) are those who directly provide non-specialised basic health services at the community level, which include Accredited Social Health Activists (ASHA), Auxiliary nurse midwives (ANM), multipurpose health workers (Male/Female), Anganwadi workers (AWW) (3-6). Guidelines by the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular diseases & Stroke (NPCDCS) recommend the training and utilisation of existing health care providers at various health system levels, like FHWs, for the screening of oral cancer (3-6).

The oral cancer screening strategies (and sample collection in case of OC) can be performed by an FHW (4, 7, 8). Hence, it is vital to assess the performance of these tests in terms of diagnostic accuracy.

2.2 Review of Literature

Studies have been conducted in multiple settings to understand the diagnostic accuracy of commonly used oral screening techniques Table 2.1.

Macey and colleagues (2015) conducted a meta-analysis to estimate the diagnostic accuracy of index tests for vital staining (14 studies), oral cytology (12 studies), light-based detection (11 studies) for the detection of oral cancer and potentially malignant disorders of the lip and oral cavity, in patients presenting with clinically evident lesions (9). The tests from the included

studies were conducted in secondary healthcare settings and by experienced specialists (9). Pooled sensitivity for vital staining, oral cytology, and light-based detection was 84%, 91%, and 91%, respectively (9). Pooled specificity for these tests was 70%, 91%, and 58%, respectively (9).

Another review by Walsh and colleagues (2013) evaluated the diagnostic accuracy of COE in apparently healthy adults in the early detection of potentially malignant disorders or cancer of the lip and oral cavity (10). However, the authors included studies irrespective of the person (medical healthcare professional/ FHW) performing screening (10). In that review, they have not pooled estimates due to the study's diversity and the participants' characteristics (10). Sensitivity from the included eight studies ranged from 50%-99% with a uniform specificity of 98% (10).

Another review by Downer et al. (2004) studied the diagnostic accuracy of modalities used for screening oral cancer and precancer in primary care. The review included eight studies; the pooled sensitivity was 84.8%, and the pooled specificity was 96.5% (11). The sensitivity values of the included studies ranged from 60.0% to 97.0%, and specificity values were at least 94.0%, except for the two Sri Lankan studies where screening returned false-positive rates of 25 and 19% (11). The review included studies irrespective of the person performing the screening.

Another review by Moles et al. (2002) yielded sensitivity and specificity of the systematic visual examination of the oral mucosa from seven studies (12). Their sensitivity values ranged from 60.0% to 95.0%, and specificity values were at least 94.0%, apart from the Sri Lankan study (included in the current study), which had a false-positive rate of 19% (12). The pooled sensitivity reported in this study was 79.6%, and pooled specificity was 97.7% (12).

Table 2. 1 Existing systematic reviews and meta-analyses on the diagnostic accuracy of oral cancer screening tests

Sl. No.	Author and Year	Studies category by test	Test conducted by	Population	No. of studies	Results
1	Macey et al. 2015	Vital staining	Doctors/Non-doctors	Patient	14	Pooled sensitivity- 84.0% Pooled specificity- 70.0%
		Cytology	Doctors/Non-doctors	Patient	12	Pooled sensitivity- 91.0% Pooled specificity- 91.0%
		Light-based detection	Doctors/Non-doctors	Patient	11	Pooled sensitivity- 91.0% Pooled specificity- 58.0%
2	Walsh et al. 2013	Conventional Oral Examination	Doctors/Non-doctors	Healthy individuals	8	Sensitivity Ranges- 50.0-99.0% Uniform specificity- 98.0%
3	Downer et al. 2004	Test performance in the clinical screening of apparently healthy individual	Doctors/Non-doctors	Healthy individuals	8	Pooled sensitivity- 84.8% Pooled specificity- 96.5%
4	Moles et al. 2002	Visual inspection of oral mucosa screening	Doctors/Non-doctors	Healthy individuals	7	Pooled sensitivity- 79.6% Pooled specificity- 97.7%

2.2.1 Research Gap

Available evidence suggests that FHW can perform screening for oral cancer. None of the existing systematic reviews and meta-analyses for oral cancer diagnostic test accuracy has pooled the studies where FHW conducted the screening. By identifying this gap, we conducted this study to assess the diagnostic accuracy of commonly used screening modalities for oral cancer, i.e., COE, TBS, OC, and CLI screened by FHW in apparently healthy individuals. This study will provide evidence for policymakers to draw upon national or regional guidelines to suggest an appropriate strategy for oral screening.

2.3 Aim

To assess the diagnostic accuracy of commonly used screening modalities for oral cancer, i.e., conventional oral examination, toluidine blue staining, oral cytology, and chemiluminescent illumination.

2.4 Objective

1. To assess the clinical effectiveness and diagnostic accuracy of oral cancer screening modalities.

2.5 Methodology

2.5.1 Data Sources and Searches

The search strategy was in three steps in the review. The initial search was through PubMed, where terms such as "oral cancer", "premalignant disorders", "screening", and "diagnostic accuracy" were used through Boolean operators like AND, OR, NOT for the retrieval of the initial few articles. This search was followed by exploring the controlled vocabulary and text words contained in the titles and abstracts. Furthermore, articles describing index terms were assessed. A subsequent search using all identified keywords and index terms was then carried on to PubMed, Scopus, Embase, Cochrane Library, and Google Scholar. Additionally, the reference list of all identified papers, reports, and articles was explored for bibliographic search. Studies published till December 2020 fitting the inclusion criteria were included in the review. The detailed search strategy for all databases is given in Annexure I Table 1-6).

2.5.2 Study selection

Search results from electronic databases and other sources were exported to the Rayyan web for systematic review (13). Removal of duplicates, screening, and selection of eligible studies

was performed by two reviewers using Rayyan web. The third reviewer resolved any disagreements about selection.

2.5.3 Inclusion criteria

The following inclusion criteria were used in including articles for review.

- Population

  Apparently healthy individuals are being screened for cancer or potentially malignant disorder (PMD) of the lip and oral cavity.

- Intervention

  Screening by FHW with any of these commonly used techniques as a part of mass screening.

  a. Conventional oral examination
  b. Toluidine blue staining
  c. Oral cytology
  d. Chemiluminescent illumination

- Comparator

  Evaluation by specialist/histopathological examination (gold standard test).

- Outcome

  Diagnostic accuracy for detecting cancers and PMDs of the oral cavity and lip by estimating:

  a. Sensitivity
  b. Specificity

Studies conducted among the patient population with oral cancer or PMD; studies where screening tests were conducted by dentists, doctors, or specialists; Conference proceedings, reviews, and case studies were excluded from the review.

2.5.4 Study design

Any observational and experimental study fitting the inclusion criteria was considered for the review.

2.5.5 Study quality assessment

The methodological quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool for quality assessment of diagnostic accuracy studies (14). Studies were rated high, unclear, and low according to the four key

domains, patient selection, index test, reference standard, and flow and timing of participants through the study. Each domain was assessed in terms of its risk of bias and applicability.

2.5.6 Data extraction

Two reviewers independently extracted data from studies included in the review. Disagreements were resolved through discussion within the review team. Details of publication, socio-demographic characteristics of the population, details of index tests, comparator, the disease being studied, and outcome estimates were extracted. Each study's diagnostic data, such as true positive, true negative, false positive, and false negative values, were entered into RevMan software (Review Manager, version 5.4.1; Nordic Cochrane Center, Copenhagen, Denmark) (15).

2.5.7 Statistical analysis

Summary estimates of sensitivity, specificity, PPV, and NPV were estimated with 95% confidence intervals. Forest plots were used to graphically display the point estimate and sensitivity and specificity confidence intervals. The summary receiver operating characteristic (SROC) curve was also plotted for the joint distribution. The pooled results were estimated using MetaDTA version 1.27 (16).

2.5.8 Subgroup analysis

To address the heterogeneity, subgroup analysis was performed based on the prevalence of the disease and study location.

2.4.9 Ethical statement and protocol registration

Ethical approval was not required because the data had been retrieved from already published studies.

2.4.10 Protocol registration

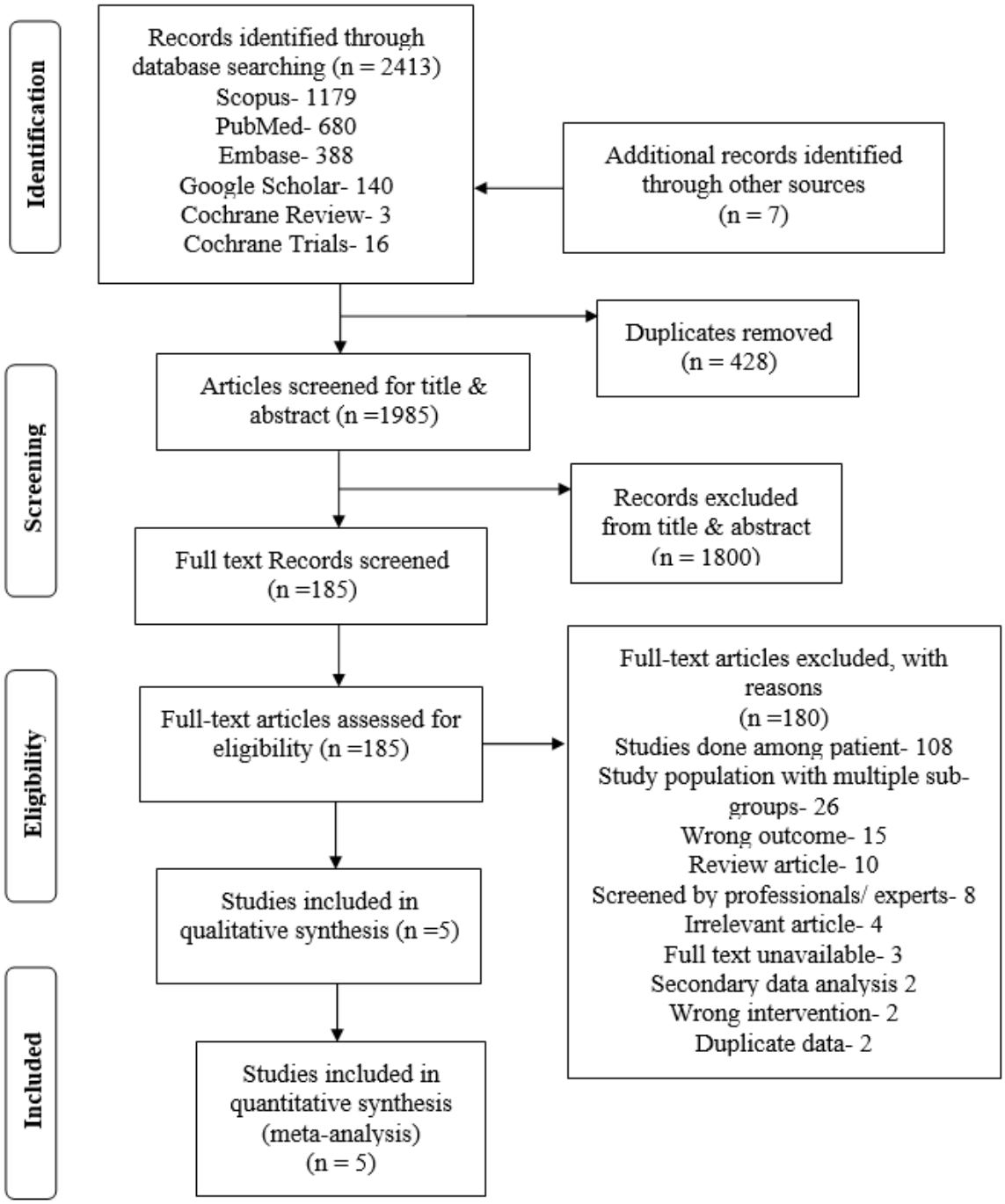
The protocol of this review was registered in the National Institute for Health Research PROSPERO, International Prospective Register of Systematic Reviews (Registration ID CRD42021267620)

2.6 Results

2.6.1 Search results and excluded studies

A total of 2,413 potentially relevant articles were identified for review from the electronic search (PubMed, Scopus, Embase, Cochrane Library, Google Scholar, and searching on relevant journals) (Figure 2.1). After the removal of 428 duplicates, 1,985 articles were eligible for the title and abstract screening. After screening the titles and abstracts, 1,800 articles were removed. Finally, full texts were assessed to assess the eligibility of the remaining 185 articles. Of these, 180 articles were excluded for various reasons. The most common reason (60%) for excluding full-text articles was that the study population in 108 articles was patients seeking healthcare (Annexure I Table 7). The study population with multiple sub-groups (normal, precancer, and cancer), which does not fit the inclusion criteria, was the second most common reason for excluding 26 articles. Other reasons for exclusions were outcomes not fitting the inclusion criteria (n=15), review articles (n=10), screening done by professionals or experts (n=8), and studies unrelated to the objective of the study (n=4) (Annexure I Table 8). A total of five articles meeting the inclusion criteria were finally included in the review for qualitative and quantitative analysis.

Figure 2. 1 PRISMA Flow diagram for selection of studies



2.6.2 Characteristics of included studies

Five articles included in the review were about COE, where FHW conducted screening among apparently healthy individuals in a community setting. No studies were identified fitting the inclusion criteria for TBS, OC, and CLI. All the included studies were conducted in South-East Asia, two in Kerala, India, and three in Sri Lanka. Indian studies included populations above 35 years of age, whereas Sri Lankan studies included adults aged more than 20 years. The prevalence of oral cancer and PMD in the included studies ranged between 1.4 and 50.9%. The sample size of the included studies ranged from 685 to 3,543. The sensitivity and specificity of COE in the included studies ranged from 59% to 97% and 75% to 98%, respectively (Table No 2.2).

The study by Mehta et al. (1986) was conducted in the Ernakulam district of Kerala to determine the feasibility of using basic health workers (BHW) to detect oral cancer during routine house visits. They included people aged 35 years and above with tobacco habits. After the oral examination by BHW, individuals with referable lesions were advised to visit Oral Cancer Detection Center, where dentists conducted a re-examination. A sample size of 1,921 was included in the analysis, and the prevalence of oral cancer and PMD in the study population was 1.4%. The reported sensitivity and specificity from the study were 59% (95 CI: 39-78) and 98% (95% CI: 97-99), respectively.

The study by Warnakulasuriya et al. (1990) was conducted in Kadugannawa, Sri Lanka, to analyse the categories of false positives referred to and the false negatives detected for oral cancer and precancer following screening by Primary Health Care (PHC) workers. Examination of the oral cavity by PHC workers was followed by re-examination by dentists at the referral centre. The study included 1,872 subjects in the age group of 20-59 years. The prevalence of oral cancer and precancer in the study population was 21.6%. The study reported sensitivity and specificity as 95% (95 CI: 92-97) and 81% (95% CI: 79-83), respectively.

The study by Warnakulasuriya et al. (1991) was conducted in Galle, Sri Lanka, to assess the reproducibility of the PHC model, where PHC workers were utilised for the early detection of oral cancer and precancer. PHC workers examined the oral cavity of the participants. Those with relevant oral lesions were instructed to attend the referral centre, where dental surgeons re-examined them. A total of 3,543 participants aged over 20 years and above were included in the study. The study population had a prevalence of 50.9% for oral cancer and precancer. The reported sensitivity and specificity were 97% (95 CI: 96-98) and 75% (95% CI: 73-77), respectively.

The study by Mathew et al. (1997) was a part of a community-based randomised intervention trial conducted in the coastal region of the Trivandrum district of Kerala. The study aimed to evaluate a model of oral cancer screening in which the screening test, oral visual inspection, is administered by trained health workers (HWs). They included 2,069 participants in the age group of 35-64 years from the seven intervention panchayats included in the trial. Screening by HWs was immediately followed by the examination by physicians who were considered the reference standard. The prevalence of oral cancer and PMD in the study population was 10.3%. The study estimated the sensitivity and specificity of COE screening by FHW as 94% (95% CI: 90-97) and 98% (95% CI: 98-99), respectively.

The study by Amarasinghe et al. (2016) was conducted in Sabaragamuwa, Sri Lanka, to reassess the validity and reliability of screening by PHC staff for the detection of oral potentially malignant disorders (OPMD) and the early detection of oral cancer. Immediately after the examination by the PHC worker, the primary investigator re-examined the same participants, which was considered the gold standard for assessing diagnostic accuracy. The study sample size was 685 participants aged 30 years and above. The prevalence of the target condition in the study population was 8.3%. The reported sensitivity and specificity in the study were 63% (95 CI: 50-75) and 83% (95% CI: 80-85), respectively.

Table 2. 2 Characteristics of included studies in the review (COE)

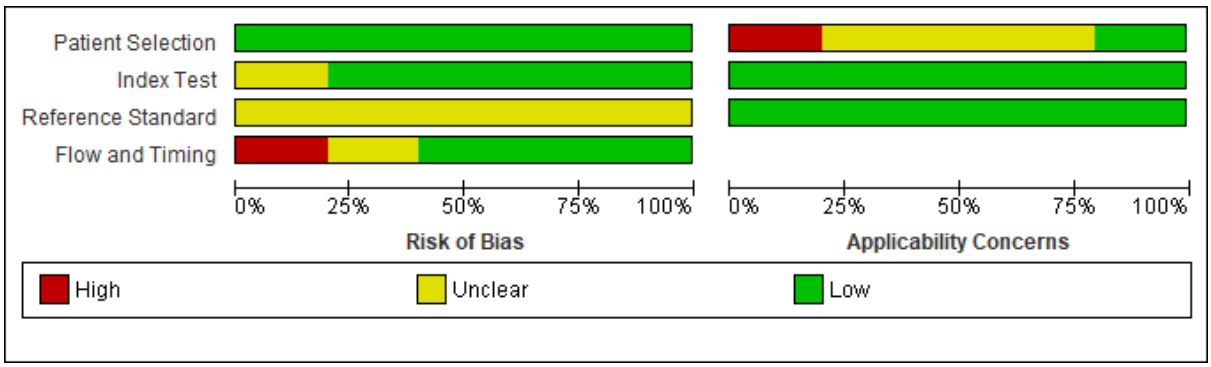
Author (Year)	**Location**	**Sample size**	**Age group**	**Prevalence (%)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
Mehta et al. (1986)	Ernakulam, Kerala, India	1921	35+ years	1.4	59% (39-78)	98% (97-99)
Warnakulasuriya et al (1990)	Kadugannawa, Sri Lanka	1872	20-59 years	21.6	95% (92-97)	81% (79-83)
Warnakulasuriya et al (1991)	Galle, Sri Lanka	3543	20+ years	50.9	97% (96-98)	75% (73-77)
Mathew et al. (1997)	Trivandrum, Kerala, India	2069	35-64 years	10.3	94% (90-97)	98% (98-99)
Amarasinghe et al (2016)	Sabaragamuwa, Sri Lanka	685	30+ years	8.3	63% (50-75)	83% (80-85)

2.6.3 Quality assessment

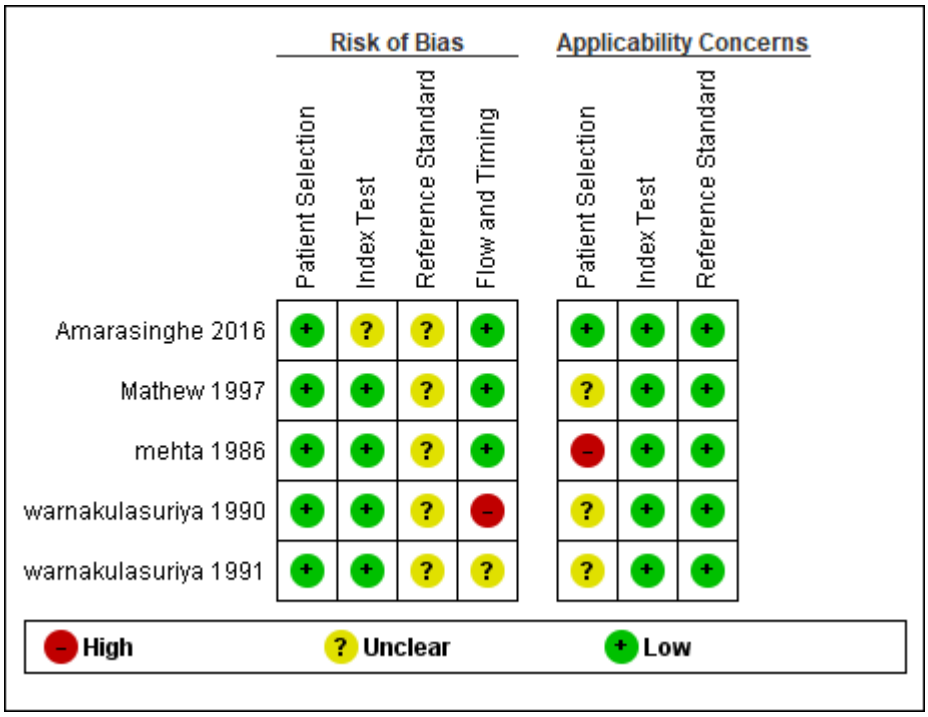
Among the included studies, there were low applicability concerns in index tests and reference standards. However, only one study had low applicability concerns in the patient selection domain. The risk of bias was low in the domain of patient selection. In the index test and flow & timing domain, 80% and 60% of studies had a low risk of bias. However, none of the studies had a low risk of bias in the reference standard domain (Figure 2.2).

Figure 2. 2 A and B Methodological quality graph of included studies

A



B



2.6.4 Pooled Estimates

Pooled diagnostic accuracy was estimated from five studies with a total of 10,069 participants above the age of 20. Pooled sensitivity of COE performed by an FHW on apparently healthy individuals was 88.8% (95% CI: 71.6-96.1), whereas pooled specificity was 91.9% (95% CI: 78.3-97.3). Figure 2.3 and Figure 2.9 show the forest plot and SROC curve of COE.

2.6.5 Subgroup analysis

Based on the study location

To assess the effect of the study location, subgroup analysis was conducted for different locations, India and Sri Lanka. Indian studies (n=2) reported pooled sensitivity and specificity of 83.9% (95% CI: 48.6 – 96.6) and 98.2% (95% CI: 97.7 – 98.6), respectively (Figure 2.4). Likewise, Sri Lankan studies (n=3) reported pooled sensitivity and specificity of 91.2% (95% CI: 71.4 – 97.7) and 79.9% (95% CI: 75.7 – 83.5), respectively (Figure 2.5).

Based on the prevalence

To assess the effect of the prevalence of oral cancer and PMD on the sensitivity and specificity, we did a subgroup analysis for different prevalences. Studies having >10% prevalence (n=3) reported pooled sensitivity and specificity of 95.9% (95% CI: 93.7 – 97.3) and 90.1% (95% CI 67.1 – 97.6), respectively (Figure 2.6). On the other hand, the pooled sensitivity and specificity of studies having <50% prevalence (n=4) was 84.5% (95% CI: 62.6 – 94.7) and 94.1% (95% CI: 82.2 – 98.2), respectively (Figure 2.7). Studies with prevalence <50% and >10% (n=2) reported pooled sensitivity and specificity of 94.6% (95% CI 92.3 – 96.2) and 94.1% (95% CI 72 – 99), respectively (Figure 2.8). Figures 2.10 to Figure 2.14 show the SROC curve for each subgroup analysis.

2.6.6 Publication bias

The small number of studies prevented any reliable estimation of publication bias.

Figure 2. 3 Forest plot of Conventional Oral Examination

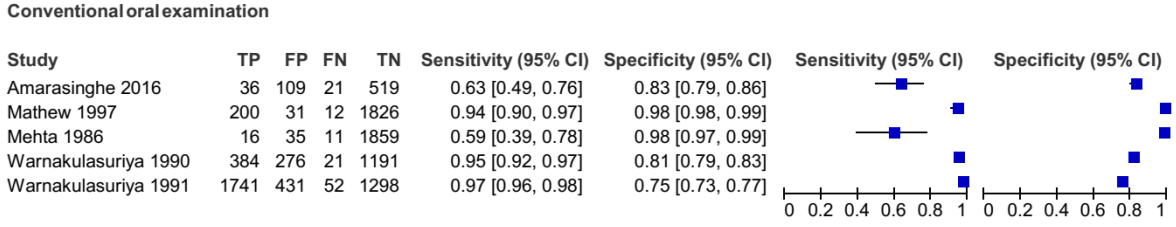


Figure 2. 4 Forest plot of Sensitivity and Specificity of Indian studies

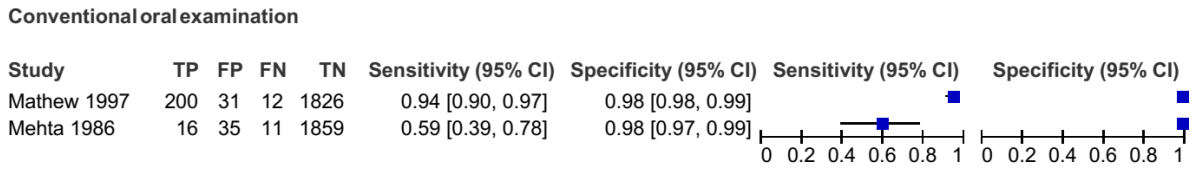


Figure 2. 5 Forest plot of Sensitivity and Specificity of Sri Lankan studies

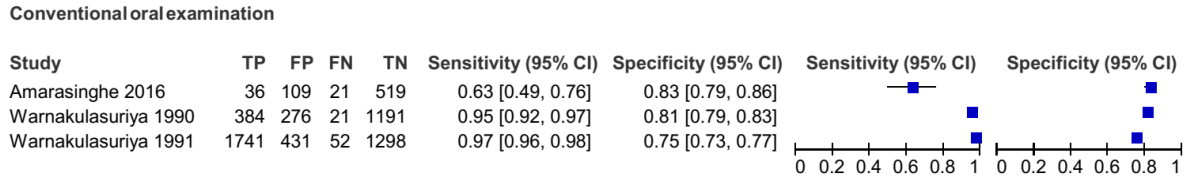


Figure 2. 6 Forest plot of Sensitivity and Specificity with a prevalence of more than 10

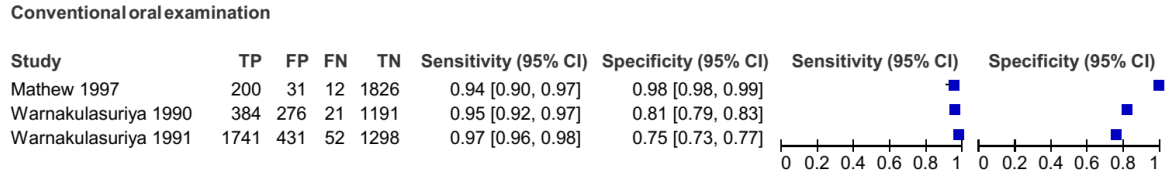


Figure 2. 7 Forest plot of Sensitivity and Specificity with a prevalence of less than 50

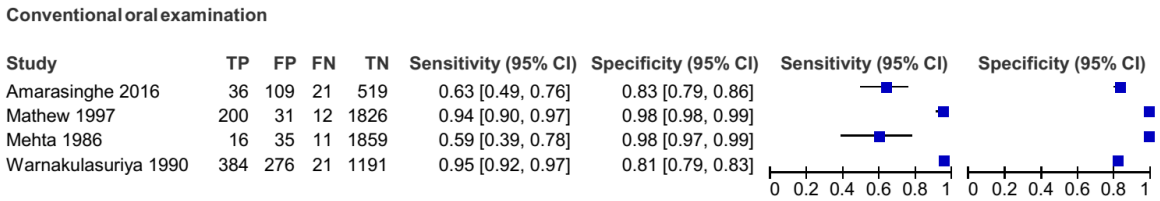


Figure 2. 8 Forest plot of Sensitivity and Specificity with prevalence less than 50, more than 10

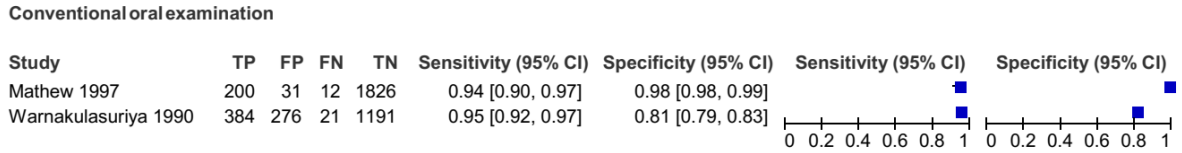


Figure 2. 9 SROC curve of included studies of COE

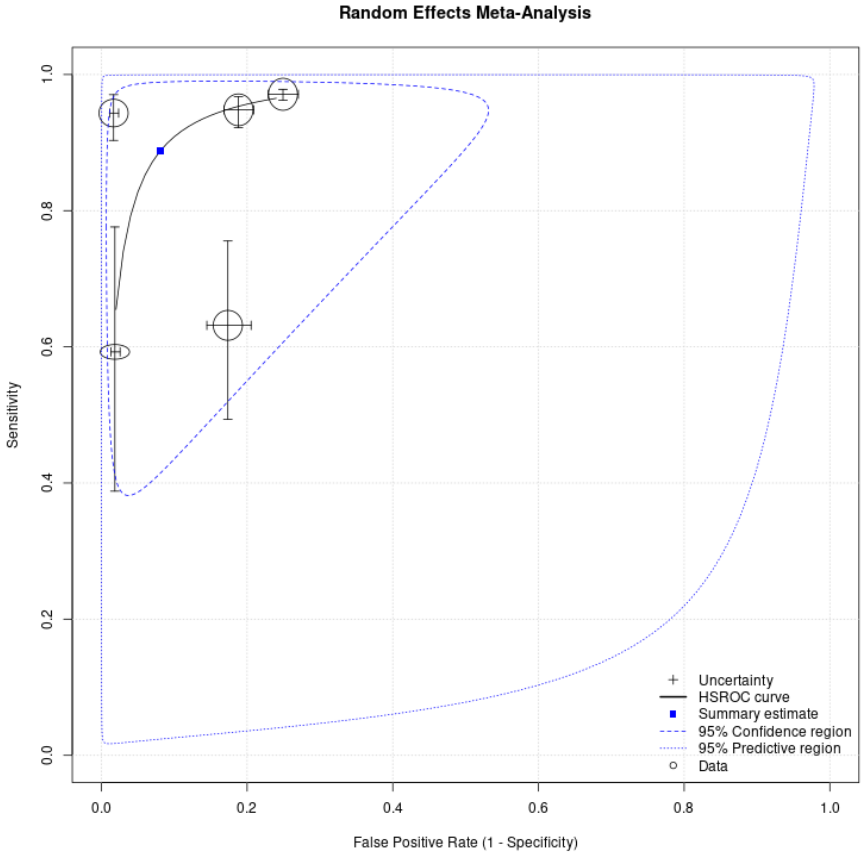


Figure 2. 10 SROC curve of Indian studies

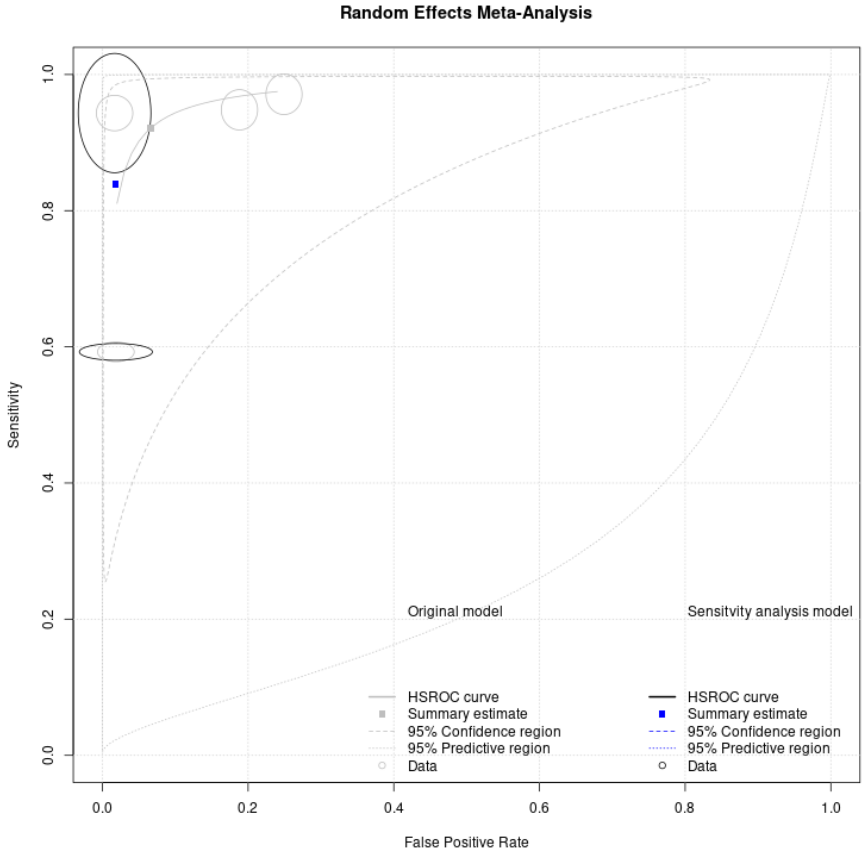


Figure 2. 11 SROC curve of Sri Lankan studies

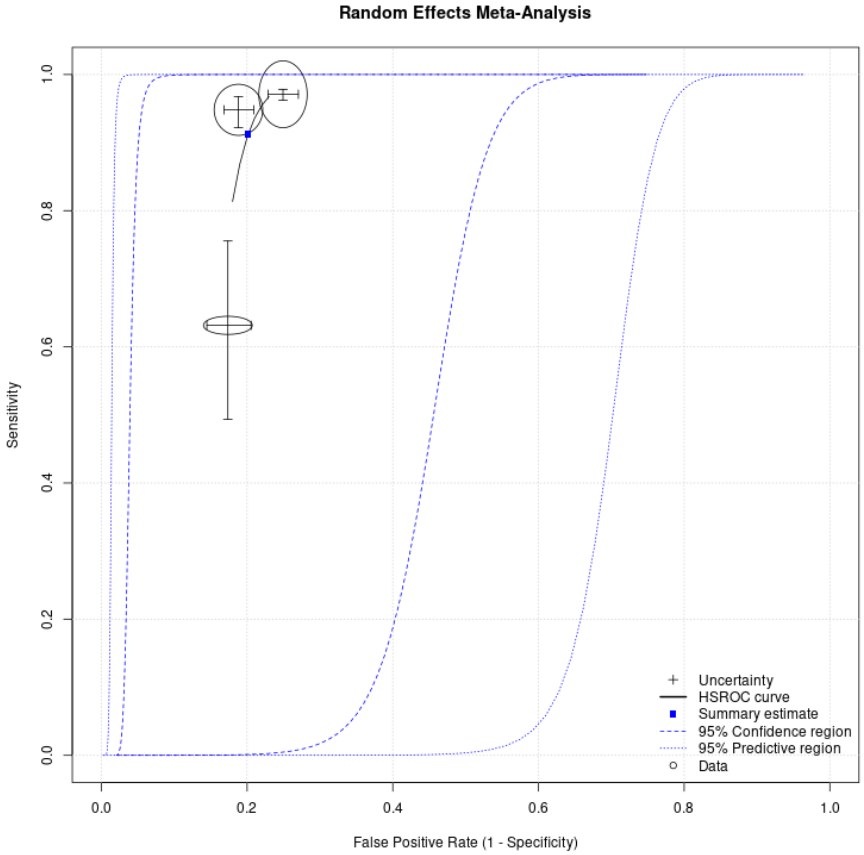


Figure 2. 12 Prevalence of more than 10

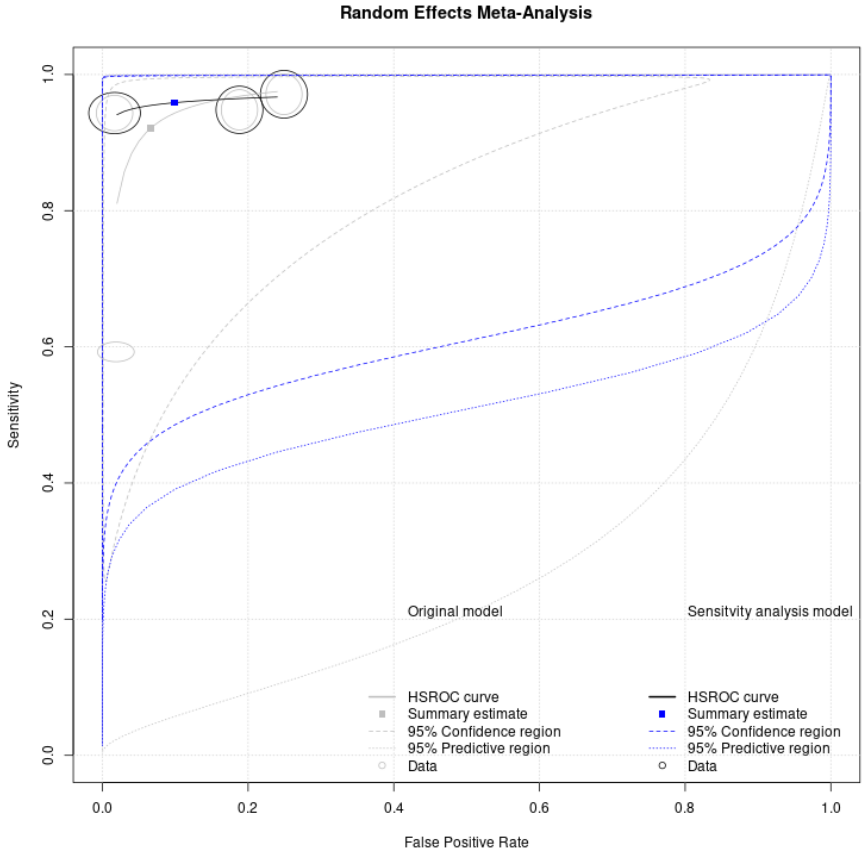


Figure 2. 13 Prevalence less than 50

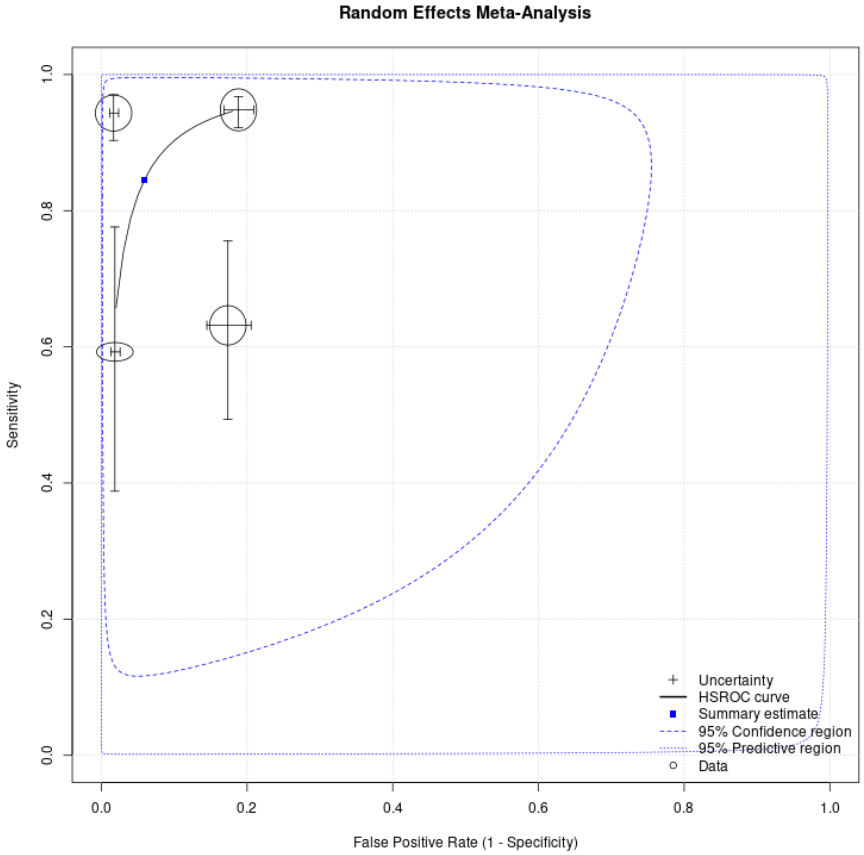
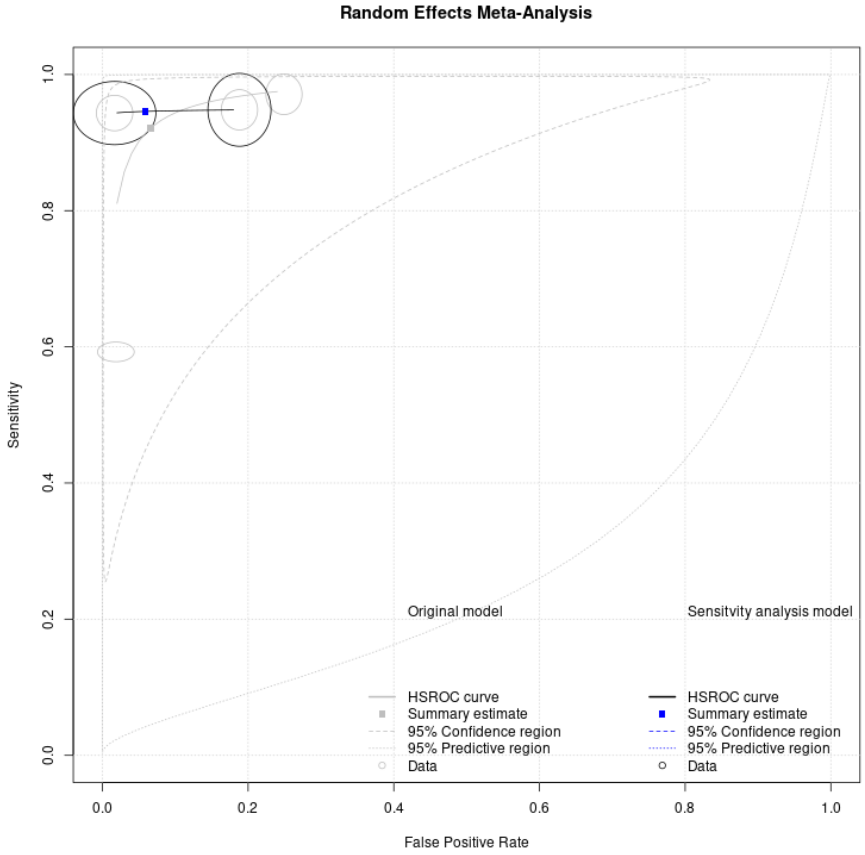


Figure 2. 14 Prevalence less than 50, more than 10



2.7 Discussion

Early detection of oral precancers and cancers is important to reduce treatment-related complications, prevent precancers from reaching invasive stages, and prevent metastatic disease. Screening at the community level for oral cancer helps in the early detection and treatment of the disease to prevent further complications. There is prior evidence that oral cancer screening can be performed by an FHW (8). Our review found no study regarding the diagnostic accuracy of TBS, OC, and CLI done by FHW. However, five studies reported the diagnostic accuracy of COE by FHW for oral screening. Studies finalised for the review were from South Asian countries (India and Sri Lanka). Pooled sensitivity of COE was 88.8% (95% CI: 71.6-96.1), and pooled specificity was 91.9% (95% CI: 78.3-97.3). Two Indian and three Sri Lankan studies reported a pooled sensitivity of 83.9% (95% CI: 48.6 – 96.6) and 91.2% (95% CI: 71.4 – 97.7), respectively. Similarly, Indian and Sri Lankan studies reported pooled specificity of 98.2% (95% CI: 97.7 – 98.6) and 79.9% (95% CI: 75.7 – 83.5), respectively. Three studies having prevalence >10% reported pooled sensitivity and specificity of 95.9% (95% CI: 93.7 – 97.3) and 90.1% (95% CI 67.1 – 97.6), respectively. Likewise, four studies having a prevalence <50% reported pooled sensitivity and specificity of 84.5% (95% CI: 62.6 – 94.7) and 94.1% (95% CI: 82.2 – 98.2), respectively. Two studies with prevalence <50% and >10% reported pooled sensitivity and specificity of 94.6% (95% CI 92.3 – 96.2) and 94.1% (95% CI 72 – 99), respectively.

The sensitivity estimates reported in our study were higher than that of previous reviews by Downer et al. and Moles et al. (11, 12). On the contrary, the specificity estimates were lower than Downer et al. and Moles et al. and higher than Macey et al. (9, 11, 12). The difference is probably because of the different research questions and inclusion criteria of the reviews. Downer et al. and Moles et al. included studies irrespective of the person performing screening. On the other hand, Macey et al. estimated the diagnostic accuracy of index tests (vital staining, Oral Cytology, Light-based detection, oral spectroscopy, Blood, and saliva analysis) for the detection of oral cancer and premalignant disorders of lip and oral cavity, in patients presenting with clinically evident lesions (9). Walsh et al. did not provide pooled estimates of the sensitivity and specificity in the review for comparison (10).

In India, the availability of doctors in remote and rural areas is low. Dentist per 10,000 population in India is 1.62 (17). According to Rural Health Statistics of 2018-19, almost 10% of the Primary

Health Centres (PHC) and 16.7% of Urban Primary Health Centres (UPHC) in India are working without a doctor (2). The availability of doctors in India is highly skewed in rural-urban distribution (18). FHW are available at the grass-root level in India and have a wider reach than doctors (19). The country has more than 10 lakh ASHA workers to serve as community-level health providers (20). Hence, it is important to assess the performance of FHW so that the possibility of provisioning oral screening services using FHW can be explored.

There were no studies in which TBS, OC, and CLI conducted by FHW were used for mass screening lip and oral cavity cancers. These techniques supplement the COE screening. Implementing screening programs with these strategies requires exclusive training and more resources and equipment, leading to high costs, and making it less feasible for mass screening in developing countries like India with a high burden of lip and oral cavity cancers (21). On the other hand, COE requires less training, equipment, and time resources, making it a desirable option for large-scale implementation in the developing world (8). Pooled estimates of sensitivity and specificity demonstrate a high level of accuracy in detecting precancerous and cancerous oral lesions by FHW. The studies included in the review were from two South-East Asian countries – India & Sri Lanka and included populations where the prevalence of oral cancer and PMD varied widely. However, the results of the sub-group analysis demonstrate that the performance of this test was largely unaffected by the site of the study and the prevalence of oral cancer and PMD.

The effectiveness of COE in reducing morbidity and mortality due to oral cancer has been studied in a randomised controlled study from Kerala, India (8). It was demonstrated that screening with COE in individuals with high-risk behaviour (tobacco and/or alcohol users) leads to a significant reduction in oral cancer incidence and mortality in the long run (8). A district-level oral cancer screening program conducted at 48 panchayats of Kannur district in Kerala, India, proved that trained FHW could be effectively used in oral cancer screening programs agreeing with our review. Almost half of the oral cancer patients detected were in the early stages of the disease in that population-based cancer screening program (22). Another community-based screening program was implemented among the socioeconomically disadvantaged women in Mumbai slums, who were between 30 and 65 years and exposed to tobacco for early detection of common cancers, including oral (23). Twenty-seven oral precancers (23 leukoplakia, one erythroplakia, two sub-mucous-fibrosis, and one dysplasia) were diagnosed among the women referred by FHW after screening with COE (23).

Multiple factors add credibility and strength to this review. Firstly, carrying out a risk of bias assessment with the standard QUADAS-2 tool for all five included studies. Secondly, a replicable search strategy that explored multiple databases like PubMed, Scopus, Embase, Cochrane Library, and Google Scholar for retrieval of literature strengthened our review. Third, we used Rayyan software for screening and eligibility assessment of retrieved studies, making our process reliable and reproducible. Fourth, we included most of the commonly used screening strategies for oral cancer and PMD in our review, making it comprehensive. Lastly, heterogeneity sources were explored and addressed by doing a sub-group analysis to assess the effect of prevalence and geographical location on results, strengthening our study estimates' credibility.

We have identified the limitations of this review. A total of 180 articles were excluded after full-text assessment, where 60% were excluded because those studies were conducted among the patients. However, considering the scarcity of doctors at the grass-root level, we wanted to assess the accuracy of screening by FHW to derive implementable results for the population-based cancer screening program. Secondly, we could not perform meta-regression in our review. However, despite the comprehensive search, only five articles were retrieved for COE. As a result, meta-regression could not be performed to explore the reasons for heterogeneity. However, we did a subgroup analysis to assess the effect of the study site and prevalence of oral cancer and PMD on the estimates of diagnostic accuracy. Thirdly, we could not find any articles about TBS, OC, and CLI, which could be because no studies were done for population-based mass screening using these techniques where FHW were involved. Lastly, prevalence among the included studies varied widely. However, we tried to address it by sub-group analysis to see the effect of the prevalence of oral cancer and PMD on summary estimates.

2.8 Conclusion

Conventional Oral Examination by trained frontline health workers had high sensitivity and specificity for oral cancer screening. The prevalence of oral cancer and PMD and the study site did not affect the high sensitivity and specificity. TBS, OC, and CLI screening techniques were not studied for mass screening by trained FHW.

The current review recommends that COE by trained FHW could be considered for screening for precancer, lip, and oral cavity cancers, especially in resource-constrained low-middle income countries.

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Chapter 3 Cost-Effectiveness Analysis

3.1 Background

The Global Cancer Observatory: Cancer Today (GLOBOCAN) estimated that the prevalence of oral cancer in India in the adult population above 30 years is 12.4 per 100,000 population (1). The main risk factors for developing oral cancer are tobacco and alcohol use (2, 3). Various commonly used oral cancer screening techniques are conventional oral examination (COE), toluidine blue staining (TBS), oral cytology (OC), and light-based detection (LBD) {which is inclusive of chemiluminescent illumination (CLI)} using devices like Velscope, ViziLite plus.

For a developing country like India, the economic burden related to oral cancer is an important factor that needs to be addressed. Treating advanced oral cancer requires a significant amount of healthcare resources, which is out of reach for an average patient in India. Hence, early detection of oral cancer is a priority.

The previous chapter reported high sensitivity and specificity of COE. Previously published literature suggested that TBS, OC, and LBD have good sensitivity and specificity in detecting oral precancers and early cancers (4). Thus, assessing the cost-effectiveness of these commonly used screening strategies is important. It will facilitate making healthcare decisions on implementing strategies that yield more health benefits with fewer resources. The present study assessed the cost-effectiveness of various commonly used oral cancer screening strategies (COE, TBS, OC and LBD) in India. In the previous chapter, the diagnostic accuracy of CLI was assessed, whereas for the cost-effectiveness analysis, the screening technique evaluated was LBD (which is inclusive of CLI).

3.2 Review of literature

We performed a literature search for studies regarding the economic evaluation of oral cancer screening strategies in India and elsewhere. A cost-effectiveness study based on a cluster-randomised controlled trial (RCT) was done in Kerala in 2009 (5). The objective of the RCT was to evaluate the effect of screening on oral cancer mortality**.** The objective of the cost-effectiveness study was to evaluate the cost-effectiveness of oral cancer screening by visual inspection. In the study, seven of 13 population clusters were randomly allocated to three rounds of screening between 1996 and 2004, while standard care was provided in six (control arm). An activity-based approach was employed to calculate costs associated with various components of the screening trial. Total costs for each cluster were estimated in 2004 United States dollars (US$). The incremental cost per life-year saved was calculated for all eligible and high-risk individuals (i.e., tobacco or alcohol users). They concluded that the incremental cost per life-year saved was US$ 835 for all individuals eligible for screening and US$ 156 for high-risk individuals. Oral cancer screening by visual inspection was performed for under US$ 6 per person (5).

Another cost-effectiveness study was done in the US by Dedhia et al. in 2011 (6). Their Markov model examined two screening strategies: no community-based screening (no screen) and yearly community-based screening (screen) for all high-risk males, defined as age over 40 years with recent, regular tobacco and/or alcohol use. They found that the no-screen arm dominated with an incremental cost of $258 and incremental effectiveness of −0.0414 QALYs. Using the $75,000/QALY metric, the maximum allowable budget for a screening program equals $3,363 ($258+$3,105) per screened person over a 40-year time course (6).

Kumdee et al. did a cost-utility analysis of the screening programs for the early detection of oral cancer in Thailand (7). Markov modelling was performed to simulate the costs and QALYs of the screening and no-screening programs in the Thai population aged over 40 years. There were four steps to the screening program in Thailand: 1) mouth self-examination (MSE); 2) visual examination by trained dental nurses (VETDN); 3) visual examination by trained dentists (VETD); and 4) visual examination by oral surgeons (VEOS). Compared to no screening, the screening programme was cost-ineffective in the Thai context. The study also states that the screening programme will be cost-effective only if the sensitivity and specificity of MSE are>60% and the sensitivity and specificity of VETDN are>90% (7)**.**

Speight et al. conducted a model-based cost-effectiveness study of oral cancer screening in primary care in the UK in 2006 (8). They studied the population over the age of 40 years. Eight strategies were compared: no screen, invitational screen-general medical practitioner, invitational screen-general dental practitioner, opportunistic screen-general medical practitioner, opportunistic screen-general dental practitioner, opportunistic high-risk screen-general medical practitioner, opportunistic high-risk screen-general dental practitioner, and invitational screen - specialist. On comparison of invitational screening (by dentist & general medical practitioner) and opportunistic high-risk screening (by dentist & general medical practitioner) with no screening, they found the ICER for the whole population (age 49–79years) ranged from £15,790 to £25,961 per QALY. Hence, no screening was the cheapest option, and opportunistic screening may be cost-effective (8).

Table 3. 1 Studies regarding the cost-effectiveness of oral cancer screening

Sl. No.	Author and Year	Country	Study type	Perspective	Population	Comparator	Result (ICER, QALY)
1	Subramanian et al. 2009 (5)	India	Cost-effectiveness study.	Societal	Healthy individuals over 35 years.	No screening	The incremental cost per life-year saved was US$ 835 for all individuals eligible for screening and US$ 156 for high-risk individuals.
2	Dedhia et al. 2011 (6)	USA	Micro-simulation modelling study	Societal	High-risk males above 40 years.	No screening	The No-Screen arm was dominated with an incremental cost of $258 and an incremental effectiveness of -0.0414 QALYs.
3	Kumdee et al. 2008 (7)	Thailand	Micro-simulation modelling study	Societal	Healthy individuals over 40 years.	No screening	The screening program yielded higher costs (1,362 Baht) and QALYs (0.0044 years) than the no-screening program, producing an ICER of 311,030 Baht per QALY gained.
4	Speight et al. 2006 (8)	UK	Micro-simulation modelling study	Societal	Healthy individuals over 40 years of age.	No screening	ICER for the population (age 49–79years) ranged from £15,790 to £25,961 per QALY.

3.2.1 Research Gap

Previous cost-effectiveness studies regarding oral cancer screening (5-8) compared oral visual examination with no-screening. Cost-effectiveness studies on oral cancer screening strategies in the Indian population using various screening techniques are limited. Hence, there is limited evidence to suggest the cost-effectiveness of oral cancer screening strategy in India. The only available cost-effectiveness study in India is based on a cluster RCT wherein the lifetime costs of the screening strategy and associated health outcomes (QALYs) were not estimated. Moreover, they studied only one screening technique. Thus, there is a need to generate evidence regarding the cost-effectiveness of oral cancer screening strategies in India, which will aid in policy making. Thus, our study was undertaken to compare the cost-effectiveness of various commonly used oral cancer screening techniques in the Indian context.

3.3 Aim

This health technology assessment study compares the cost-effectiveness of various commonly used oral cancer screening techniques.

3.4 Objectives

1. To evaluate the cost-effectiveness of commonly used screening modalities for oral cancer screening in India.
2. To determine the most appropriate strategy between mass screening and high-risk strategy.
3. To determine the most optimal interval (out of three, five, and ten years) between periodic screening check-ups for oral cancer.

3.5 Methodology

A cost-effectiveness study of four oral cancer screening strategies using a societal perspective in the Indian population was conducted.

3.5.1 Model Overview

The present study was a model-based cost-effectiveness (CE) analysis for estimating the lifetime costs and health outcomes in a hypothetical cohort of one lakh men and women above 30 years of age using the societal perspective (9). Based on the previously published and validated literature on mathematical models for oral cancer (6), we developed a probabilistic Markov model (Figure

1) using Microsoft Excel software, considering the natural history of the progression of oral cancer from one health state to another. The Markov model denotes different health states and their movement from one state to another. The cycle length of the model was taken as one year. The present model was run for 70 cycles. Thus, the hypothetical cohort of men and women moved in annual cycles through different health states of the model following the natural history of oral cancer progression.

Costs and health outcomes were estimated for both the screened and unscreened groups. For the no-screening group, the cohort followed the natural history of the progression of the disease and was diagnosed and treated based on their health-seeking behaviour. For the screening group, screening strategies used were conventional oral examination, oral cytology, toluidine blue staining, and chemiluminescent illumination. The screening intervals were taken as three, five, and ten years for each screening strategy. The outcomes were measured regarding QALYs gained, ICER and deaths averted. A discount rate of 3% was used to discount the future costs and consequences.

3.5.2 Markov Models

The main risk factors for developing oral cancer are tobacco in its different available forms and alcohol use (2). Tobacco use, including smokeless tobacco and betel quid chewing, excessive alcohol use, poor oral hygiene, and long-term viral infections, including the human papillomavirus, are all risk factors for oral cancer (2, 3). Tobacco and alcohol are the established risk factors for oral cancer. A cluster-RCT done by Sankaranarayanan et al. in Kerala, India, to assess the effect of screening on oral cancer mortality concluded that oral visual screening significantly reduced oral cancer mortality in high-risk individuals. They identified the high-risk group as users of tobacco or alcohol, or both. Due to the high prevalence of risk factors (tobacco and alcohol) in the Indian population and its established relation with the causation of oral cancer (10), we identified the high-risk individuals as defined by Sankaranarayanan et al. Hence two Markov models were developed. Model A adopted a mass screening strategy versus no screening, whereas Model B adopted a high-risk screening strategy versus no screening.

Model A Mass (Population) screening strategy: Mass (Population) screening strategy is directed at screening the population above 30 years of age irrespective of the individual risk levels.

Model B High-risk screening strategy: The high-risk strategy aims to bring preventive care to individuals at higher risk of oral cancer, as defined above.

Two models were developed so that both strategies could be compared in terms of cost-effectiveness.

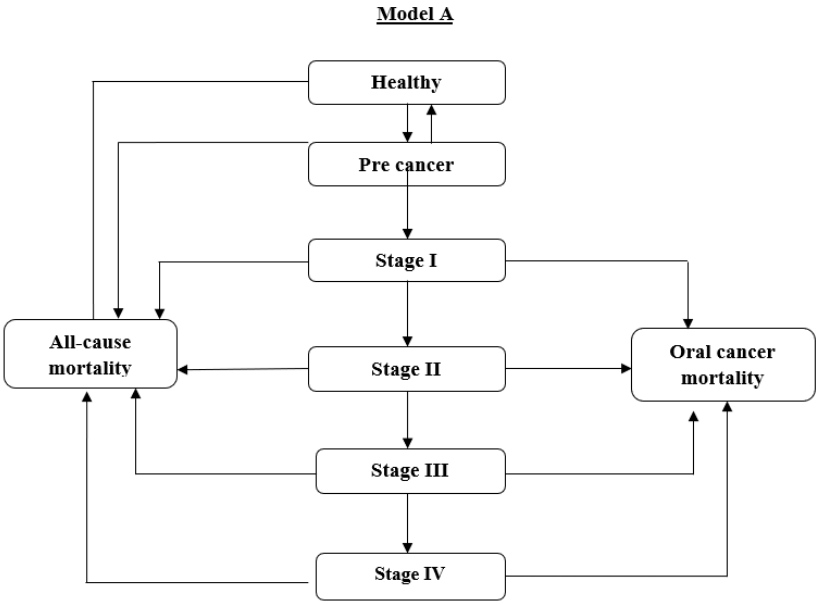
Model A

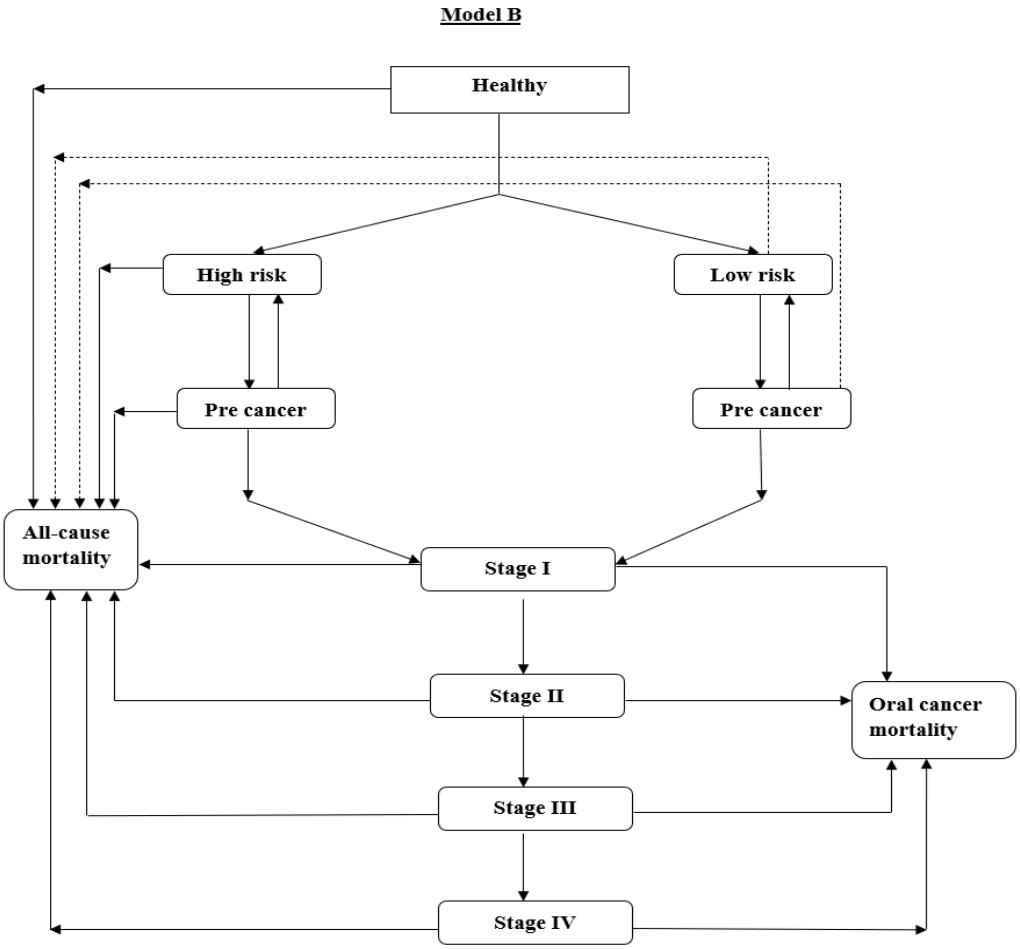
In a hypothetical cohort of men and women, an apparently healthy individual can move into the precancerous state or remain in the same state in the next cycle. (Figure 1) Persistent precancer can regress to a healthy state or transform into invasive cancer. Finally, the patient can die in each health state due to all-cause mortality and oral cancer in various stages of cancer. The progression from one health state to another was according to the natural history of oral cancer.

Model B

Due to the established association of oral cancer with tobacco and alcohol, we developed an extended design Markov model. In this model, we divided the hypothetical cohort into two groups: high-risk individuals and low-risk individuals. (Figure 2) People with tobacco and/or alcohol habits were termed high-risk individuals (10). The proportion of high-risk individuals was based on National Family and Health Survey (NFHS) 4 survey data and census data (11,12) (Table 3.2 A1). In this model, screening was done only for the high-risk group. Eventually, people from both (high and low-risk) groups progressed to precancers following the natural history of progression. From the precancerous state, individuals progress to the various stages of invasive oral cancer following the natural history of the disease.

Figure 3. 1 Model A and B





Through this modelling approach, we compared four screening strategies in apparently healthy individuals of age 30 years and above at different time intervals of screening, namely three, five, and ten years. In the mass-screening strategy, screening was done using four screening modalities at three screening intervals for the whole population, resulting in 12 screening scenarios versus no screening. In the second scenario, screening was done using four screening modalities at three screening intervals for the high-risk group only, resulting in another 12 screening scenarios versus no screening. Thus, there were 24 screening scenarios to be compared against no screening in the entire modelling process.

The age group to be screened was as per India's National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular diseases & Stroke (NPCDCS) guidelines regarding the eligibility criteria for oral cancer screening (9). Following the guidelines, screening was assumed to be undertaken at the level of sub-centres by the Auxiliary Nurse Midwives (ANM), supported by the concerned dental surgeon (9). While the screening results by conventional oral examination, toluidine blue staining, and light-based detection were immediately available, the screening result by oral cytology was assumed to be available in one to two weeks following the screening. Those who screened positive with any strategies were then offered a confirmatory diagnostic test at the Community Health Centre (CHC) or district hospital. For the treatment of the precancerous and cancerous lesions, patients were assumed to be referred to the tertiary care hospital. In the no-screening group, the proportion of people showing symptoms in each stage was used to know the health-seeking behaviour of people. For the no-screening group, it was assumed that any person diagnosed with oral cancer would avail health care treatment from a mix of public and private healthcare facilities based on the utilisation pattern (35% and 65% in public and private facilities respectively, reported from the National Sample Survey, i.e., 75th round 2017-2018) (13).

3.5.3 Model Parameters

A) For assessment of burden (Incident cases and Oral cancer deaths)

i. For estimation of Incident cases

Incidence of precancer

The table below (Table 3.2 A1) shows the model input parameters for assessing incident cases in the CE analysis. The incidence of precancers in the total population was estimated from already

published literature (10). The incidence of precancers in high-risk and low-risk was estimated using the incidence of precancers and the distribution of high-risk and low-risk individuals (10).

Stage-wise prevalence of oral cancer

As shown below in Table 3.2 A1, the stage-wise prevalence was estimated based on the yearly prevalence of oral cancer in the Indian population derived from GLOBOCAN and the stage distribution of oral cancer extracted from the literature (1, 14).

Annual probabilities of progression/regression

As shown below in Table 3.2 A1, the raw annual probabilities of transition from one health state to another were derived from already published literature (8). The incidence rate was converted to probability using the standard conversion method (15). The raw probabilities were adjusted for the unscreened and screening arms. For the unscreened arm, the raw probabilities were adjusted for the proportion of individuals showing symptoms in each stage and treatment coverage.

The adjustment was made using the formula,

$$(\text{raw probability of progression from one health state to another}) \times (1 - [\text{stage} - \text{wise treatment coverage in the unscreened arm}])$$

In the screening arm, the raw probabilities were adjusted for screening coverage, treatment coverage, and sensitivity of the screening test. For the second model, i.e., the high-risk screening strategy, the proportion of the high-risk population, the proportion of the population showing symptoms in each stage, and treatment coverage were considered for adjusting the raw probabilities.

The proportion of individuals showing symptoms

As shown in Table 3.2 A2, the proportion of patients showing symptoms in each stage was assumed based on discussion with clinicians. The treatment coverage was 90% in the unscreened population (16). The proportion of individuals in each risk group was estimated from NFHS-4 and population projections of the 2011 census (11, 12). The raw probabilities of progression/regression in the high-risk and low-risk were adjusted for certain parameters as follows:

The adjustments were made for the high-risk group using the formula,

$$\text{(Raw probability of progression from one health state to another in high} - \text{risk individual)} \times [1 - \text{(Sensitivity of each screening strategy)} \times \text{(screening coverage)} \times \text{(treatment coverage screened arm)}] \times (1 - \text{treatment coverage unscreened arm})$$

The adjustments were made for the low-risk group using the formula,

$$\text{(Raw probability of progression from one health state to another in low} - \text{risk individual)} \times (1 - \text{treatment coverage unscreened arm})$$

Sensitivity and specificity of screening strategies

The sensitivity and specificity of conventional oral examination were generated from the meta-analysis. For other screening strategies, sensitivity and specificity were extracted from the literature (4). The table below shows the values used as model input parameters. The sensitivity of diagnosing stage I oral cancer was assumed to be the same as that of the precancerous states. For stages II to IV, the sensitivity was assumed to be 100%. The coverage of screening attendance for each screening strategy was assumed as 80 % (16).

Further, a loss of 10% each was considered for those screened positive and undergoing subsequent treatment. The number of false-positive individuals was also accounted for in the analysis. The false-positive individuals were estimated using the specificity of each screening strategy and the number of healthy individuals in each screening cycle. The formula used for estimating false-positive cases was:

$$\text{(Population in healthy health} - \text{state)} \times (1 - \text{Specificity of the screening strategy)}$$

Table 3. 2 (A1, A2, and B) For assessment of burden (Incident cases and oral cancer deaths)

(A1) For assessment of burden (Incident cases)

S. No	Data required	Base value (95% CI)/(SE)	Distribution	Data source
Burden Indicators				
1	**Incidence of precancer**			
	Total population	0.004	Not applicable	Estimated from Sankaranarayanan et al.
	High-risk group	0.005		Assumed based on the incidence of precancers in the total population and the percentage of the population with habits and with no habits.
	Low-risk group	0.003		
2	**Prevalence of oral cancer (stage-wise)**			
	Pre-cancer	2660.06	Not applicable	From GLOBOCAN, the prevalence of oral cancer in adults over 30 years is 12.4 per 100,000. Thus, based on stage distribution, stage-wise prevalence is estimated by Sankaranarayanan et al.
	Stage I	5.80		
	Stage II	3.16		
	Stage III	2.30		
	Stage III	1.05		
3	**Annual probabilities progression**			
	Precancer to Stage I	0.04 (0.01)	Beta	Kumdee et. al.
	Stage I to stage II	0.53 (0.27)	Beta	
	Stage II to Stage III	0.59 (0.25)	Beta	
	Stage III to Stage IV	0.67 (0.25)	Beta	
4	**Annual probability of regression**			
	Precancerous lesion to healthy	0.30 (0.10)	Beta	Kumdee et. al.
5	**The proportion of individuals in risk groups**			
	Population with habits (High-risk group)	0.31	Not applicable	Estimation is done based on NFHS 4 survey data and the 2011 census.
	Population with no habits (Low-risk group)	0.69		
6	**Probability of cure of precancer**	0.58	Not applicable	Kumdee et. al.

(A2) For assessment of burden (Incident cases) (Continuation...)

S. No	Data required	Base value (95% CI)/(SE)	Distribution	Data source
Burden Indicators				
1	**Sensitivity and Specificity**			
	Sensitivity of tests			
	Conventional Oral Examination	0.89 (0.72,0.96)	Normal	Meta-analysis
	Toluidine Blue Staining	0.84 (0.74,0.90)	Normal	Macey et al.
	Oral Cytology/Brush Biopsy	0.91 (0.81,0.96)	Normal	
	Light-based detection	0.91 (0.77,0.97)	Normal	
2	**Specificity of tests**			
	Conventional Oral Examination	0.92 (0.78,0.97)	Normal	Meta-analysis
	Toluidine Blue Staining	0.70 (0.59,0.79)	Normal	Macey et al.
	Oral Cytology/Brush Biopsy	0.91 (0.81,0.95)	Normal	
	Light-based detection	0.58 (0.22,0.87)	Normal	
3	**The proportion of individuals showing symptoms In unscreened arm**			
	Precancer	0.35	Not applicable	Assumed based on discussion with clinicians.
	Stage 1	0.50		
	Stage 2	0.50		
	Stage 3	0.75		
	Stage 4	1.00		

ii. For estimation of oral cancer deaths and all-cause deaths

Age-specific all-cause mortality

The probability of age-specific all-cause mortality was obtained from the Census of India Sample Registration System (SRS) life tables for the population (17). It is listed in the table (Table 3.2 B) below.

Probability of oral cancer deaths

The probability of death due to oral cancer was estimated from stage-wise survival rates obtained from the literature (18). The five-year survival rates obtained from the literature were adjusted to yearly survival rates using the standard conversion formula

$$Adjusted\ survival = Observed\ survival\ rate^{\frac{Ts}{To}},$$

Where Ts is the standardised time, and To is the observed time

Finally, the yearly survival rates were converted to a yearly stage-wise probability of death due to oral cancer using the standard conversion method [(1-e^-rate). It is listed in the table below (Table 3.2 B):

Table 3. 2 (B) For assessment of burden (Oral cancer deaths)

S. No	Data required	Base value (95% CI)/(SE)	Distribution	Data source
Burden Indicators (Oral cancer deaths)				
1	**Annual all-cause mortality rate per 100,000**			
	Age 30-34 years	0.00916	Not applicable	SRS Life table
	Age 35-39 years	0.01257		
	Age 40-44 years	0.01780		
	Age 45-49 years	0.02496		
	Age 50-54 years	0.04153		
	Age 55-60 years	0.06382		
	Age 61-65 years	0.09067		
2	**Stage-wise survival rate of oral cancer**			
	Stages	**Percentage**	Not applicable	Thavarool et al.
	Stage I	86.50		
	Stage II	72.00		
	Stage III	60.00		
	Stage IV	62.20		

B) For assessment of cost

The cost of screening and treatment interventions is integral to an economic modelling study (19). The cost of each screening strategy and stage-wise treatment were estimated using standard economic costing methods. A combination of top-down and bottom-up costing approaches was undertaken to estimate the costs using data from already published literature. The costing process involved utilising both the costs – the health system cost and the out-of-pocket expenditure- to derive the cumulative costs for the cost-effectiveness analysis.

Cost of screening

All four screening strategies' costs were estimated based on human resources employed and the unit cost of material used to perform screening.

The cost of a conventional oral examination was estimated using ANM's monthly salary and working hours, the time required for one screening test, and the number of screenings per day. The cost of the toluidine blue stain test was estimated using the cost of the material, and the cost of the human resource used. The cost of oral cytology was estimated using the cost of laboratory process,

consumables, sample collection and the cost of human resources involved. The cost of the LBD test was estimated from the cost of the device and the cost per screening incurred. The details of the costing of the screening tests are given in Annexure II Table 4. The support activities cost was applied to each screening strategy to get the cumulative cost incurred per person. The support activities included organising the camp, administration, registration, transport, supervision, and miscellaneous activities required for the screening process.

While costing the cost incurred on false-positive cases was also addressed. The number of false-positive individuals was estimated using the specificity of each screening strategy. The cost for false-positive individuals was done by applying the screening and diagnosis costs to the number of false-positive cases.

For the no-screening arm, it was considered that any individual who suffers from oral cancer symptoms would visit a health facility for care. Thus, they will be screened using standard (OPD visit + Biopsy) protocol for oral cancer screening. After confirmation of the disease, the individual will be treated according to the regimen described in Annexure II Table 4. The cost of treatment was the same for both screening and no-screening arms.

Cost of diagnosis

The cost of diagnosis was estimated considering the standard protocol of oral examination, i.e., the cost of OPD consultation and the biopsy cost.

Cost of treatment

In the public facility, we considered both health system costs and OOPE. Stage-wise types and frequency of treatment regimens, drugs, the number of hospital days, the number of follow-up visits, etc., were estimated by the treatment regimen as per Indian clinical practice consensus guidelines for the management of oral cavity cancer (20-22) (Details given in Annexure II Table 5). The distribution or utilisation of various radiotherapy machines was derived from previous literature (23, 24). This information was utilised in the estimation of radiotherapy costs for the treatment of oral cancer. The costs of the treatment procedures were derived from already published literature.

The OOP expenditure incurred on treating invasive cancer in a private healthcare facility was considered for the private facility. Data regarding this expenditure was extracted from the NSS

report (Health in India) 2017-2018 (13). The distribution of people in public and private facilities for treating oral cancer was also taken from the same report.

The composite cost was then calculated considering public and private facility costs and their utilisation pattern. The analysis used this composite cost as the input cost parameter to estimate lifetime cost. (Table 3.3)

Table 3. 3 For assessment of cost

Cost data				
1	**Screening costs in INR**	**Costs**	**Distribution**	**Source of Data**
	Conventional Oral Examination	254.23	Uniform	Details are given in Annexure II
	Toluidine Blue Staining	261.87	Uniform	
	Oral Cytology/Brush Biopsy	690.67	Uniform	
	Light-based detection	402.75	Uniform	
2	**Diagnostic costs (INR)**			
	Clinical oral examination+ Oral biopsy	565.00	Uniform	As per CGHS rates, 2014
3	**Treatment costs in (INR)**			
	Precancerous	12280.00	Uniform	Estimated cost (as per CGHS, Chauhan et al
	Stage I/II	93051.65	Uniform	
	Stage III	111498.58	Uniform	
	Stage IV	95979.68	Uniform	
4	**GDP per capita, India (INR)**	1,32,750.55	Not applicable	https://tradingeconomics.com/india/gdp-per-capita2021
	Willingness to pay for Screening and treatment.			

C) For assessment of QALY

As shown in the table below, stage-wise utility values were extracted from the literature and then applied to the population in each health state in every cycle to estimate quality-adjusted life years (7, 25). (Table 3.4)

Table 3. 4 For assessment of QALY

Health utility values				
1	**Utility values**			
	Perfect health	1.00		
	Precancerous	0.830 (0.020)	Beta	Kumdee e al.
	Stage I	0.698 (0.086)	Beta	Prinja et al.
	Stage II	0.594 (0.061)	Beta	
	Stage III	0.639 (0.042)	Beta	
	Stage IV	0.357 (0.041)	Beta	

3.5.4 Outcome Evaluation

The outcomes were measured broadly in terms of disease burden (incident cases, oral cancer deaths averted), cost (incremental cost and ICER) and health outcomes (QALYs).

Estimation of incident cases

The total number of incident cases was calculated for each stage of oral cancer in each cycle by using the probabilities of progression and regression from one health state to another. The total number of oral cancer cases in every cycle provided the total number of incident cases in every screening scenario and the no-screening group.

Estimation of Deaths averted

The number of deaths due to oral cancer was calculated in each cycle. Oral cancer deaths were calculated by multiplying the stage-wise probability of death due to oral cancer with the population in each health state. The number of deaths averted was calculated by subtracting the lifetime deaths in the screening arm from that in the no-screening arm.

Incremental cost

The incremental cost was calculated by subtracting the lifetime cost in the no-screening arm from that in the screening arm for each screening strategy and screening interval.

Incremental cost-effectiveness ratio

The incremental cost-effectiveness ratio (ICER) is the summary measure used to report the cost-effectiveness of competing interventions. It is defined as the ratio of the cost difference between two alternatives to the difference in effectiveness between the same two alternatives. The ICER was calculated as the ratio of incremental cost and the incremental effect.

Estimation of Quality-adjusted life years (QALYs)

It measures the effectiveness of the screening strategy, which was calculated using the length of life and quality of health, i.e., utility scores of each health state. The utility score for healthy was considered as 1 and 0 for death. Stage-wise utility scores for oral cancer were extracted from the literature (7, 25). The number of individuals in each health state was estimated using transition probabilities. These numbers of individuals (in every health state) were multiplied by the utility values of each stage to estimate QALYs. A similar process was repeated in every cycle to estimate lifetime QALYs.

Incremental QALYs

Incremental QALYs were calculated by subtracting lifetime QALYs in the no-screening arm from that in the screening arm for each screening strategy and screening interval.

3.5.5 Discounting

As per HTA guidelines, a discount rate of 3% was used to discount future costs and consequences (26).

3.5.6 Willingness to pay

Gross domestic product (GDP) per capita was used as the willingness to pay (WTP) for both screening and treatment cost threshold in the cost-effectiveness analysis (CEA) (27).

3.5.7 Cost-effectiveness analysis and screening scenarios

Economic evaluation is the tool used in HTA to support decision-making in health, where the costs and the consequences of competing interventions are compared. Base CE analysis (Deterministic sensitivity analysis) followed the Markov modelling approach, where four different screening strategies were compared with no screening. Three screening intervals were assumed for every screening strategy – three, five, and ten years. Costs, QALYs, and cost-effectiveness (CE) ratio

were estimated for each screening strategy and the no-screening group. Incremental cost and effectiveness were calculated as the difference between the screening strategy and the no screening. ICER was calculated as the ratio of incremental cost and the incremental effect.

3.5.8 Threshold analysis

According to the NFHS-5, screening coverage for oral cancer in India is less than 1% (28). For the base case, screening coverage was assumed as 80%. It is much higher than the current screening coverage in India. A threshold analysis was conducted to address this difference. ICER values were noted for all the screening strategies at the following levels of screening coverage: 1%-5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, and 80% to assess the effect of varying levels of screening coverage.

3.5.9 Sensitivity analysis

Probabilistic sensitivity analysis (PSA) was undertaken to assess the uncertainty in model parameter values. Each parameter in PSA was given specific distribution according to its nature. Uniform distribution was assumed for cost estimates. Beta distribution was assumed for utility values, transition probabilities, and mortality rates. Normal distribution was assumed for pooled estimates of sensitivity and specificity. Using Monte Carlo Simulation, 1000 iterations were done to estimate the total cost and effects (QALY), Incremental cost-effectiveness ratio (ICER) with minimum and maximum values, Net Monetary Benefit (NMB), and probability of cost-effectiveness for all screening strategies. The probability of cost-effectiveness was calculated at different Willingness-to-pay (WTP).

3.5.10 Budget Impact Analysis

A Budget Impact Analysis (BIA) was done to estimate the financial consequences of implementing oral cancer screening in India. The analysis was conducted yearly for two years. The total intervention cost for the population above 30 years of age in India was estimated for each screening strategy at various screening intervals. The annual health budget of India 2022-2023 was considered for the analysis (29). The impact of the intervention cost on India's healthcare budget was estimated and presented as a percentage of the total health budget for the financial year 2022-2023.

3.6 Results

The result of this economic modelling study will be discussed under the following heads- Incidence of oral cancer, deaths due to oral cancer averted, the total cost incurred across various strategies, total QALYs gained, ICER and sensitivity analysis.

3.6.1 Incidence of oral cancer

The total number of new cases of oral cancer in a cohort of 1 lakh population in various screening scenarios (mass-screening, high-risk screening, and no screening strategy) after 70 cycles of the run are listed below (Table 3.5). The no-screening arm had the maximum number of new cases (5,673.59 cases). Mass screening strategies at an interval of three years showed the least number of incident cases. Mass screening with LBD three years had the least incident cases (3,271.68 cases). It was followed by OC three years (3,276.92 cases), COE three years (3,309.91 cases) and TBS three years (3,403.39 cases). Among the high-risk strategies, screening at an interval of three years with OC, LBD (3,573.95 cases each), TBS (3,583.81 cases), and COE (3,599.55 cases) showed the least number of incident cases. When comparing mass and high-risk screening strategies, high-risk screening at an interval of five and ten years showed fewer incident cases than mass screening at the same intervals.

Table 3. 5 Outcome indicator incident cases in a cohort of 1 lakh population among various screening scenarios

Screening Strategy		**Incident cases**	
No Screening		5,673.59	
		Mass-screening	High-risk screening
COE	**Three years**	3,309.91	3,599.55
	Five years	3,923.18	3,811.77
	Ten years	4,550.84	3,984.32
TBS	**Three years**	3,403.39	3,583.81
	Five years	4,009.21	3,865.98
	Ten years	4,613.27	4,026.57
OC	**Three years**	3,276.92	3,573.95
	Five years	3,889.13	3,790.32
	Ten years	4,527.76	3,967.46
LBD	**Three years**	3,271.68	3,573.95
	Five years	3,889.13	3,790.32
	Ten years	4,525.92	3,967.46

3.6.2 Oral cancer Deaths averted

The total number of oral cancer deaths and the number of oral cancer death averted in all the screening strategies are listed in Table 3.6. When compared across the 24 screening strategies versus no-screening, it was observed that the no-screening arm had the maximum number of oral cancer deaths (1,180.45 deaths). Mass screening at three years intervals averted the maximum number of deaths. Among them, OC and LBD (459.76 deaths averted) averted the maximum, followed by COE (451.69 deaths averted) and TBS (431.30 deaths averted). The high-risk screening followed it at an interval of 3 years by OC, LBD (417.76 deaths averted), TBS (416.43

deaths averted), and COE (412.16 deaths averted). High-risk screening at an interval of five and ten years had a lesser number of oral cancer deaths as compared to mass screening strategies at the same intervals.

Table 3. 6 Outcome indicator oral cancer deaths averted in a cohort of 1 lakh population among various screening scenarios

Screening strategy		**Death due to oral cancer**		**Deaths averted**	
No Screening		1,180.45			
		Mass-screening	High-risk screening	Mass-screening	High-risk screening
COE	**Three years**	728.76	768.29	451.69	412.16
	Five years	840.30	793.64	340.15	386.81
	Ten years	954.50	815.00	225.95	365.46
TBS	**Three years**	749.15	764.02	431.30	416.43
	Five years	858.29	805.62	322.16	374.83
	Ten years	967.70	824.56	212.75	355.89
OC	**Three years**	720.70	762.69	459.76	417.76
	Five years	819.81	788.90	360.64	391.55
	Ten years	949.23	811.18	231.22	369.28
LBD	**Three years**	720.70	762.69	459.76	417.76
	Five years	833.18	788.90	347.28	391.55
	Ten years	949.23	811.18	231.22	369.28

3.6.3 Lifetime Cost Incurred

The total costs of mass screening and high-risk screening strategies across all screening intervals are listed below (Table 3.7). The no-screening arm incurred a lifetime cost of 21,34,93,287.27 INR. Among mass-screening and high-risk screening strategies, it was seen that high-risk screening incurred less cost across all comparisons. Amongst the 24 screening strategies, COE HR ten years incurred the least cost (18,27,94,468.26 INR), and OC three years incurred the maximum lifetime cost (58,07,51,021.64 INR). Thus, the high-risk screening was cost-saving when compared to the mass-screening strategy.

In the mass-screening scenario, the lifetime cost incurred across all 12 screening strategies ranged from 25,23,89,378.34 INR to 58,07,51,021.64 INR. In the mass screening strategy, the minimum lifetime cost incurred was by COE ten years, i.e., 25 crores, and the maximum cost was by OC three years, i.e., 58 crores.

In the high-risk screening scenario across all 12 screening strategies, the lifetime cost incurred ranged from 18,27,94,468.26 INR to 29,04,12,200.01 INR. In the high-risk screened arm, the minimum lifetime cost was incurred by COE ten years, i.e., 18 crores and the maximum cost was incurred by OC three years, i.e., 29 crores.

The cost of screening was highest for OC three years (32,84,47,216.49 INR) and the least for COE ten years HR (1,39,87,824.13 INR) among all the strategies. Likewise, the cost of treatment was highest for LBD 5 years (31,57,86,039.84 INR) and lowest for COE ten years HR (16,79,44,813.34 INR).

3.6.4 Lifetime Quality Adjusted Life Years (QALYs) gained

The total cost and health outcomes of all the mass and high-risk screening strategies versus no screening are listed in Table 3.7. Screening yielded a higher number of QALYs when compared with no screening. The no-screening arm yielded 17,77,201.71 QALYs. Mass screening at an interval of three years with OC and LBD yielded a maximum number of QALYs (17,83,881.01 each) followed by COE (17,83,762.19) and TBS (17,83,459.80). Among high-risk screening strategies, screening at an interval of three years yielded the maximum number of QALYs, where TBS (17,83,104.70) had maximum QALYs followed by OC and LBD with 17,82,926.02 QALYs each, and COE with 17,82,840.02 QALYs. Mass screening at an interval of three years with OC

and LBD yielded maximum incremental QALYs (6,679.29), followed by COE (6,560.48) and TBS (6,258.09).

3.6.5 ICER

The cost outcomes of all the screening strategies are listed below (Table 3.7 A and B). Amongst the screening techniques, it was observed that high-risk screening approach was cost-saving as compared to the mass-screening strategy. The high-risk screening techniques (ICER values) namely COE 5 years (-2331.41INR/QALY) (-29.21 USD/QALY), COE 10 years (-7213.46 INR/QALY) (-90.68 USD/QALY), TBS 10 years (-4815.80 INR/QALY) (-60.54 USD/QALY), and LBD 10 years (-1075.17 INR/QALY) (-13.51 USD/QALY) were dominant over no-screening (no-screening was costlier and less effective). The high-risk screening by COE at 10-years was the most-cost saving approach. The graphical representation of the ICER values derived from the CE analysis are shown in Figure 3.2.

Table 3. 7 Outcome indicators in a cohort of 1 lakh population among various screening scenarios

(A) COE and TBS

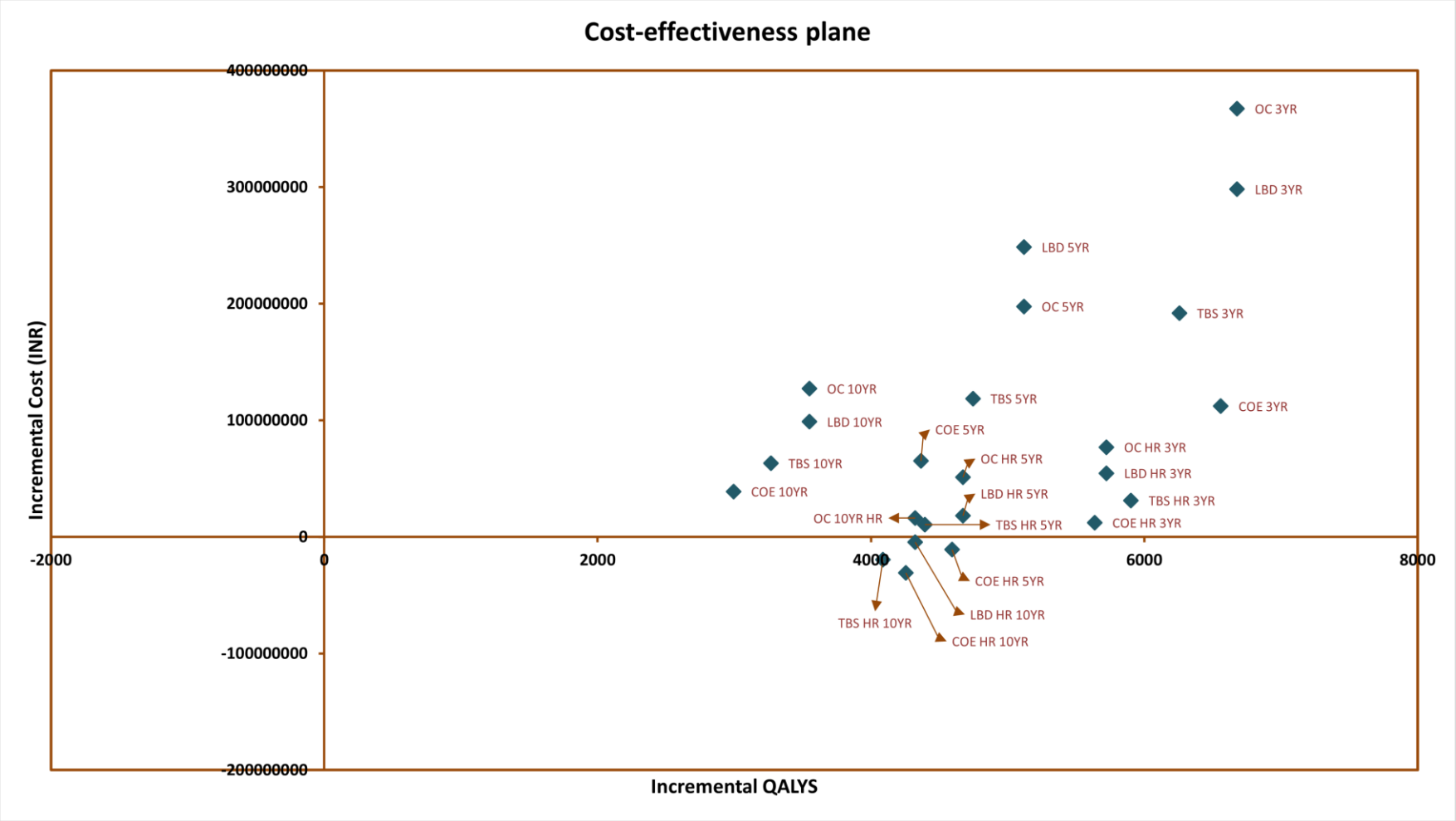
Screening Strategy		Screening Cost	Treatment Cost	Total Cost (INR)	QALYs	Incremental Cost (INR)	Incremental QALYS	ICER (INR per QALYs gained)
No Screening				21,34,93,287.27	17,77,201.71			
COE	**Three years**	12,08,92,397.42	19,71,95,526.10	32,55,31,121.20	17,83,762.19	11,20,37,833.93	6,560.48	17,077.70
	Three years HR	3,94,61,220.30	18,37,88,920.54	22,56,51,433.66	17,82,840.02	1,21,58,146.39	5,638.31	2,156.35
	Five years	7,66,48,669.90	19,72,65,938.44	27,86,28,112.12	17,81,569.17	6,51,34,824.85	4,367.46	14,913.66
	Five years HR	2,50,40,816.76	17,62,20,571.38	20,27,80,688.58	17,81,796.62	(1,07,12,598.69)	4,594.91	(2,331.41) Dominant
	Ten years	4,35,94,795.56	20,61,13,795.51	25,23,89,378.34	17,80,197.68	3,88,96,091.07	2,995.97	12,982.82
	Ten years HR	1,39,87,824.13	16,79,44,813.34	18,27,94,468.26	17,81,457.48	(3,06,98,819.01)	4,255.77	(7,213.46) Dominant
TBS	**Three years**	12,45,06,080.39	25,29,89,275.32	40,53,90,056.25	17,83,459.80	19,18,96,768.98	6,258.09	30,663.80
	Three years HR	4,06,57,102.52	19,50,44,583.42	24,47,11,064.67	17,83,104.70	3,12,17,777.40	5,902.99	5,288.47
	Five years	7,89,42,621.66	23,54,90,519.10	33,20,97,814.83	17,81,948.80	11,86,04,527.56	4,747.08	24,984.71
	Five years HR	2,92,99,045.03	18,89,46,440.26	22,39,35,608.11	17,81,595.62	1,04,42,320.84	4,393.91	2,376.54
	Ten years	4,49,58,903.47	22,15,90,865.18	27,65,96,675.49	17,80,469.49	6,31,03,388.22	3,267.78	19,310.79
	Ten years HR	1,47,06,832.89	17,58,72,036.79	19,38,06,328.95	17,81,289.71	(1,96,86,958.32)	4,088.00	(4,815.80) Dominant

(B) OC and LBD

Screening Strategy		Screening Cost	Treatment Cost	Total Cost (INR)	QALYs	Incremental Cost (INR)	Incremental QALYS	ICER (INR per QALYs gained)
No Screening				21,34,93,287.27	17,77,201.71			
OC	**Three years**	32,84,47,216.49	23,53,38,799.13	58,07,51,021.64	17,83,881.01	36,72,57,734.37	6,679.29	54,984.51
	Three years HR	10,72,25,942.96	18,04,83,443.43	29,04,12,200.01	17,82,926.02	7,69,18,912.74	5,724.30	13,437.25
	Five years	20,82,41,922.31	19,75,59,377.12	41,11,05,295.12	17,82,321.41	19,76,12,007.85	5,119.70	38,598.36
	Five years HR	6,80,34,795.65	19,49,74,168.40	26,47,19,039.27	17,81,876.29	5,12,25,752.00	4,674.58	10,958.36
	Ten years	11,85,89,232.80	21,90,27,133.68	34,06,32,976.45	17,80,753.03	12,71,39,689.18	3,551.32	35,800.69
	Ten years HR	3,76,68,762.58	18,97,91,669.25	22,95,59,511.34	17,81,524.49	1,60,66,224.07	4,322.77	3,716.65
LBD	**Three years**	19,15,25,521.18	28,09,64,002.22	51,15,75,807.73	17,83,881.01	29,80,82,520.46	6,679.29	44,627.85
	Three years HR	6,24,07,999.04	19,67,16,313.91	26,81,33,691.67	17,82,926.02	5,46,40,404.40	5,724.30	9,545.34
	Five years	12,14,31,573.46	31,57,86,039.84	46,19,69,593.21	17,82,321.41	24,84,76,305.94	5,119.70	48,533.38
	Five years HR	3,96,72,954.39	18,61,99,753.59	23,15,72,958.72	17,81,876.29	1,80,79,671.45	4,674.58	3,867.66
	Ten years	6,91,52,288.73	22,89,47,057.64	31,21,76,859.58	17,80,753.03	9,86,83,572.31	3,551.32	27,787.86
	Ten years HR	2,26,23,750.94	18,16,94,755.90	20,88,45,581.77	17,81,524.49	(46,47,705.50)	4,322.77	(1,075.17) Dominant

(Note: The four strategies dominated no-screening. Dominant strategies are strategies which dominate the no-screening arm, which means it incurs less cost and is more effective when compared to no-screening)

Figure 3. 2 Graphical representation of ICER values derived from deterministic sensitivity analysis



3.6.6 Threshold analysis

Threshold analysis was conducted at different levels of screening coverage, from 1% to 80%. When the coverage of the screening programme was 80%, high-risk techniques COE five and ten years, TBS ten years, and LBD ten years were cost-saving. These four techniques were cost-saving when the coverage was 70% and 60%. When the coverage of the screening programme was 50%, high-risk techniques COE three, five and ten years, TBS ten years, and LBD ten years were cost-saving. When the coverage was 40%, high-risk techniques COE three, five and ten years, TBS five and ten years, and LBD five and ten years were cost-saving. When the coverage was 30%, high-risk techniques COE three, five and ten years, TBS three, five and ten years, OC ten years, and LBD five and ten years were cost-saving. When the coverage was 20%, all high-risk techniques were cost-saving. When the coverage was 10%, along with all high-risk techniques, mass screening with COE three years was also cost-saving. When the coverage was 5%, all high-risk techniques were cost-saving. When the coverage was 4%, all high-risk techniques except COE three years were cost-saving. All high-risk techniques were cost-saving when the coverage was 3% and 2%. When the coverage was 1%, high-risk techniques COE five and ten years, TBS ten years, and LBD ten years were cost-saving. The threshold analysis demonstrated that when the screening coverage was below five per cent, high-risk strategies COE five and ten years, TBS, and LBD ten years were cost-saving. These four high-risk techniques were cost-saving at all levels of screening coverage. (Table 3.8)

3.6.7 Sensitivity Analysis

In Probabilistic Sensitivity Analysis (PSA), the incremental cost-effectiveness ratio (ICER) for each screening strategy is calculated from 1000 iterations. Figure 3.3 (A-D) represents the cost-effectiveness plane for each screening strategy with incremental effect on the X-axis and incremental cost on the Y-axis.

Table 3. 8 Threshold analysis of ICERs at a different level of screening coverage

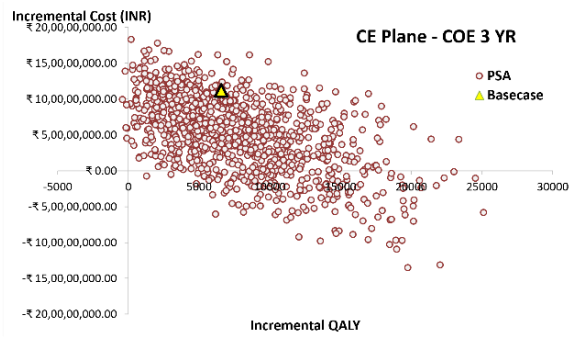
Strategies	ICER values at different levels of screening coverages (%)												
	1	2	3	4	5	10	20	30	40	50	60	70	80
COE three yr	82,647.68	1,01,261.85	1,37,525.52	2,38,873.98	20,85,465.66	(25,132.97)	7,243.83	13,154.41	15,376.28	16,387.30	16,859.16	17,049.32	17,077.70
COE three yr HR	(1,26,767.93)	(1,04,096.76)	(87,642.24)	(75,162.04)	(65,376.47)	(37,105.90)	(15,889.31)	(7,457.41)	(3,153.91)	(697.95)	772.24	1,654.15	2,156.35
COE five yr	19,535.32	19,342.74	19,134.65	18,907.18	18,655.05	16,601.97	25,145.13	20,102.74	18,602.27	17,520.40	16,584.32	15,724.06	14,913.66
COE five yr HR	(84,343.90)	(75,892.12)	(68,769.55)	(62,688.42)	(57,438.43)	(39,260.41)	(21,631.63)	(13,302.75)	(8,669.99)	(5,874.24)	(4,120.89)	(3,013.31)	(2,331.41)
COE ten yr	4,640.19	3,767.76	2,784.64	1,665.58	377.01	(11,095.81)	82,568.25	28,996.70	21,599.96	18,205.90	16,019.27	14,360.89	12,983.91
COE ten yr HR	(40,647.73)	(39,036.44)	(37,524.96)	(36,104.72)	(34,768.10)	(29,124.47)	(21,399.69)	(16,471.91)	(13,153.75)	(10,844.62)	(9,208.08)	(8,040.99)	(7,213.46)
TBS three yr	(69,774.98)	(98,697.18)	(1,51,526.67)	(2,78,961.08)	(10,20,690.25)	1,23,179.79	57,568.64	44,905.86	39,278.52	35,964.33	33,701.22	32,008.66	30,663.80
TBS three yr HR	(60,339.33)	(51,589.81)	(44,628.87)	(38,962.54)	(34,263.42)	(19,252.87)	(6,384.81)	(873.08)	1,993.97	3,612.61	4,543.12	5,053.65	5,288.47
TBS five yr	(73,145.67)	(1,01,970.24)	(1,54,384.13)	(2,79,660.36)	(9,78,855.77)	1,20,778.10	54,003.08	40,907.44	34,916.20	31,259.76	28,665.18	26,648.27	24,984.71
TBS five yr HR	(61,141.59)	(54,616.49)	(49,079.32)	(44,324.86)	(40,201.01)	(25,801.14)	(11,747.70)	(5,191.19)	(1,662.55)	349.74	1,498.93	2,113.46	2,376.54
TBS ten yr	(78,774.20)	(1,07,207.86)	(1,58,439.88)	(2,78,479.91)	(8,91,594.67)	1,17,489.76	48,928.82	35,602.36	29,508.68	25,780.65	23,122.50	21,041.89	19,310.79
TBS ten yr HR	(32,112.56)	(30,816.47)	(29,597.44)	(28,449.16)	(27,366.01)	(22,767.14)	(16,413.18)	(12,336.85)	(9,594.95)	(7,700.04)	(6,374.80)	(5,449.82)	(4,815.80)
OC three yr	(24,826.44)	(49,120.40)	(97,664.88)	(2,42,797.61)	(5,10,39,606.87)	1,07,151.29	68,346.50	60,854.81	57,851.60	56,358.74	55,563.87	55,154.43	54,984.51
OC three yr HR	(1,35,464.05)	(1,09,511.94)	(90,754.83)	(76,568.20)	(65,465.58)	(33,446.91)	(9,288.45)	543.34	5,769.95	8,940.40	11,015.32	12,437.02	13,437.25

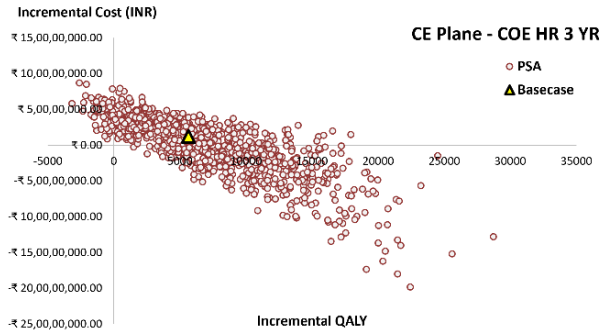
OC five yr	61,492.18	67,373.36	79,122.12	1,13,916.60	29,73,115.24	28,473.56	37,621.29	39,019.05	39,332.87	39,300.27	39,122.26	38,876.22	38,598.36
OC five yr HR	(44,599.80)	(38,687.19)	(33,722.52)	(29,497.30)	(25,860.02)	(13,349.08)	(1,381.93)	4,164.71	7,179.32	8,942.51	9,999.37	10,621.23	10,958.36
OC ten yr	(77,711.16)	(1,14,859.05)	(1,87,824.24)	(3,97,076.31)	(66,25,463.06)	1,29,178.87	65,447.25	52,178.27	46,041.94	42,283.43	39,610.36	37,526.55	35,800.69
OC ten yr HR	(18,963.52)	(17,794.81)	(16,701.29)	(15,676.36)	(14,714.18)	(10,680.65)	(5,260.44)	(1,900.74)	282.91	1,734.20	2,700.22	3,329.49	3,716.65
LBD three yr	(1,63,221.88)	(2,29,463.82)	(3,61,727.23)	(7,56,948.46)	(13,90,49,171.66)	1,95,140.57	88,406.79	66,877.97	57,527.07	52,247.67	48,829.24	46,421.55	44,627.85
LBD three yr HR	(90,049.16)	(72,222.59)	(59,348.56)	(49,620.53)	(42,015.30)	(20,160.83)	(3,900.45)	2,499.86	5,731.22	7,547.79	8,610.41	9,223.19	9,545.34
LBD five yr	(4,64,558.03)	(6,27,460.00)	(9,51,197.46)	(19,06,656.14)	(8,02,84,407.02)	4,25,574.91	1,58,760.97	1,04,997.33	81,557.92	68,229.09	59,504.74	53,268.55	48,533.38
LBD five yr HR	(60,648.43)	(53,797.79)	(48,044.99)	(43,148.60)	(38,933.13)	(24,429.00)	(10,541.51)	(4,092.17)	(577.66)	1,485.13	2,727.49	3,463.65	3,867.66
LBD ten yr	(1,53,939.21)	(2,12,270.63)	(3,26,887.50)	(6,55,673.52)	(1,04,43,276.44)	1,71,581.77	71,870.71	51,453.04	42,237.50	36,752.05	32,965.75	30,098.86	27,787.86
LBD ten yr HR	(24,574.65)	(23,365.87)	(22,234.80)	(21,174.63)	(20,179.32)	(16,006.20)	(10,395.77)	(6,915.30)	(4,650.71)	(3,143.44)	(2,138.14)	(1,481.33)	(1,075.17)

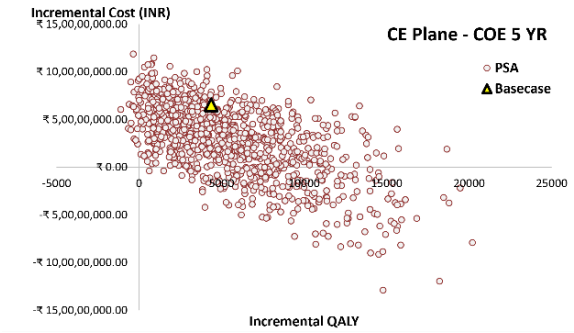
ICERs in red colour indicate they are cost-saving

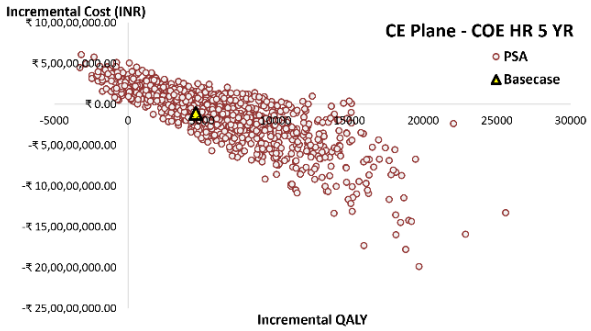
Figure 3. 3 (A-D) CE plane for COE, TBS, OC, and LBD

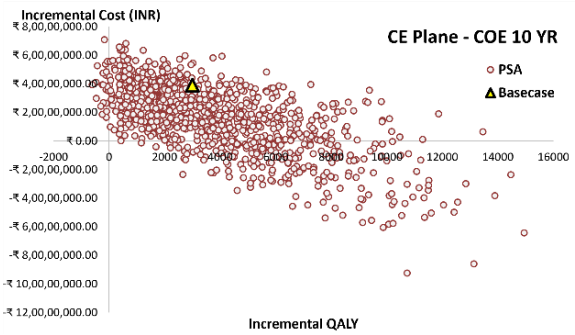
(A) CE Plane for COE

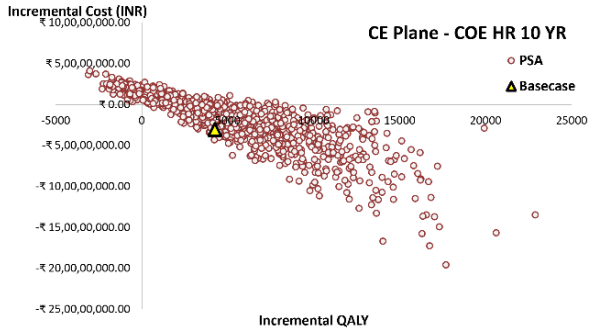




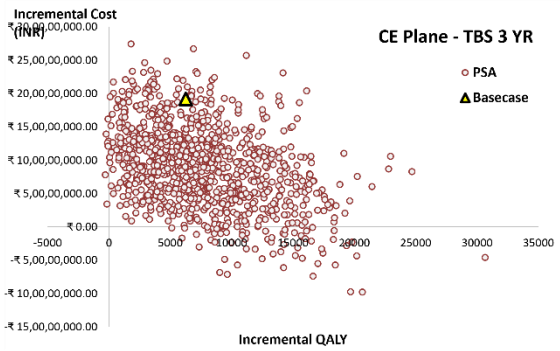


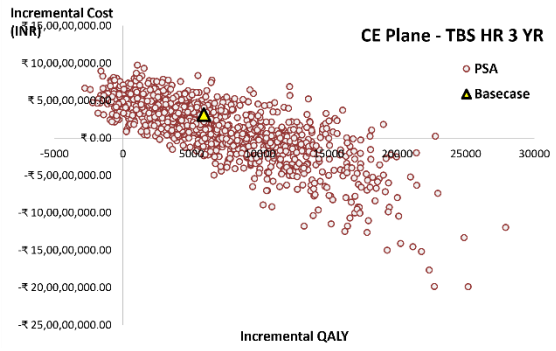


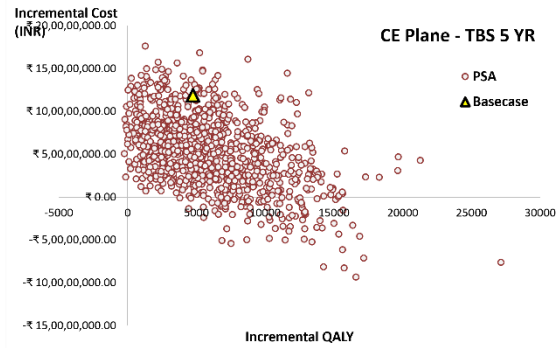


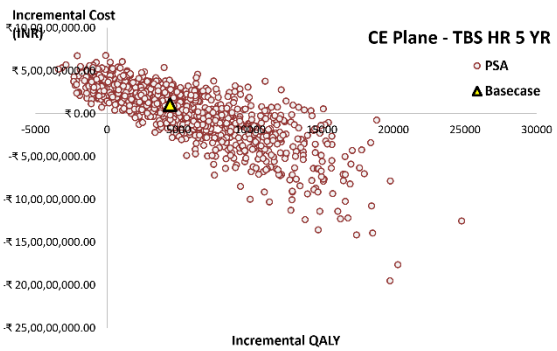


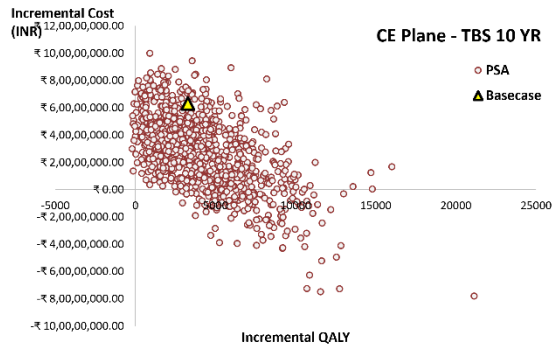
(B) CE Plane for TBS

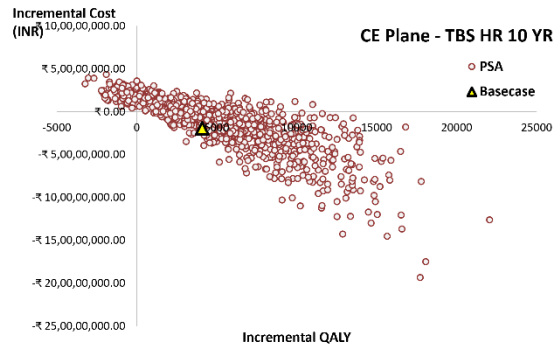




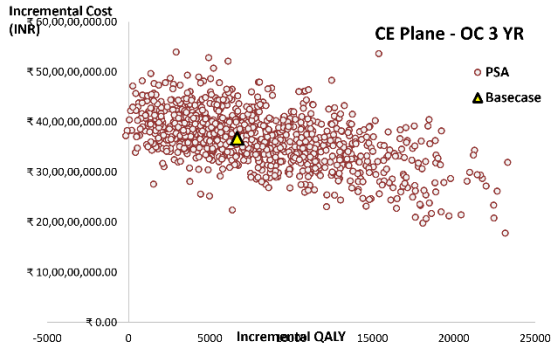


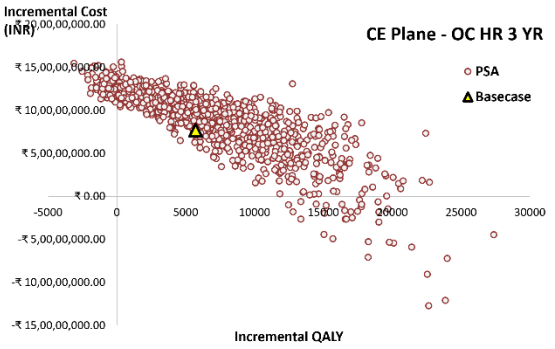


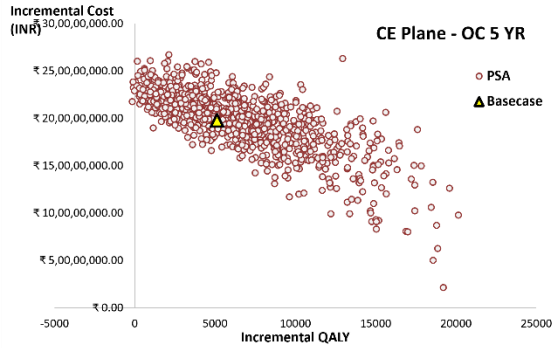


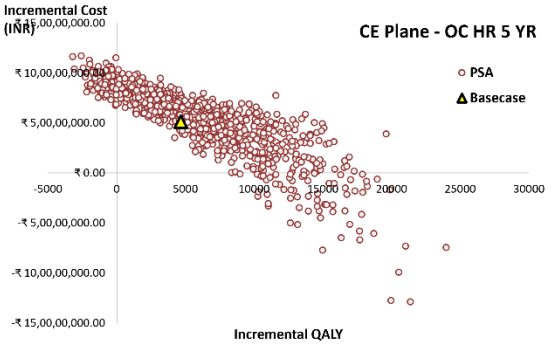


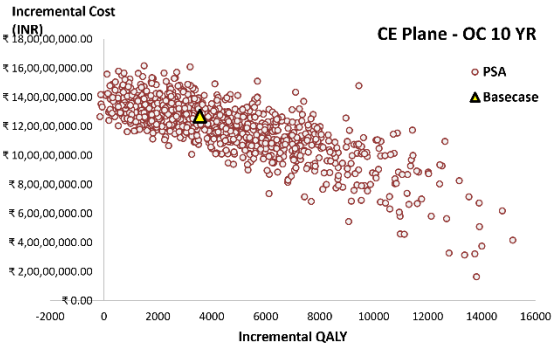
(C) CE Plane for OC

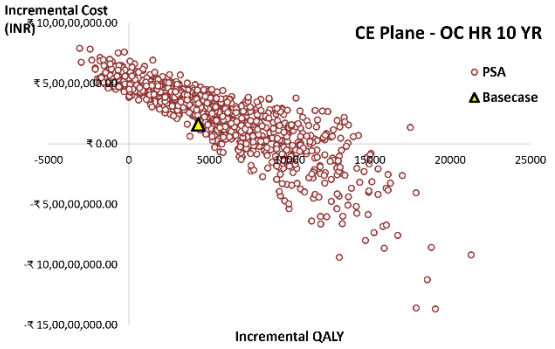




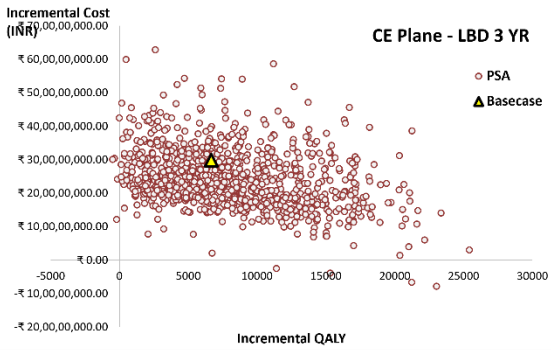


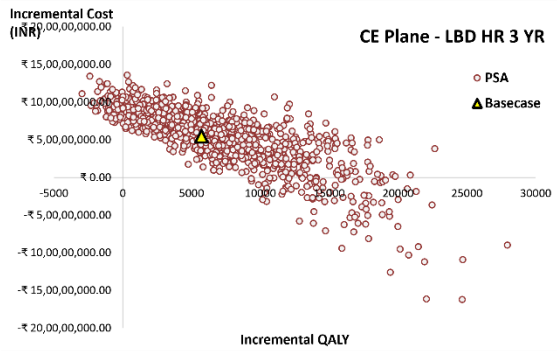


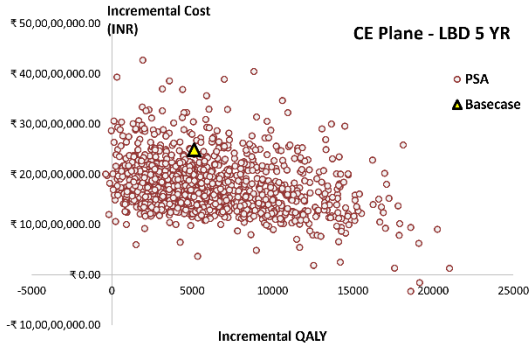


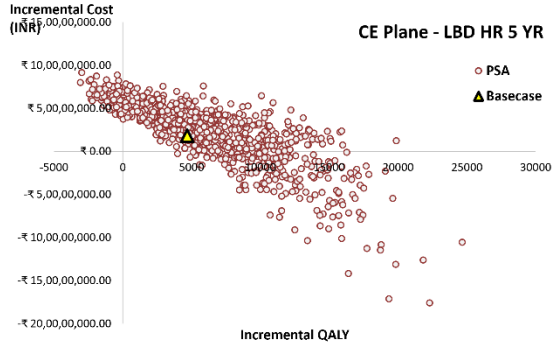


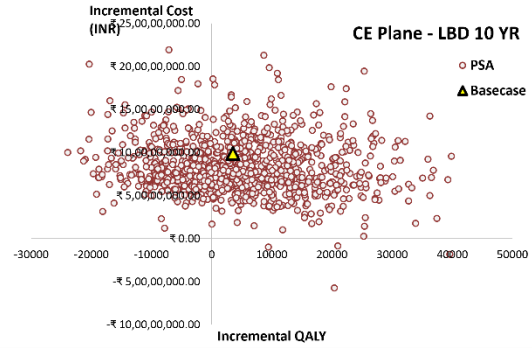
(D) CE Plane for LBD

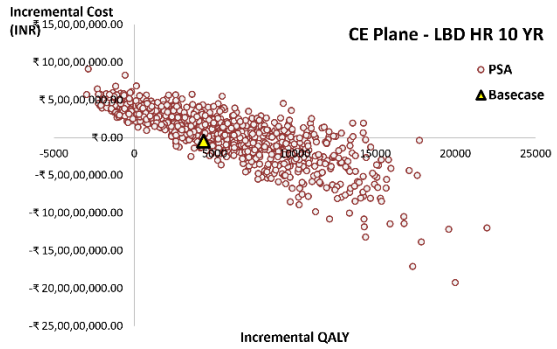








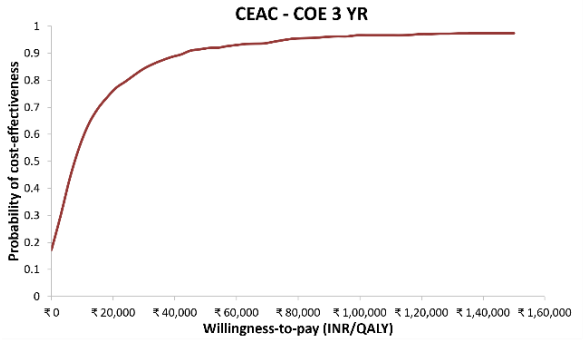


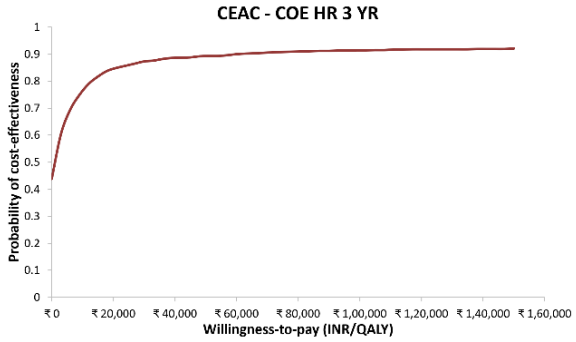


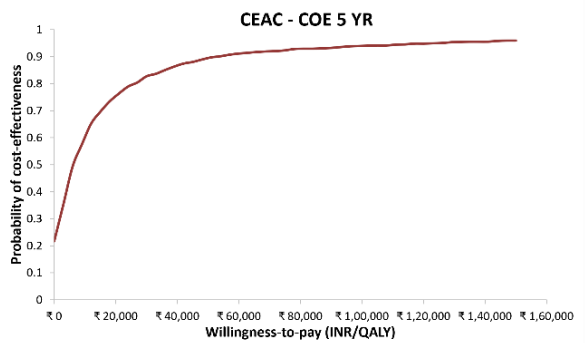
Cost-Effectiveness Acceptability Curve (CEAC) is plotted for each screening strategy with different WTP in INR/QALY on the X-axis and probability of cost-effectiveness on the Y-axis (Figure 3.4 (A-D). For different WTP, the probability of cost-effectiveness for 24 screening strategies is shown in Table 3.9. The probability of cost-effectiveness was higher for high-risk screening across various screening strategies and intervals compared to the mass screening. At different WTPs, high-risk screening had more than an 80% probability of being cost-effective. At the WTP of INR 1,50,000, the high-risk screening strategies (probability of being cost-effective), namely COE ten years (91.1%), TBS ten years (90.2%), COE five years (90.1%), and LBD ten years (90%) had 90% or higher probability of being cost-effective.

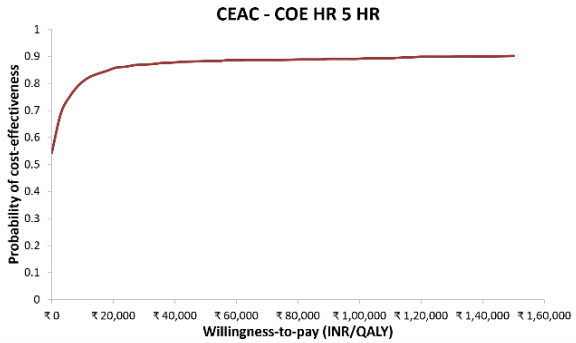
Figure 3. 4 (A-D) Cost-effective acceptability curve (CEAC) for COE, TBS, OC, and LBD

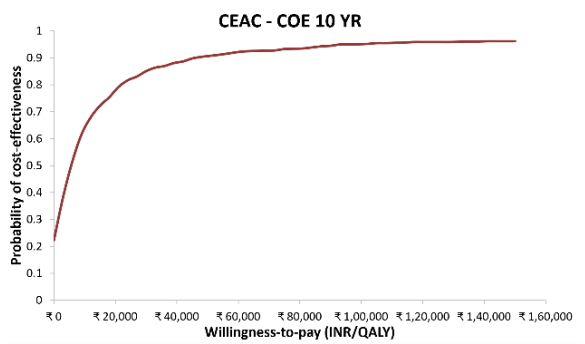
(A) CEAC for COE (mass-screening and high-risk strategy)

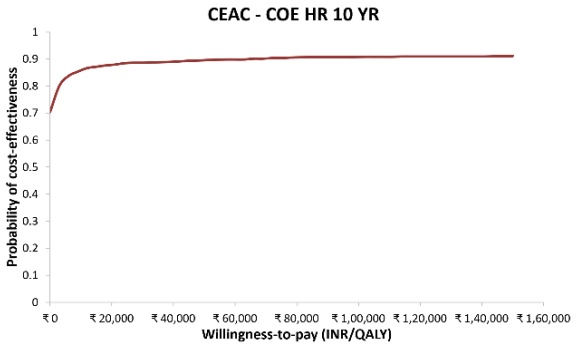




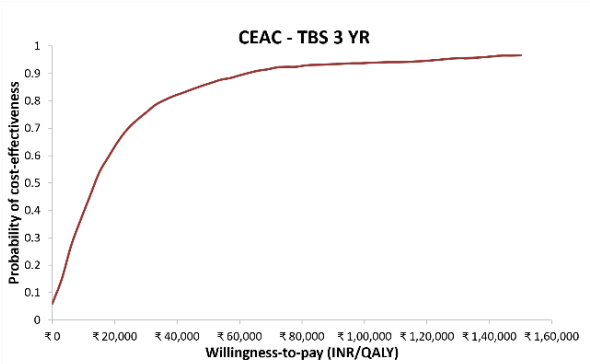


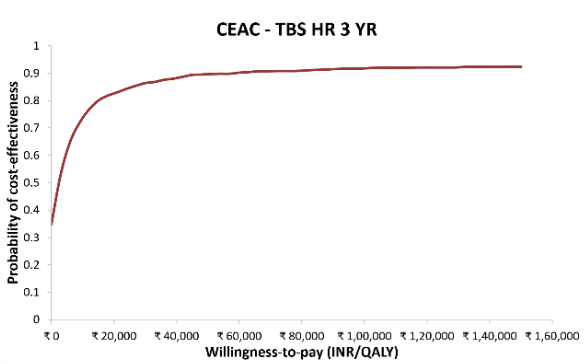


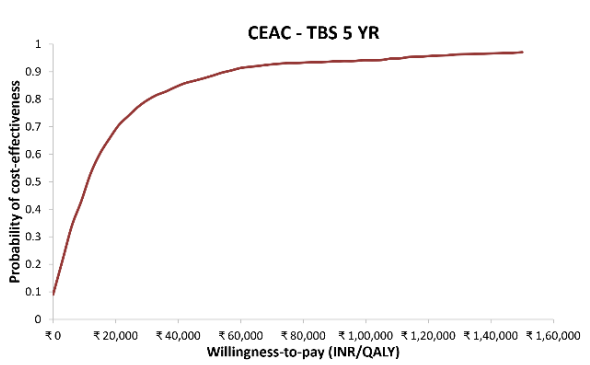


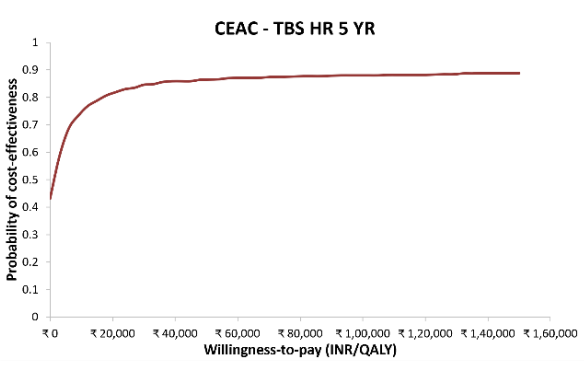


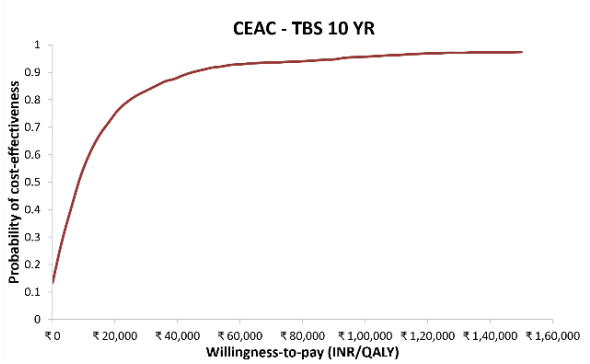
(B) CEAC for TBS (mass-screening and high-risk strategy)

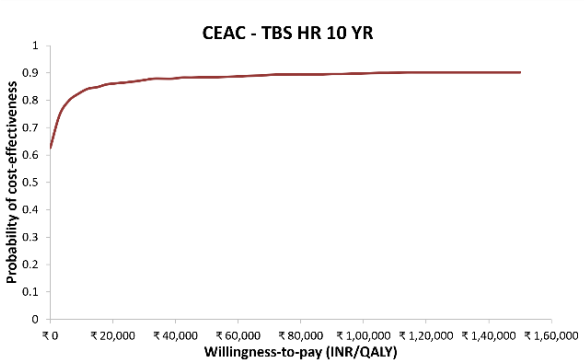




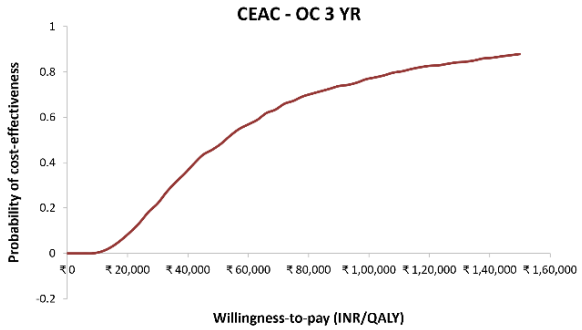


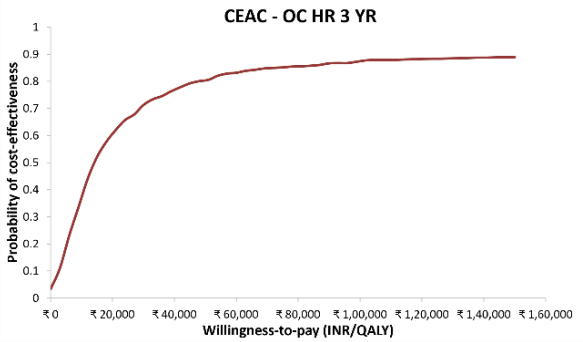


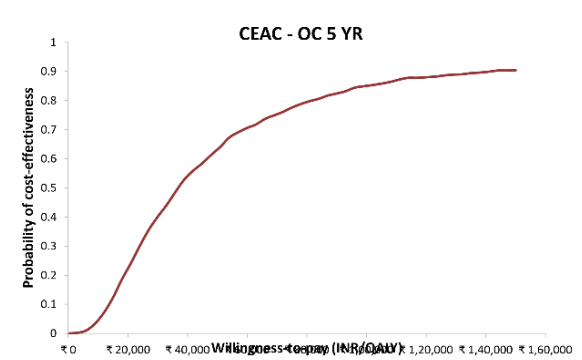


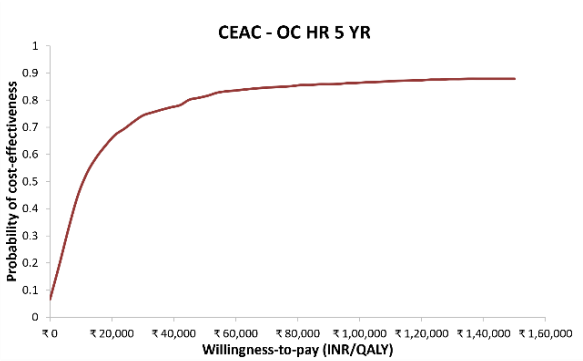


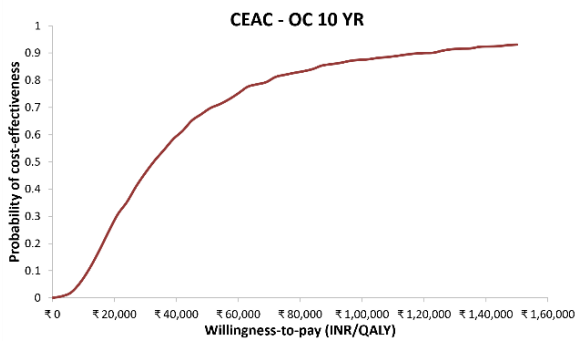
(C) CEAC for OC (mass-screening and high-risk strategy)

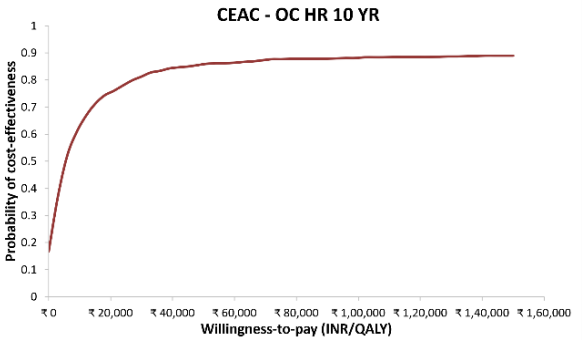




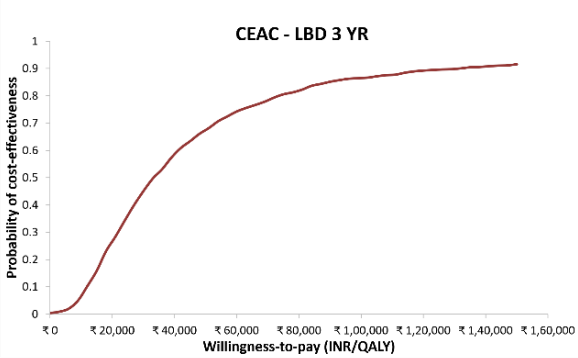


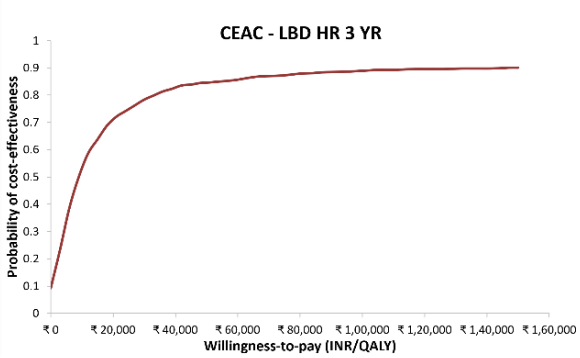


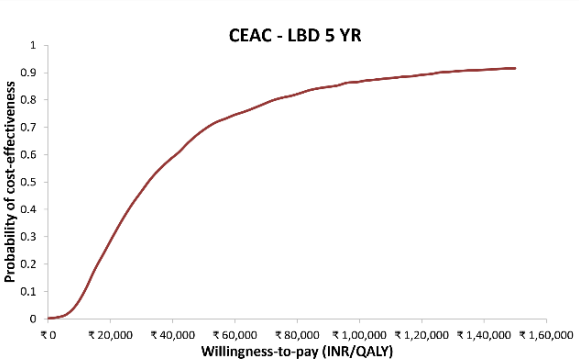


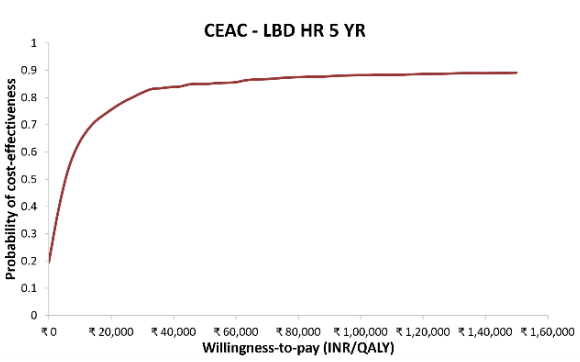


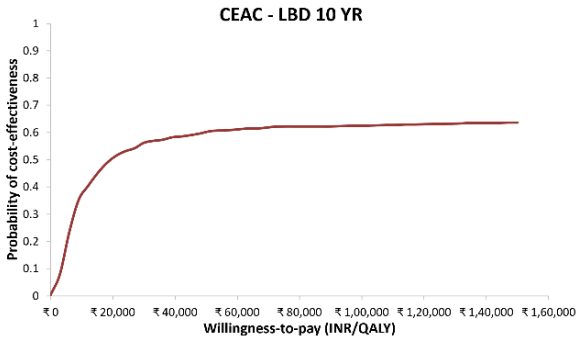
(D) CEAC for LBD (mass-screening and high-risk strategy)











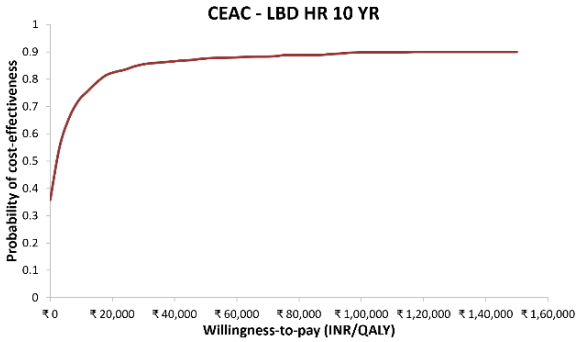


Table 3. 9 Probability of cost-effectiveness at different willingness-to-pay (WTP) for each screening scenario

WTP (in INR)		0	15000	30000	45000	60000	75000	90000	105000	120000	135000	150000
COE	Three years	0.172	0.694	0.843	0.909	0.93	0.948	0.961	0.966	0.971	0.973	0.974
	Three years HR	0.438	0.817	0.873	0.888	0.9	0.908	0.912	0.915	0.918	0.918	0.921
	Five years	0.217	0.696	0.827	0.88	0.911	0.923	0.932	0.941	0.948	0.955	0.959
	Five years HR	0.542	0.835	0.869	0.88	0.885	0.886	0.89	0.892	0.898	0.899	0.901
	Ten years	0.223	0.722	0.85	0.897	0.921	0.932	0.944	0.954	0.958	0.96	0.961
	Ten years HR	0.703	0.871	0.886	0.893	0.898	0.903	0.907	0.908	0.909	0.909	0.911
TBS	Three years	0.06	0.538	0.757	0.843	0.893	0.924	0.934	0.94	0.946	0.957	0.966
	Three years HR	0.348	0.8	0.864	0.894	0.902	0.908	0.915	0.92	0.921	0.923	0.924
	Five years	0.09	0.603	0.796	0.867	0.914	0.932	0.938	0.943	0.957	0.965	0.971
	Five years HR	0.431	0.788	0.846	0.859	0.871	0.875	0.879	0.88	0.882	0.887	0.888
	Ten years	0.133	0.671	0.833	0.901	0.929	0.938	0.947	0.96	0.969	0.973	0.974
	Ten years HR	0.626	0.848	0.874	0.883	0.887	0.894	0.896	0.9	0.902	0.902	0.902
OC	Three years	0	0.031	0.22	0.434	0.568	0.672	0.737	0.784	0.826	0.85	0.878
	Three years HR	0.033	0.521	0.713	0.793	0.832	0.852	0.867	0.879	0.883	0.887	0.89
	Five years	0	0.123	0.401	0.585	0.706	0.776	0.824	0.858	0.88	0.894	0.904
	Five years HR	0.066	0.59	0.744	0.802	0.836	0.85	0.859	0.867	0.874	0.879	0.879
	Ten years	0	0.172	0.46	0.652	0.752	0.82	0.859	0.882	0.9	0.917	0.931
	Ten years HR	0.167	0.712	0.813	0.85	0.864	0.877	0.879	0.884	0.885	0.888	0.89
LBD	Three years	0.004	0.159	0.451	0.634	0.743	0.806	0.852	0.872	0.893	0.905	0.916
	Three years HR	0.093	0.638	0.784	0.839	0.857	0.873	0.885	0.893	0.896	0.898	0.901
	Five years	0.002	0.18	0.466	0.644	0.746	0.808	0.848	0.874	0.892	0.908	0.916
	Five years HR	0.195	0.713	0.818	0.848	0.856	0.872	0.878	0.883	0.886	0.889	0.891
	Ten years	0.004	0.449	0.562	0.59	0.611	0.622	0.622	0.626	0.63	0.635	0.636
	Ten years HR	0.358	0.789	0.855	0.87	0.88	0.888	0.892	0.899	0.9	0.9	0.9

3.6.8 Budget Impact Analysis

The budget impact analysis showed that oral screening using COE for the high-risk population at ten years interval would cost Rs. 25,72,75,41,030.81 for the first year, which is 0.03% of the annual healthcare budget of India (86,200.65 crores). For the second-year implementation, it would cost Rs. 28,30,02,95,133.90, which is 0.03% of the annual healthcare budget of India (86,200.65 crores). Thus, the budget impact analysis indicates that the implementation of nationwide oral screening using conventional oral examination for high-risk population above 30 years of age at ten years interval would account for only 0.03% of the annual healthcare budget of India in the year 2022-2023.

3.7 Discussion

It was observed from the CE analysis that the high-risk screening strategy was cost-saving, cost-effective and averted a higher number of oral cancer deaths as compared to no –screening.

Our findings were similar to the cost-effectiveness study of oral cancer screening in India done by Subramanian et al. (5). However, our results differ from the study regarding oral cancer screening by trained health workers for the population aged over 40 years in the United States. The study concluded that the no-screen arm was dominant, indicating a poor value for money (6). However, the authors stated that the program would likely be cost-saving if changed to high-risk males over 40. Another study in Thailand by Kumdee et al. for oral cancer screening in the Thai population stated that the screening was not cost-effective (7). They stated that screening could be cost-effective only if: 1) the sensitivity and specificity of MSE are more than 60%, 2) the sensitivity and specificity of VETDN are greater than 90%, or 3) the low accuracy steps like MSE or VETDN are removed from the screening program. It could be because the age-standardised incidence rate (ASIR) of oral cancer in the Thai population was less than that in India, especially in males (3.9 VS 12.6 per 100,000). Another study by Speight et al. in the UK estimated that the ICER for the whole population (age 49–79 years) ranged from £15,790 to £25,961 per QALY. Hence, it was suggested that no screening was always the cheapest option, and opportunistic screening by general dental practitioners may be cost-effective (8). The results of this study differed from our study. Our study had four dominant screening strategies when compared to the no-screening arm.

The optimal use of resources currently available for critical healthcare expenditure is the need of the hour in a country like India. Thus, in our study, we estimated the burden (incident cases and oral cancer deaths averted), lifetime cost, and health outcomes (INR/QALY's gained) of oral cancer screening followed by diagnosis and treatment in either public or private settings. It will provide insight to the government and the patients regarding the expenditure on the screening and treatment of oral cancer in India.

Through our study, it was evident that screening significantly reduced the number of incident cases when compared to no screening. At intervals of five and ten years, the high-risk scenario observed fewer incident cases than the mass screening across various screening strategies. It implies that fewer oral cancer incident cases in high-risk screening scenarios will, in turn, decrease the requirement for resources in treatment and management, as well as the associated economic burden. It was also observed from our analysis that screening resulted in a lesser

number of oral cancer deaths when compared to no screening. A high-risk screening strategy was cost-effective as compared to mass screening across all strategies.

A previous study by Sankaranarayanan et al. in Kerala, India, has demonstrated that high-risk screening can potentially reduce oral cancer mortality (10). Our analysis revealed that the high-risk screening strategies were more cost-saving than mass screening. It implies that screening high-risk individuals will require fewer resources and human resources. Thus, optimal utilisation of resources would be possible in a cost-saving manner. The high-risk screening strategy dominated the no-screening arm with its four strategies: COE five and ten years, TBS ten years, and LBD ten years. Thus, screening high-risk individuals could be ideal for a resource-constrained country like ours. Prior published literature also suggests the target population should be a high-risk group (10). Programs like tobacco counselling camps could go hand in hand with combating the risk factor and screening the target population to reduce the associated morbidity and mortality.

The cost-effectiveness analysis revealed that COE screening was the most appropriate approach for high-risk individuals. The other commonly used techniques are TBS, OC and LBD. TBS screening strategy requires the application of toluidine blue dye or stain to the suspected mucosa and then visualisation to detect the suspected lesion (30). OC require the scrapping of cells from the oral mucosa with a brush, and cytology is prepared from the collected material and is seen by pathologists (31, 32). It implies that it requires specialists and is a technology-intensive strategy. LBD is done using commercially available equipment for illumination, like Velscope and ViziLite plus, to detect precancerous and cancerous lesions (30, 33). The cost and expertise required to use the device make it a less desirable option for mass screening. These strategies are resource-intensive and need evaluation by specialists. Hence, they are not widely used for screening in a developing country like India.

On the other hand, COE requires less training, equipment, and time resources, making it a desirable option for large-scale implementation in the developing world. It is easy to implement and requires less training of human resources, fewer resources, and minimal refresher training of human resources is required. The time and human resources thus spared can be utilised for other national programmes to combat other public health issues.

The current screening coverage in India is poor, as reported by the latest NFHS-5 survey data (28). Hence, we need to increase the participation of high-risk individuals to maximise the

benefits of screening in India. Screening is a long-term process that requires consistent effort and commitment from all health system stakeholders to attain the desirable outcomes.

Our study was the first of its kind for the Indian population. We estimated the lifetime cost and health outcomes of oral cancer screening, followed by diagnosis and treatment in either public or private settings. Secondly, our cost analysis captures the practical programmatic guidelines of the NPCDCS program. Thirdly, while estimating the cost of cancer treatment, the health system cost and OOP expenditure were estimated following standard costing methodologies. Lastly, we addressed parameter uncertainties in our results by performing sensitivity analysis.

Our study had some limitations. The values of transition probabilities were derived from international literature because of the scarcity of progression data for the Indian population. However, Thailand is closer to India regarding development and socio-economic status. In our study, we made assumptions and estimations based on previously published literature that could affect our study's outcomes. Likewise, in our study, we used reimbursement rates of CGHS for the estimation of various screening costs. However, we tried to address the uncertainty around these values by performing a sensitivity analysis in our study.

3.8 Conclusion

High-risk oral cancer screening of the population above 30 years of age at various screening intervals is cost-effective compared to the mass-screening strategy. Amongst various screening strategies, the most cost-saving was COE in high-risk individuals at an interval of ten years.

To reduce the associated burden, oral screening of high-risk populations should be considered in a resource-constrained country like India. High-risk screening using COE at ten years interval will yield maximum benefits and should be considered for oral screening in India.

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Conclusions & Policy Recommendations

1. Oral cancer is the second and third most cancer in India in terms of incidence and mortality affected patients. Hence, we need to incorporate a mode of secondary prevention into action. Early detection and treatment of precancerous lesions can reduce cancer-specific morbidity and mortality. The finding of our clinical-effectiveness study states that conventional oral examination by trained frontline health workers had high sensitivity and specificity for oral screening. The prevalence of oral cancer, PMD and the study site did not affect the high sensitivity and specificity. TBS, OC, and CLI screening techniques were not studied for mass screening by trained FHW. COE after training FHW could be considered for screening oral cancer and potentially malignant disorders, especially in low-middle income countries.
2. Our cost-effectiveness analysis showed that screening was always better than the no-screening approach in reducing the burden and its cost-effectiveness. Screening (mass/high-risk) leads to a reduction in incident cases and oral cancer deaths as compared to no-screening The high-risk screening approach was more cost-effective as compared to mass screening across various screening strategies and screening intervals. Hence, high-risk screening will reduce the requirement of resources for treating and managing oral cancer and the associated economic burden. Thus, screening high-risk populations could be considered in a resource-constrained country like India.
3. Our study also demonstrated that screening the high-risk group by COE was the most cost-effective approach compared to other techniques, namely TBS, OC and LBD. The screening at an interval of ten years had the highest probability of being cost-effective. High-risk screening using COE at ten years interval was the most cost saving strategy among all the screening strategies. Hence, high-risk screening using COE at ten years interval should be considered for oral screening in India.

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Annexure I

A. Search Strategy

1. Study selection criteria

1.1 Inclusion criteria:

- Language: Articles in any language.
- Year of publication: Studies published up to 31st December 2020.
- Data type: Primary research or secondary data analysis of the available data.
- Study design: Observational as well as experimental studies
- Study setting: Community based
- Study population: Apparently healthy individuals participating in mass screening
- Study intervention: Examination with Conventional Oral Examination, Toluidine blue staining, Oral cytology/ brush biopsy, and Chemiluminescent illumination conducted by Frontline health workers.
- Study comparator: examination and clinical evaluation by a physician with specialist knowledge or training, working to the current diagnostic guidelines or Histopathological confirmation.
- Outcomes: Sensitivity and Specificity
- In case of duplicate data or articles based on the same study population, the article providing the largest sample and most complete appropriate data will be included.

1.2 Exclusion criteria:

- Studies conducted among the patient population
- Study where screening was conducted by doctors, dentists, or experts
- Studies reporting duplicate data
- Studies that have not reported sensitivity and specificity
- Studies reported diagnostic accuracy of screening tests other than COE, TBS, OC, and CLI

2. Keywords used for PubMed search

Table 1 Keywords used for PubMed search

BLOCKS	
1	**Oral Cancer/ Premalignant disorders** 1. mouth neoplasms [MeSH Terms] OR "oral cavity cancer" [tw] OR "oral cavity carcinoma" [tw] 2. "oral squamous cell carcinoma" [tw] OR "oral cavity squamous cell carcinoma" [tw] 3. "Oral Precancerous conditions" [tw] OR "oral precancerous lesions" [tw] 4. "oral premalignant condition" [tw] 5. Leukoplakia, oral [MeSH Terms] OR erythroplasia [MeSH Terms] OR erythroplakia [tw] OR erythroleukoplakia [tw] OR "speckled leukoplakia" [tw] 6. oral submucous fibrosis [MeSH Terms] OR "oral submucosa fibrosis" [tw] 7. "actinic cheilitis" [tw] 8. lip neoplasms [MeSH Terms] OR "carcinoma lip" [tw] 9. tongue neoplasms [MeSH Terms] OR "carcinoma tongue" [tw] 10. gingival neoplasms [MeSH Terms] 11. palatal neoplasms [MeSH Terms] 12. salivary gland neoplasms [MeSH Terms] OR parotid neoplasms [MeSH Terms] OR sublingual gland neoplasms [MeSH Terms] OR submandibular gland neoplasms [MeSH Terms] 13. oropharyngeal neoplasms [MeSH Terms]
2	**Screening** 1. early detection of cancer [MeSH Terms] 2. mass screening [MeSH Terms] OR "community screening" [tw] OR "oral screening" [tw] OR "oral cancer screening" [tw] OR "screening for oral cancer" [tw] 3. "Mouth self-examination" [tw] OR "oral self-examination" [tw] OR "Conventional oral examination" [tw] 4. tolonium chloride [MeSH Terms] OR coloring agents [MeSH Terms] OR "Toluidine blue staining" [tw] OR "visual diagnostic tool" [tw] 5. luminescent measurements [MeSH Terms] OR luminescence [MeSH Terms] OR luminescent agents [MeSH Terms] OR "Chemiluminescent illumination" [tw] OR optical imaging [Mesh Terms] OR staining and labeling [Mesh Terms] OR acetic acid [Mesh Terms] OR "acetic acid wash" [tw] OR ViziLite [tw] 6. frozen sections [MeSH Terms] OR "Oral cytology" [tw] OR "brush biopsy" [tw] OR "Oral brush biopsy" [tw] OR "brush cytology" [tw] OR "conventional cytology" [tw] OR "liquid-based cytology" [tw] OR "oral brush cytology" [tw] OR "cytobrush technique" [tw] OR "punch biopsy" [tw]
3	**Diagnostic accuracy** 1. sensitivity and specificity [MeSH Terms] 2. predictive value of tests [MeSH Terms] 3. False negative reactions [MeSH Terms] 4. False positive reactions [MeSH Terms] 5. "true positive" [tw] OR "true positive rate" [tw] OR "false positive" [tw] OR "false positive rate" [tw] OR "true negative" [tw] OR "true negative rate" [tw] OR "false negative" [tw] OR "false negative rate" [tw] 6. "diagnostic accuracy" [tw] 7. Reproducibility of results [MeSH Terms] 8. Data Accuracy [MeSH Terms] 9. ROC curve [MeSH Terms]

3. Search results

Table 2 PubMed search results

Search Number	**Search query**	Results
1	mouth neoplasms[MeSH Terms]	70,185
2	“oral cavity cancer”	1,053
3	“oral cavity carcinoma”	168
4	“oral squamous cell carcinoma”	10,561
5	“oral cavity squamous cell carcinoma”	678
6	“Oral Precancerous conditions”	41
7	“oral precancerous lesions”	204
8	“oral premalignant condition”	4
9	Leukoplakia, oral[MeSH Terms]	3,742
10	erythroplasia[MeSH Terms]	471
11	erythroplakia	763
12	erythroleukoplakia	66
13	“speckled leukoplakia”	26
14	oral submucous fibrosis[MeSH Terms]	892
15	“oral submucosa fibrosis”	5
16	“actinic cheilitis”	339
17	lip neoplasms[MeSH Terms]	4,220
18	“carcinoma lip”	6

Search Number	**Search query**	Results
19	tongue neoplasms[MeSH Terms]	10,235
20	“carcinoma tongue”	39
21	gingival neoplasms[MeSH Terms]	2,396
22	palatal neoplasms[MeSH Terms]	3,013
23	salivary gland neoplasms[MeSH Terms]	17,686
24	parotid neoplasms[MeSH Terms]	8,878
25	sublingual gland neoplasms[MeSH Terms]	139
26	submandibular gland neoplasms[MeSH Terms]	1,165
27	oropharyngeal neoplasms[MeSH Terms]	8,709
28	((((((((((((((((((((((((mouth neoplasms[MeSH Terms]) OR (“oral cavity cancer”)) OR (“oral cavity carcinoma”)) OR (“oral squamous cell carcinoma”)) OR (“oral cavity squamous cell carcinoma”)) OR (“Oral Precancerous conditions”)) OR (“oral precancerous lesions”)) OR (“oral premalignant condition”)) OR (Leukoplakia, oral[MeSH Terms])) OR (erythroplasia[MeSH Terms])) OR (erythroplakia)) OR (erythroleukoplakia)) OR (“speckled leukoplakia”)) OR (oral submucous fibrosis[MeSH Terms])) OR (“oral submucosa fibrosis”)) OR (“actinic cheilitis”)) OR (lip neoplasms[MeSH Terms])) OR (“carcinoma lip”)) OR (tongue neoplasms[MeSH Terms])) OR (“carcinoma tongue”)) OR (gingival neoplasms[MeSH Terms])) OR (palatal neoplasms[MeSH Terms])) OR (salivary gland neoplasms[MeSH Terms])) OR (parotid neoplasms[MeSH Terms])) OR (sublingual gland neoplasms[MeSH Terms])) OR (submandibular gland neoplasms[MeSH Terms])) OR (oropharyngeal neoplasms[MeSH Terms])	81,051
29	early detection of cancer[MeSH Terms]	27,247
30	mass screening[MeSH Terms]	1,31,375
31	“community screening”	680

Search Number	**Search query**	Results
32	“oral screening”	138
33	“oral cancer screening”	317
34	“screening for oral cancer”	86
35	“Mouth self-examination”	16
36	“oral self-examination”	15
37	“Conventional oral examination”	47
38	tolonium chloride[MeSH Terms]	1,819
39	coloring agents[MeSH Terms]	1,25,795
40	“Toluidine blue staining”	1,186
41	“visual diagnostic tool”	3
42	luminescent measurements[MeSH Terms]	2,61,493
43	luminescence[MeSH Terms]	53,305
44	luminescent agents[MeSH Terms]	77,936
45	“Chemiluminescent illumination”	6
46	optical imaging[MeSH Terms]	50,282
47	staining and labeling[MeSH Terms]	1,80,048
48	acetic acid[MeSH Terms]	1,49,702
49	“acetic acid wash”	32
50	ViziLite	25
51	frozen sections[MeSH Terms]	4,964
52	“Oral cytology”	118

Search Number	**Search query**	Results
53	“brush biopsy”	344
54	“Oral brush biopsy”	53
55	“brush cytology”	780
56	“conventional cytology”	662
57	“liquid-based cytology”	1,644
58	“oral brush cytology”	14
59	“cytobrush technique”	54
60	“punch biopsy”	2,341
61	((((((((((((((((((((((((((((((early detection of cancer[MeSH Terms]) OR (mass screening[MeSH Terms])) OR (“community screening”)) OR (“oral screening”)) OR (“oral cancer screening”)) OR (“screening for oral cancer”)) OR (“Mouth self-examination”)) OR (“oral self-examination”)) OR (“Conventional oral examination”)) OR (tolonium chloride[MeSH Terms])) OR (coloring agents[MeSH Terms])) OR (“Toluidine blue staining”)) OR (“visual diagnostic tool”)) OR (luminescent measurements[MeSH Terms])) OR (luminescence[MeSH Terms])) OR (luminescent agents[MeSH Terms])) OR (“Chemiluminescent illumination”)) OR (optical imaging[MeSH Terms])) OR (staining and labeling[MeSH Terms])) OR (acetic acid[MeSH Terms])) OR (“acetic acid wash”)) OR (ViziLite)) OR (frozen sections[MeSH Terms])) OR (“Oral cytology”)) OR (“brush biopsy”)) OR (“Oral brush biopsy”)) OR (“brush cytology”)) OR (“conventional cytology”)) OR (“liquid-based cytology”)) OR (“oral brush cytology”)) OR (“cytobrush technique”)) OR (“punch biopsy”)	9,14,501
62	sensitivity and specificity[MeSH Terms]	5,99,299
63	predictive value of tests[MeSH Terms]	2,08,481
64	False negative reactions[MeSH Terms]	17,966

Search Number	**Search query**	Results
65	False positive reactions[MeSH Terms]	28,033
66	“true positive”	6,695
67	“true positive rate”	1,022
68	“false positive”	66,422
69	“false positive rate”	7,629
70	“true negative”	2,744
71	“true negative rate”	246
72	“false negative”	41,083
73	“false negative rate”	4,348
74	“diagnostic accuracy”	47,332
75	Reproducibility of results[MeSH Terms]	4,12,250
76	Data Accuracy[MeSH Terms]	2,979
77	ROC curve[MeSH Terms]	61,112
78	((((((((((((((sensitivity and specificity[MeSH Terms]) OR (predictive value of tests[MeSH Terms])) OR (False negative reactions[MeSH Terms])) OR (False positive reactions[MeSH Terms])) OR (“true positive”)) OR (“true positive rate”)) OR (“false positive”)) OR (“false positive rate”)) OR (“true negative”)) OR (“true negative rate”)) OR (“false negative”)) OR (“false negative rate”)) OR (“false negative rate”)) OR (“diagnostic accuracy”)) OR (Reproducibility of results[MeSH Terms])) OR (Data Accuracy[MeSH Terms])) OR (ROC curve[MeSH Terms])	9,54,425

Search Number	**Search query**	Results
79	((((((((((((((((((((((((((mouth neoplasms[MeSH Terms]) OR (“oral cavity cancer”)) OR (“oral cavity carcinoma”)) OR (“oral squamous cell carcinoma”)) OR (“oral cavity squamous cell carcinoma”)) OR (“Oral Precancerous conditions”)) OR (“oral precancerous lesions”)) OR (“oral premalignant condition”)) OR (Leukoplakia, oral[MeSH Terms])) OR (erythroplasia[MeSH Terms])) OR (erythroplakia)) OR (erythroleukoplakia)) OR (“speckled leukoplakia”)) OR (oral submucous fibrosis[MeSH Terms])) OR (“oral submucosa fibrosis”)) OR (“actinic cheilitis”)) OR (lip neoplasms[MeSH Terms])) OR (“carcinoma lip”)) OR (tongue neoplasms[MeSH Terms])) OR (“carcinoma tongue”)) OR (gingival neoplasms[MeSH Terms])) OR (palatal neoplasms[MeSH Terms])) OR (salivary gland neoplasms[MeSH Terms])) OR (parotid neoplasms[MeSH Terms])) OR (sublingual gland neoplasms[MeSH Terms])) OR (submandibular gland neoplasms[MeSH Terms])) OR (oropharyngeal neoplasms[MeSH Terms])) AND ((((((((((((((((((((((((((((((early detection of cancer[MeSH Terms]) OR (mass screening[MeSH Terms])) OR (“community screening”)) OR (“oral screening”)) OR (“oral cancer screening”)) OR (“screening for oral cancer”)) OR (“Mouth self-examination”)) OR (“oral self-examination”)) OR (“Conventional oral examination”)) OR (tolonium chloride[MeSH Terms])) OR (coloring agents[MeSH Terms])) OR (“Toluidine blue staining”)) OR (“visual diagnostic tool”)) OR (luminescent measurements[MeSH Terms])) OR (luminescence[MeSH Terms])) OR (luminescent agents[MeSH Terms])) OR (“Chemiluminescent illumination”)) OR (optical imaging[MeSH Terms])) OR (staining and labeling[MeSH Terms])) OR (acetic acid[MeSH Terms])) OR (“acetic acid wash”)) OR (ViziLite)) OR (frozen sections[MeSH Terms])) OR (“Oral cytology”)) OR (“brush biopsy”)) OR (“Oral brush biopsy”)) OR (“brush cytology”)) OR (“conventional cytology”)) OR (“liquid-based cytology”)) OR (“oral brush cytology”)) OR (“cytobrush technique”)) OR (“punch biopsy”))) AND ((((((((((((((((sensitivity and specificity[MeSH Terms]) OR (predictive value of tests[MeSH Terms])) OR (False negative reactions[MeSH Terms])) OR (False positive reactions[MeSH Terms])) OR (“true positive”)) OR (“true positive rate”)) OR (“false positive”)) OR (“false positive rate”)) OR (“true negative”)) OR (“true negative rate”))	680

Search Number	Search query	Results
	OR (“false negative”)) OR (“false negative rate”)) OR (“false negative rate”)) OR (“diagnostic accuracy”)) OR (Reproducibility of results[MeSH Terms])) OR (Data Accuracy[MeSH Terms])) OR (ROC curve[MeSH Terms]))	

4. Keywords used for Embase search

Table 3 Keywords used for Embase search with results

Blocks		
A	‘mouth cancer’/exp OR ‘precancer’/exp OR ‘leukoplakia’/exp OR ‘erythroplasia’/exp OR ‘lip carcinoma’/exp OR ‘tongue carcinoma’/exp OR ‘gingiva tumor’/exp OR ‘jaw tumor’/exp OR ‘salivary gland tumor’/exp OR ‘parotid gland cancer’/exp OR ‘oropharynx tumor’/exp	142416
B	‘cancer screening’/exp OR ‘early cancer diagnosis’/exp	88781
C	‘diagnostic accuracy’/exp OR (‘sensitivity’/exp AND ‘specificity’/exp) OR ‘predictive value’/exp OR ‘validity’/exp OR ‘data accuracy’/exp	557920
	A AND B AND C	388

5. Keywords used for Scopus search

Table 4 Keywords used for Scopus search with results

Search query	**Results**
((TITLE-ABS-KEY (“mouth cancer”)) OR (TITLE-ABS-KEY (“precancer”)) OR (TITLE-ABS-KEY (leukoplakia)) OR (TITLE-ABS-KEY (erythroplasia)) OR (TITLE-ABS-KEY (“lip carcinoma”)) OR (TITLE-ABS-KEY (“tongue carcinoma”)) OR (TITLE-ABS-KEY (“gingiva tumor”)) OR (TITLE-ABS-KEY (“jaw tumor”)) OR (TITLE-ABS-KEY (“salivary gland tumor”)) OR (TITLE-ABS-KEY ("parotid gland cancer")) OR (TITLE-ABS-KEY ("oropharynx tumor"))) AND ((TITLE-ABS-KEY (“Cancer Screening”)) OR (TITLE-ABS-KEY (“early detection”)) OR (TITLE-ABS-KEY (“early cancer diagnosis”))) AND ((TITLE-ABS-KEY (“diagnostic accuracy”)) OR (TITLE-ABS-KEY (sensitivity)) OR (TITLE-ABS-KEY (specificity)) OR (TITLE-ABS-KEY (“predictive value”)) OR (TITLE-ABS-KEY (validity)) OR (TITLE-ABS-KEY (“Data Accuracy”))) AND (EXCLUDE (PUBYEAR, 2021))	1179

6. Keywords used for Cochrane Library search

Table 5 Keywords used for Cochrane Library search with results

BLOCKS		
1	**Oral Cancer/ Premalignant disorders** mouth neoplasms [MeSH Terms] OR "oral squamous cell carcinoma" [tw] OR "Oral Precancerous conditions" [tw] OR Leukoplakia, oral [MeSH Terms] OR erythroplasia [MeSH Terms] OR oral submucous fibrosis [MeSH Terms] OR lip neoplasms [MeSH Terms] OR tongue neoplasms [MeSH Terms] OR gingival neoplasms [MeSH Terms] OR palatal neoplasms [MeSH Terms] OR salivary gland neoplasms [MeSH Terms] OR parotid neoplasms [MeSH Terms] OR submandibular gland neoplasms [MeSH Terms] OR oropharyngeal neoplasms [MeSH Terms]	920
2	**Screening** early detection of cancer [MeSH Terms] OR mass screening [MeSH Terms] OR "Conventional oral examination" [tw] OR tolonium chloride [MeSH Terms] OR coloring agents [MeSH Terms] OR luminescent measurements [MeSH Terms] OR luminescence [MeSH Terms] OR luminescent agents [MeSH Terms] OR optical imaging [Mesh Terms] OR staining and labeling [Mesh Terms] OR acetic acid [Mesh Terms] OR frozen sections [MeSH Terms] OR "Oral cytology" [tw] OR "brush biopsy" [tw] OR "brush cytology" [tw] OR "punch biopsy" [tw]	9890
3	**Diagnostic accuracy** sensitivity and specificity [MeSH Terms] OR predictive value of tests [MeSH Terms] OR False negative reactions [MeSH Terms] OR False positive reactions [MeSH Terms] OR "diagnostic accuracy" [tw] OR Reproducibility of results [MeSH Terms] OR Data Accuracy [MeSH Terms] OR ROC curve [MeSH Terms]	26241
	#1 AND #2 AND #3 Cochrane reviews – 3 & Trials — 16	19

7. Keywords used for Google Scholar search

Table 6 Keywords used for Google Scholar search with result

allintitle: (((Oral cancer) OR (premalignant)) AND ((screening) OR (early detection)))	140

B. Articles excluded from the review

Table 7 Reason for exclusion – studies conducted among the patient population

S. No	Authors	Title	Year	Journal
1	Kujan et al.	Efficacy of oral brush cytology cell block immunocytochemistry in the diagnosis of oral leukoplakia and oral squamous cell carcinoma.	2020	Journal of oral pathology & medicine
2	Velleuer et al.	Diagnostic accuracy of brush biopsy-based cytology for the early detection of oral cancer and precursors in Fanconi anemia.	2020	Cancer cytopathology
3	Hosmani et al.	Comparison of the Efficacy of Sediment Cytology over Oral Brush Cytology in Oral Leukoplakia.	2020	Acta cytologica
4	Morikawa et al.	Image processing analysis of oral cancer, oral potentially malignant disorders, and other oral diseases using optical instruments.	2020	International journal of oral and maxillofacial surgery
5	Shi et al.	Potential role of autofluorescence imaging in determining biopsy of oral potentially malignant disorders: A large prospective diagnostic study.	2019	Oral oncology
6	Kujan et al.	CDK4, CDK6, cyclin D1 and Notch1 immunocytochemical expression of oral brush liquid-based cytology for the diagnosis of oral leukoplakia and oral cancer.	2019	Journal of oral pathology & medicine
7	Sadullahoğlu et al. et al.	The risk of malignancy according to Milan reporting system of salivary gland fine-needle aspiration with Becton Dickinson SurePath liquid-based processing.	2019	Diagnostic cytopathology
8	Osaka et al.	Evaluation of Liquid Based Cytology for Tongue Squamous Cell Carcinoma: Comparison with Conventional Cytology.	2019	The Bulletin of Tokyo Dental College

S. No	Authors	Title	Year	Journal
9	Saini et al.	Efficacy of Fluorescence Technology vs Conventional Oral Examination for the Early Detection of Oral Pre-Malignant Lesions. A Clinical Comparative Study.	2019	Endocrine, metabolic & immune disorders drug targets
10	Chiang et al.	Comparative evaluation of autofluorescence imaging and histopathological investigation for oral potentially malignant disorders in Taiwan.	2019	Clinical oral investigations
11	Alsarraf et al.	Liquid-based oral brush cytology in the diagnosis of oral leukoplakia using a modified Bethesda Cytology system.	2018	Journal of oral pathology & medicine
12	Yamamoto et al.	Detection accuracy for epithelial dysplasia using an objective autofluorescence visualisation method based on the luminance ratio.	2017	International journal of oral science
13	Ganga et al.	Evaluation of the diagnostic efficacy and spectrum of autofluorescence of benign, dysplastic and malignant lesions of the oral cavity using VELscope.	2017	Oral oncology
14	Amirchaghmaghi et al.	The diagnostic value of the native fluorescence visualisation device for early detection of premalignant/malignant lesions of the oral cavity.	2018	Photodiagnosis and photodynamic therapy
15	Goodson et al.	Efficacy of oral brush biopsy in potentially malignant disorder management.	2017	Journal of oral pathology & medicine
16	Yan et al.	Portable LED-induced autofluorescence spectroscopy for oral cancer diagnosis.	2017	Journal of biomedical optics
17	Sekine et al.	Diagnostic accuracy of oral cancer cytology in a pilot study.	2017	Diagnostic pathology
18	Jajodia et al.	Brush Cytology and AgNOR in the Diagnosis of Oral Squamous Cell Carcinoma.	2017	Acta cytologica
19	Lalla et al.	Assessment of oral mucosal lesions with autofluorescence imaging and reflectance spectroscopy.	2016	Journal of the American Dental Association (1939)
20	Kaur et al.	Evaluation of brush cytology and DNA image cytometry for the detection of cancer of the oral cavity.	2016	Diagnostic cytopathology
21	Moro et al.	The GOCCLESÂ® medical device is effective in detecting oral cancer and dysplasia in dental clinical setting. Results from a multicentre clinical trial.	2015	Acta otorhinolaryngologica Italica
22	Nanayakkara et al.	Comparison of spatula and cytobrush cytological techniques in early detection of oral malignant and premalignant lesions: a prospective and blinded study.	2016	Journal of oral pathology & medicine

S. No	Authors	Title	Year	Journal
23	Chainani-Wu et al.	Toluidine blue aids in detection of dysplasia and carcinoma in suspicious oral lesions.	2015	Oral diseases
24	Awan et al.	Assessing the accuracy of autofluorescence, chemiluminescence and toluidine blue as diagnostic tools for oral potentially malignant disorders—a clinicopathological evaluation.	2015	Clinical oral investigations
25	Sahebjamee et al.	Conventional versus Papanicolaou-stained cytobrush biopsy in the diagnosis of oral squamous cell carcinoma.	2014	Oral health and dental management
26	Petruzzi et al.	Evaluation of autofluorescence and toluidine blue in the differentiation of oral dysplastic and neoplastic lesions from non-dysplastic and neoplastic lesions: a cross-sectional study.	2014	Journal of biomedical optics
27	Hanken et al.	The detection of oral pre- malignant lesions with an autofluorescence based imaging system (VELscope™) — a single blinded clinical evaluation.	2013	Head & face medicine
28	Junaid et al.	Toluidine blue: yet another low-cost method for screening oral cavity tumour margins in third world countries.	2013	JPMA. The Journal of the Pakistan Medical Association
29	Kolokythas et al.	A prototype tobacco-associated oral squamous cell carcinoma classifier using RNA from brush cytology.	2013	Journal of oral pathology & medicine
30	Kämmerer et al.	Prospective, blinded comparison of cytology and DNA-image cytometry of brush biopsies for early detection of oral malignancy.	2013	Oral oncology
31	Rana et al.	Clinical evaluation of an autofluorescence diagnostic device for oral cancer detection: a prospective randomised diagnostic study.	2012	European journal of cancer prevention
32	Marzouki et al.	Use of fluorescent light in detecting malignant and premalignant lesions in the oral cavity: a prospective, single-blind study.	2012	Journal of otolaryngology - head & neck surgery
33	Afrogheh et al.	An evaluation of the Shandon Papspin liquid-based oral test using a novel cytologic scoring system.	2012	Oral surgery, oral medicine, oral pathology and oral radiology
34	Awan et al.	Utility of toluidine blue as a diagnostic adjunct in the detection of potentially malignant disorders of the oral cavity—a clinical and histological assessment.	2012	Oral diseases
35	Junaid et al.	A comparative analysis of toluidine blue with frozen section in oral squamous cell carcinoma.	2012	World journal of surgical oncology
36	Mojsa et al.	Value of the ViziLite Plus System as a diagnostic aid in the early detection of oral cancer/premalignant epithelial lesions.	2012	The Journal of craniofacial surgery

S. No	Authors	Title	Year	Journal
37	Jeng et al.	Novel quantitative analysis using optical imaging (Velscope) and spectroscopy (raman) techniques for oral cancer detection	2020	Cancers
38	Morikawa et al.	Non-invasive early detection of oral cancers using fluorescence visualisation with optical instruments	2020	Cancers
39	Jabbar et al.	The diagnostic efficacy of visually enhanced lesion scope (Velscope) in identifying benign, dysplastic and cancerous oral lesions	2020	Indian J. Forensic Med. Toxicol.
40	Leuci et al.	May velscope be deemed an opportunistic oral cancer screening by general dentists? A pilot study	2020	J. Clin. Med.
41	Rahman et al.	A study to evaluate the efficacy of toluidine blue and cytology in detecting oral cancer and dysplastic lesions.	2012	Quintessence international (Berlin, Germany : 1985)
42	Farah et al.	Efficacy of tissue autofluorescence imaging (VELScope) in the visualisation of oral mucosal lesions.	2012	Head & neck
43	Sweeny et al.	Assessment of tissue autofluorescence and reflectance for oral cavity cancer screening.	2011	Otolaryngology head and neck surgery
44	Matsumoto K	Detection of potentially malignant and malignant lesions of oral cavity using autofluorescence visualisation device.	2011	Kokubyo Gakkai zasshi. The Journal of the Stomatological Society, Japan
45	Pérez-Sayáns et al.	Non-computer-assisted liquid-based cytology for diagnosis of oral squamous cell carcinoma.	2012	Biotechnic & histochemistry
46	Paderni et al.	Direct visualisation of oral-cavity tissue fluorescence as novel aid for early oral cancer diagnosis and potentially malignant disorders monitoring.	2011	International journal of immunopathology and pharmacology
47	Cancela-Rodríguez et al.	The use of toluidine blue in the detection of pre-malignant and malignant oral lesions.	2011	Journal of oral pathology & medicine
48	Awan et al.	Evaluation of an autofluorescence based imaging system (VELscopeâ" ¢) in the detection of oral potentially malignant disorders and benign keratoses.	2011	Oral oncology
49	Scheer et al.	Autofluorescence imaging of potentially malignant mucosa lesions.	2011	Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics
50	Upadhyay et al.	Reliability of toluidine blue vital staining in detection of potentially malignant oral lesions —time to reconsider.	2011	Asian Pacific journal of cancer prevention : APJCP
51	Güneri et al.	The utility of toluidine blue staining and brush cytology as adjuncts in clinical examination of suspicious oral mucosal lesions.	2011	International journal of oral and maxillofacial surgery

S. No	Authors	Title	Year	Journal
52	Moro et al.	Autofluorescence and early detection of mucosal lesions in patients at risk for oral cancer.	2010	The Journal of craniofacial surgery
53	Morikawa et al.	The utility of optical instrument “ORALOOK®” in the early detection of high-risk oral mucosal lesions	2019	Anticancer Res.
54	Delavarian et al.	Evaluation of the diagnostic value of a Modified Liquid-Based Cytology using OralCDx Brush in early detection of oral potentially malignant lesions and oral cancer.	2010	Medicina oral, patologia oral y cirugia bucal
55	Koch et al.	Effectiveness of autofluorescence to identify suspicious oral lesions—a prospective, blinded clinical trial.	2011	Clinical oral investigations
56	Koch et al.	Diagnostic efficiency of differentiating small cancerous and precancerous lesions using mucosal brush smears of the oral cavity—a prospective and blinded study.	2011	Clinical oral investigations
57	Nagaraju et al.	Diagnostic efficiency of toluidine blue with Lugol’s iodine in oral premalignant and malignant lesions.	2010	Indian journal of dental research
58	Mehrotra et al.	A cross-sectional study evaluating chemiluminescence and autofluorescence in the detection of clinically innocuous precancerous and cancerous oral lesions.	2010	Journal of the American Dental Association (1939)
59	Jayaprakash et al.	Autofluorescence-guided surveillance for oral cancer.	2009	Cancer prevention research (Philadelphia, Pa.)
60	McIntosh et al.	The assessment of diffused light illumination and acetic acid rinse (Microlux/DL) in the visualisation of oral mucosal lesions.	2009	Oral oncology
61	Allegra et al.	The usefulness of toluidine staining as a diagnostic tool for precancerous and cancerous oropharyngeal and oral cavity lesions.	2009	Acta otorhinolaryngologica Italica : organo ufficiale della Societa italiana di otorinolaringologia e chirurgia cervico-facciale
62	Bhoopathi et al.	Low positive predictive value of the oral brush biopsy in detecting dysplastic oral lesions.	2009	Cancer
63	Navone R	Cytology of the oral cavity: a re-evaluation.	2009	Pathologica
64	Adil et al.	Comparative study on the efficacy of Tissue Autofluorescence (Visually Enhanced Lesion Scope) and Toluidine Blue as a screening method in oral potentially malignant and malignant lesions	2017	J. Med. Sci.

S. No	Authors	Title	Year	Journal
65	Mehrotra et al.	The use of an oral brush biopsy without computer-assisted analysis in the evaluation of oral lesions: a study of 94 patients.	2008	Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics
66	Bhalang et al.	The application of acetic acid in the detection of oral squamous cell carcinoma.	2008	Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics
67	Mallia et al.	Laser-induced autofluorescence spectral ratio reference standard for early discrimination of oral cancer.	2008	Cancer
68	Driemel et al.	Performance of conventional oral brush biopsies.	2008	HNO
69	Navone et al.	The impact of liquid-based oral cytology on the diagnosis of oral squamous dysplasia and carcinoma.	2007	Cytopathology
70	Epstein et al.	Analysis of oral lesion biopsies identified and evaluated by visual examination, chemiluminescence and toluidine blue.	2008	Oral oncology
71	Remmerbach et al.	Minimally invasive brush-biopsy: innovative method for early diagnosis of oral squamous cell carcinoma.	2007	Schweizer Monatsschrift fur Zahnmedizin
72	Lane et al.	Simple device for the direct visualisation of oral-cavity tissue fluorescence.	2006	Journal of biomedical optics
73	Chang et al.	Topical application of photofrin for photodynamic diagnosis of oral neoplasms.	2005	Plastic and reconstructive surgery
74	Hayama et al.	Liquid-based preparations versus conventional cytology: specimen adequacy and diagnostic agreement in oral lesions.	2005	Medicina oral, patologia oral y cirugia bucal
75	Poate et al.	An audit of the efficacy of the oral brush biopsy technique in a specialist Oral Medicine unit.	2004	Oral oncology
76	Maraki et al.	Cytologic and DNA-cytometric very early diagnosis of oral cancer.	2004	Journal of oral pathology & medicine
77	Zheng et al.	The use of digitised endoscopic imaging of 5-ALA-induced PPIX fluorescence to detect and diagnose oral premalignant and malignant lesions in vivo.	2004	International journal of cancer
78	Navone et al.	[Usefulness of oral exfoliative cytology for the diagnosis of oral squamous dysplasia and carcinoma].	2004	Minerva stomatologica
79	Svistun et al.	Vision enhancement system for detection of oral cavity neoplasia based on autofluorescence.	2004	Head & neck

S. No	Authors	Title	Year	Journal
80	Epstein et al.	The utility of tolonium chloride rinse in the diagnosis of recurrent or second primary cancers in patients with prior upper aerodigestive tract cancer.	2003	Head & neck
81	Betz et al.	A comparative study of normal inspection, autofluorescence and 5-ALA-induced PPIX fluorescence for oral cancer diagnosis.	2002	International journal of cancer
82	Onofre et al.	Reliability of toluidine blue application in the detection of oral epithelial dysplasia and in situ and invasive squamous cell carcinomas.	2001	Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics
83	Leunig et al.	Detection of squamous cell carcinoma of the oral cavity by imaging 5-aminolevulinic acid-induced protoporphyrin IX fluorescence.	2000	The Laryngoscope
84	Zenk et al.	[Visualising carcinomas of the mouth cavity by stimulating synthesis of fluorescent protoporphyrin IX].	1999	Mund-, Kiefer- und Gesichtschirurgie : MKG
85	Wang et al.	Diagnosis of oral cancer by light-induced autofluorescence spectroscopy using double excitation wavelengths.	1999	Oral oncology
86	Betz et al.	Autofluorescence imaging and spectroscopy of normal and malignant mucosa in patients with head and neck cancer.	1999	Lasers in surgery and medicine
87	Martin et al.	The application of toluidine blue as a diagnostic adjunct in the detection of epithelial dysplasia.	1998	Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics
88	Kulapaditharom et al.	Laser-induced fluorescence imaging in localisation of head and neck cancers.	1998	The Annals of otology, rhinology, and laryngology
89	Epstein et al.	The utility of toluidine blue application as a diagnostic aid in patients previously treated for upper oropharyngeal carcinoma.	1997	Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics
90	Ingrams et al.	Autofluorescence characteristics of oral mucosa.	1997	Head & neck
91	Warnakulasuriya et al.	Sensitivity and specificity of OraScan toluidine blue mouthrinse in the detection of oral cancer and precancer.	1996	Journal of oral pathology & medicine
92	Amorin et al.	[White lesions of the oral mucosa. Auxiliary diagnostic methods].	1990	Anales de la Facultad de Odontologia
93	Mashberg et al.	Screening for oral and oropharyngeal squamous carcinomas.	1984	CA: a cancer journal for clinicians
94	Mashberg A	Reevaluation of toluidine blue application as a diagnostic adjunct in the detection of asymptomatic oral squamous carcinoma: a continuing prospective study of oral cancer III.	1980	Cancer

S. No	Authors	Title	Year	Journal
95	Reddy et al.	Correlative study of exfoliative cytology and histopathology of oral carcinomas.	1975	Journal of oral surgery (American Dental Association : 1965)
96	Vahidy et al.	Toludine blue test for detection of carcinoma of the oral cavity: an evaluation.	1972	Journal of surgical oncology
97	Dabelsteen et al.	The limitations of exfoliative cytology for the detection of epithelial atypia in oral leukoplakias.	1971	British journal of cancer
98	Kameyama et al.	Clinico statistical observation of squamous cell cancer in oral cavity for past 10 years (1973-1982) and a trial for early detection of oral cancer	1988	Japanese Journal of Oral and Maxillofacial Surgery
99	Deuerling et al.	Evaluation of the accuracy of liquid-based oral brush cytology in screening for oral squamous cell carcinoma	2019	Cancers
100	Jain et al.	Role of Chemiluminescence examination as non-invasive diagnostic tool in early detection of Leukoplakia	2018	Journal of Oral Biology and Craniofacial Research
101	Chaudhry et al.	Comparison of chemiluminescence and toluidine blue in the diagnosis of dysplasia in leukoplakia: a cross-sectional study	2016	Journal of investigative and clinical dentistry
102	Casparis et al.	Transepithelial brush biopsy - Oral CDxÂ® - A noninvasive method for the early detection of precancerous and cancerous lesions	2014	Journal of Clinical and Diagnostic Research
103	Gupta et al.	Clinical correlative study on early detection of oral cancer and precancerous lesions by modified oral brush biopsy and cytology followed by histopathology	2014	Journal of Cancer Research and Therapeutics
104	Ujaoney et al.	Evaluation of chemiluminescence, toluidine blue and histopathology for detection of high-risk oral precancerous lesions: A cross-sectional study	2012	BMC Clinical Pathology
105	Seijas-Naya et al.	Applications of OralCDx Â® methodology in the diagnosis of oral leukoplakia	2012	Medicina Oral, Patologia Oral y Cirugia Bucal
106	Sharma et al.	Non -invasive diagnostic tools in early detection of oral epithelial dysplasia	2011	Journal of Clinical and Experimental Dentistry
107	Gupta et al.	Utility of toluidine blue staining and brush biopsy in precancerous and cancerous oral lesions	2007	Acta Cytologica
108	Field et al.	Oral mucosal screening as an integral part of routine dental care.	1995	British dental journal

Table 8 Reason for exclusion – other

S. No	Authors	Title	Year	Journal	Reason for exclusion
1	Huang et al.	Two-channel autofluorescence analysis for oral cancer.	2018	Journal of biomedical optics	Study population with multiple sub-groups
2	Yang et al.	In Vivo Multimodal Optical Imaging: Improved Detection of Oral Dysplasia in Low-Risk Oral Mucosal Lesions.	2018	Cancer prevention research (Philadelphia, Pa.)	Study population with multiple sub-groups
3	Olms et al.	Clinical comparison of liquid-based and conventional cytology of oral brush biopsies: a randomised controlled trial.	2018	Head & face medicine	wrong outcome
4	Cânjău et al.	Fluorescence influence on screening decisions for oral malignant lesions.	2018	Romanian journal of morphology and embryology	Study population with multiple sub-groups
5	Pandey et al.	Oral Brush Liquid-Based Cytology: A Study of Concordance between a Cytotechnologist and a Cytopathologist.	2018	Acta cytologica	Agreement was assessed, not validation
6	Sharbatdaran et al.	Assessment of oral cytological features in smokers and nonsmokers after application of toluidine blue.	2017	Diagnostic cytopathology	wrong outcome
7	Remmerbach et al.	Liquid-based versus conventional cytology of oral brush biopsies: a split-sample pilot study.	2017	Clinical oral investigations	Agreement was assessed, not validation
8	Brands et al.	The prognostic value of GLUT-1 staining in the detection of malignant transformation in oral mucosa.	2017	Clinical oral investigations	Study population with multiple sub-groups
9	Liu et al.	Quantitative risk stratification of oral leukoplakia with exfoliative cytology.	2015	PloS one	Study population with multiple sub-groups
10	Higgins et al.	Design and characterisation of a handheld multimodal imaging device for the assessment of oral epithelial lesions.	2014	Journal of biomedical optics	wrong outcome
11	Gonzalez et al.	Exfoliative cytology as a tool for monitoring pre-malignant and malignant lesions based on combined stains and morphometry techniques.	2015	Journal of oral pathology & medicine	Study population with multiple sub-groups
12	Monteiro et al.	Outcomes of invitational and opportunistic oral cancer screening initiatives in Oporto, Portugal.	2015	Journal of oral pathology & medicine	Screened by Dental students, Values not given clearly
13	Francisco et al.	Fluorescence spectroscopy for the detection of potentially malignant disorders and squamous cell carcinoma of the oral cavity.	2014	Photodiagnosis and photodynamic therapy	Study population with multiple sub-groups

S. No	Authors	Title	Year	Journal	Reason for exclusion
14	Klatt et al.	Fractal dimension of time-resolved autofluorescence discriminates tumour from healthy tissues in the oral cavity.	2014	Journal of cranio-maxillo-facial surgery	Study population with multiple sub-groups
15	Chaudhari et al.	Comparison of different screening methods in estimating the prevalence of precancer and cancer amongst male inmates of a jail in Maharashtra, India.	2013	Asian Pacific journal of cancer prevention : APJCP	Screened by an expert
16	Bhoopathi et al.	Utility of oral cancer diagnostic adjuncts in the adult US populations.	2013	Journal of oral pathology & medicine	Secondary data analysis
17	Ebenezar et al.	Noninvasive fluorescence excitation spectroscopy for the diagnosis of oral neoplasia in vivo.	2012	Journal of biomedical optics	Study population with multiple sub-groups
18	Macaulay et al.	High throughput image cytometry for detection of suspicious lesions in the oral cavity.	2012	Journal of biomedical optics	Study population with multiple sub-groups
19	Qaiser et al.	Novel use of fluorescein dye in detection of oral dysplasia and oral cancer	2020	Photodiagn. Photodyn. Ther.	Study population with multiple sub-groups
20	Sartori et al.	Accuracy of screening for potentially malignant disorders of the oral mucosa by dentists in primary care.	2012	Oral health & preventive dentistry	Screened by general dental practitioner
21	Awan et al.	Utility of chemiluminescence (ViziLiteâ" ¢) in the detection of oral potentially malignant disorders and benign keratoses.	2011	Journal of oral pathology & medicine	Study population with multiple sub-groups
22	Balevi B	Assessing the usefulness of three adjunctive diagnostic devices for oral cancer screening: a probabilistic approach.	2011	Community dentistry and oral epidemiology	Secondary data analysis
23	Scott et al.	Pilot study to estimate the accuracy of mouth self-examination in an at-risk group.	2010	Head & neck	Moth self examination
24	Mallia et al.	Clinical grading of oral mucosa by curve-fitting of corrected autofluorescence using diffuse reflectance spectra.	2010	Head & neck	Study population with multiple sub-groups
25	Huber MA	Assessment of the VELscope as an adjunctive examination tool.	2009	Texas dental journal	wrong outcome
26	Roblyer et al.	Objective detection and delineation of oral neoplasia using autofluorescence imaging.	2009	Cancer prevention research (Philadelphia, Pa.)	Study population with multiple sub-groups
27	Schwarz et al.	Noninvasive evaluation of oral lesions using depth-sensitive optical spectroscopy.	2009	Cancer	Study population with multiple sub-groups

S. No	Authors	Title	Year	Journal	Reason for exclusion
28	Huff et al.	Sensitivity of direct tissue fluorescence visualisation in screening for oral premalignant lesions in general practice.	2009	General dentistry	wrong outcome
29	Moyer et al.	Screening for oral cancer: US Preventive Services Task Force recommendation statement	2014	Ann. Intern. Med.	Review article
30	Mallia et al.	Laser-induced autofluorescence spectral ratio reference standard for early discrimination of oral cancer.	2008	Cancer	Population-patient,Study population with multiple sub-groups
31	Schwarz et al.	Autofluorescence and diffuse reflectance spectroscopy of oral epithelial tissue using a depth-sensitive fiber-optic probe.	2008	Applied optics	Study population with multiple sub-groups
32	Saini et al.	Oral cancer: Initial diagnosis influences final prognosis	2014	Pravara Med. Rev.	Letter to editor
33	Kao et al.	Screening for oral cancers-Which method is most effective?	2011	J. Chin. Med. Assoc.	Editorial
34	Mehrotra et al.	The efficacy of oral brush biopsy with computer-assisted analysis in identifying precancerous and cancerous lesions	2011	Head Neck Oncol.	Screened by specialists and residents-in-training, Patient inclusion criteria
35	Hirata K	Discussion of adjunctive diagnostic modalities available for screening of oral leukoplakia.	2006	Hawaii dental journal	Review article
36	Majumder et al.	Relevance vector machine for optical diagnosis of cancer.	2005	Lasers in surgery and medicine	Study population with multiple sub-groups
37	Ram et al.	Chemiluminescence as a diagnostic aid in the detection of oral cancer and potentially malignant epithelial lesions.	2005	International journal of oral and maxillofacial surgery	Study population with multiple sub-groups
38	de Veld et al.	Clinical study for classification of benign, dysplastic, and malignant oral lesions using autofluorescence spectroscopy.	2004	Journal of biomedical optics	Study population with multiple sub-groups
39	Huber et al.	Acetic acid wash and chemiluminescent illumination as an adjunct to conventional oral soft tissue examination for the detection of dysplasia: a pilot study.	2004	Quintessence international (Berlin, Germany : 1985)	Pilot study, Irrelevant abstract
40	Sweeny et al.	Assessment of autofluorescence for oral cancer screening	2011	Otolaryngol. Head Neck Surg.	Study population with multiple sub-groups

S. No	Authors	Title	Year	Journal	Reason for exclusion
41	Remmerbach et al.	Oral brush biopsy analysis by matrix assisted laser desorptionizationi on- time of flight mass spectrometry profiling - A pilot study	2011	Oral Oncol.	Study population with multiple sub-groups
42	Ramadas et al.	Interim results from a cluster randomised controlled oral cancer screening trial in Kerala, India.	2003	Oral oncology	Same population study already included, duplication
43	Drinnan AJ	Screening for oral cancer and precancer--a valuable new technique.	2000	General dentistry	Review article
44	Gillenwater et al.	Noninvasive diagnosis of oral neoplasia based on fluorescence spectroscopy and native tissue autofluorescence.	1998	Archives of otolaryngology--head & neck surgery	Study population with multiple sub-groups
45	Burzynski et al.	Evaluation of oral cancer screening.	1997	Journal of cancer education	wrong outcome
46	Dhingra et al.	Early diagnosis of upper aerodigestive tract cancer by autofluorescence.	1996	Archives of otolaryngoloy--head & neck surgery	Study population with multiple sub-groups
47	Mashberg et al.	Early diagnosis of asymptomatic oral and oropharyngeal squamous cancers.	1995	CA: a cancer journal for clinicians	Review article
48	Mashberg A	Tolonium (toluidine blue) rinse--a screening method for recognition of squamous carcinoma. Continuing study of oral cancer IV.	1981	JAMA	wrong outcome
49	Pizer et al.	An assessment of toluidine blue for the diagnosis of lip lesions.	1979	Virginia medical	No Abstract & Full text available
50	Bánóczy J	Exfoliative cytologic examinations in the early diagnosis of oral cancer.	1976	International dental journal	Review article
51	Reddy et al.	Toluidine blue staining of oral cancer and precancerous lesions.	1973	The Indian journal of medical research	No Abstract & Full text available
52	Rosen et al.	Detection of early oral cancer by toluidine blue.	1971	Journal of the Canadian Dental Association	No Abstract & Full text available
53	Jaber et al.	Oral cancer prevention and early detection	2012	International journal of health care quality assurance	wrong outcome
54	Eckert et al.	A review of oral cancer screening and detection in the metropolitan Detroit cancer control program.	1982	Progress in clinical and biological research	Review article

S. No	Authors	Title	Year	Journal	Reason for exclusion
55	Warnakulasuriya et al.	Utilisation of primary health care workers for early detection of oral cancer and precancer cases in Sri Lanka	1984	Bulletin of the World Health Organization	wrong outcome
56	Clark Alison	Oral cancer prevention and early detection	1999	Nursing Standard (through 2013)	Discussion
57	Kaleem et al.	Reliability and validity of light-based screening techniques in detection of oral premalignant lesions	2018	King Khalid University Journal of Health Sciences	Screened by researcher and specialist dental surgeon
58	Simonato et al.	Fluorescence visualisation improves the detection of oral, potentially malignant, disorders in population screening	2019	Photodiagnosis and Photodynamic Therapy	Screened by General practice dentist
59	Huang et al.	Novel quantitative analysis of autofluorescence images for oral cancer screening	2017	Oral Oncology	Study population with multiple sub-groups
60	Charanya et al.	Adjunctive aids for the detection of oral premalignancy	2016	Journal of Pharmacy and Bioallied Sciences	Review article
61	Bhatia et al.	Assessment of a decision making protocol to improve the efficacy of VELscopeâ" ¢ in general dental practice: A prospective evaluation	2014	Oral Oncology	Screened by general dental practitioner
62	Sambandham et al.	The application of Vizilite in oral cancer	2013	Journal of Clinical and Diagnostic Research	Review article
63	Ali et al.	Diagnostic test for cancer detection in dental & ent clinics: The toluidine blue test	2012	JK Practitioner	Review article
64	Chang et al.	Visual screening of oral cavity cancer in a male population: Experience from a medical center	2011	Journal of the Chinese Medical Association	Screened by an experienced otolaryngologists or dentists
65	Elango et al.	Mouth self-examination to improve oral cancer awareness and early detection in a high-risk population	2011	Oral Oncology	Moth self examination
66	Rahman et al.	Evaluation of a low-cost, portable imaging system for early detection of oral cancer	2010	Head and Neck Oncology	Study population with multiple sub-groups
67	Sankaranarayanan et al.	Early findings from a community-based, cluster-randomised, controlled oral cancer screening trial in Kerala, India	2000	Cancer	Same population study already included, duplication

S. No	Authors	Title	Year	Journal	Reason for exclusion
68	Macey et al.	Diagnostic tests for oral cancer and potentially malignant disorders in patients presenting with clinically evident lesions	2015	Cochrane Database of Systematic Reviews	Review article
69	Jullien et al.	Attendance and compliance at an oral cancer screening programme in a general medical practice.	1995	European journal of cancer. Part B, Oral oncology	wrong outcome
70	Su et al.	A community-based RCT for oral cancer screening with toluidine blue.	2010	Journal of dental research	wrong outcome
71	Frenández et al.	An evaluation of the oral cancer control program in Cuba.	1995	Epidemiology (Cambridge, Mass.)	wrong outcome
72	Ikeda et al.	Epidemiological study of oral leukoplakia based on mass screening for oral mucosal diseases in a selected Japanese population.	1991	Community dentistry and oral epidemiology	wrong outcome

Annexure II

Details of costing

Introduction

The cost of screening and treatment interventions is integral to an economic modelling study (1). The cost for each screening strategy and stage-wise treatment was estimated using standard economic costing methods. A combination of the top-down and bottom-up costing approaches using secondary data was undertaken.

Aims

This economic costing aims to estimate the cost of each screening strategy and treatment intervention used in the stage-wise treatment of oral cancer.

Objectives

1. To estimate the cost incurred on each screening strategy, namely COE (conventional oral examination), TBS (toluidine blue staining), OC (Oral cytology), and Light-based detection (LBD).
2. To estimate the cost incurred in the stage-wise treatment of oral cancer.

Methodology

Secondary data was undertaken using a combination of top-down and bottom-up costing approaches to estimate the cost per person screened with screening strategies and per person stage-wise treatment cost for oral cancer.

Costing of screening strategies

The costing was based on the salary of human resources employed for the screening activity and the cost of the material used in the screening strategy. Guidelines on NPCDCS mention that in a sub-centre with a catchment area of 5000 Population-level, the number of people above 30 years of age is 925 (2). Thus, this is the target population for oral cancer screening.

Considering only Sunday is a holiday for ANM. The salary of the human resource was apportioned according to the working hours and the time devoted to screening one individual (3).

The cost of material was extracted from already published literature. The cost of screening test conventional oral examination was estimated using ANM's monthly salary and working hours, the time required for one screening, and the number of screenings per day. The cost of the

toluidine blue staining screening test was estimated using the cost of material extracted from literature and human resource used (4). The cost of oral cytology was used from the CGHS rate list (5, 6). Costs of the light-based detection screening strategy were estimated using device cost incurred for one screening and human resources used to do the screening (7). The cost for support activities which included an invitation, organising for screening, administration, registration, transport activities, training, miscellaneous and supervision required for the screening process, was extracted from already published literature (8). It was added to each screening strategy to derive a cumulative cost for each strategy used in the cost-effectiveness analysis. Details of the costs are given in Table 4.

Cost of diagnosis

The cost of diagnosis was estimated considering the standard protocol of oral examination, i.e., the cost of OPD consultation and the confirmatory test undertaken next.

Costing for stage-wise treatment interventions in the public facility

The costing was done after finalising the treatment protocol that a public tertiary care facility hospital followed to treat an oral cancer patient. Stage-wise types and frequency of treatment regimens, drugs, number of hospital days, and number of follow-up visits were taken from Indian clinical practice consensus guidelines for managing oral cavity cancer (9) and discussed with the expert oncologist. Following the standard economic costing methods, data on the health system cost of oral cancer was estimated using data extracted from already published literature (10). In addition, OOP expenditure incurred by the patients (in different stages of cancer) on various therapeutic interventions was also extracted from the available literature (11) (Table 5).

Following the treatment regimen, the costs available for the treatment interventions used in various stages are applied to estimate the stage-wise cost of treating oral cancer. As the treatment for pre-cancer was excision biopsy, the costing was done using costs for treatment procedures and related events like hospital bed days and follow-up visits extracted from literature (5, 6). Medicinal treatment of pre-cancer was also estimated. The proportion of surgically treated and medically treated was taken at 70% and 30%, respectively. The treatment regimen for stage I and II are primary resection of the lesion with ipsilateral neck dissection.

Similarly, for stage I and stage II cancer following the treatment regimen, costs were extracted for surgery and related events from already published literature, and cost for stage I and II was

derived (10). The treatment regimen for stages III and IV A is primary resections of the lesion with bilateral neck dissection, adjuvant chemotherapy, and adjuvant radiotherapy; thus, the costs for surgery and adjuvant chemotherapy were extracted from literature, and the radiotherapy therapy costs were calculated based on the utilisation pattern of the different radiotherapy machines used to provide radiation to patients. (Table 1, 2) The treatment regimen for stage IV B is palliative radiotherapy and palliative chemotherapy. The costs for the same were extracted from already published literature. Following this, the total cost of stages III and IV was estimated (10). The costs of all these treatment procedures were estimated using costs from CGHS 2014 and 2015 and already published literature in this regard (5, 6, 10).

Estimation of Radiotherapy cost

Radiotherapy therapy costs were calculated based on the utilisation pattern of the different radiotherapy machines used to provide radiation therapy to patients. Details in the table below

Table 1 Radiotherapy Modalities and their utilisation pattern

Radiotherapy modalities	**Utilisation proportion**	**Source of Data**
2D RT (cobalt)	0.50	The assumption, as per discussion with expert Radiologists
2DRT (DBX/DBH)	0.15	
3DCRT(DBX/DBH)	0.20	
IMRT (DHX/DBX)	0.15	
IMRT (IGRT)	0.00	

Table 2 Per patient radiotherapy cost

Treatment modalities via machines used	**Per patient cost**	**Source of Data**
2D RT (cobalt)	17,896	Chauhan et al
2D RT (DHX/DBX))	35,246	
3D CRT (DHX/DBX)	52,133	
IMRT (DHX/DBX)	69,920	
IMRT (IGRT)	163728	

Out-of-pocket expenditure

Stage-wise OOP expenditure was extracted from literature (11) (Table 3). This cost was added to each stage health system cost already estimated to derive a cumulative cost which included both the health system cost and the OOP expenditure. Details of the costs are given in (Table 5)

Table 3 Out-of-pocket expenditure

Stages	**Mean OOPE**	**Source of Data**
Stage I	1862	Prinja et al
Stage II	4581	
Stage III	4788	
Stage IV	7540	

Private facility cost

For the private facility, the OOP expenditure incurred on treating a patient of invasive cancer in a private health care facility was considered from the NSS 75th report (Health in India) 2017-2018 (12).

Table 4 Detailed costing for screening strategies

Details	Amount	Time	Number
Conventional oral examination			
Human Resources*			
Salary of ANM (INR)	12,000		
Total working days for ANM in a month (days)		26	
Working hours for ANM per day(hours)		6	
Total working hours for ANM in a month(hours)		156	
Total earnings of ANM per hour	77		
People over 30 years in a 5000(sub-centre) level population			925
Time is taken to conduct screening of 1 person(minutes)		15	
Time is taken to conduct screening of 925 people (minutes)		13875	
The amount the ANM gets for conducting the screening of 925 people	17,788.46		
The amount the ANM gets for conducting one screening	19.23		
Support activities (8)	235.00		
Total cost per screening using a conventional oral examination	**254.23**		
Toluidine blue staining			
Cost of 500ml of toluidine stain bottle (As per information available from material cost as per public facility)	600		
Cost per ml of toluidine blue stain	1.2		
The quantity of stain required per test is 1 ml, thus the cost per screening.	1.2		
Human Resources			
Salary of ANM (INR)	12,000		
Total working days for ANM in a month (days)		26	
Working hours for ANM per day (hours)		6	
Total working hours for ANM in a mouth (hours)		156	
Total earnings of ANM per hour (INR)	77		
The census shows people over 30 years in a 5000 (sub-centre) level population.			925
Time is taken to conduct screening of 1 person (minutes)		20	
Time is taken to conduct screening of 925 people (minutes)		18500	
The amount the ANM gets for conducting the screening of 925 people	23,742		
The amount the ANM gets for conducting one screening	25.67		
Support activities (8)	235.00		
Total costs per screening using toluidine blue stain	**261.87**		

Oral cytology			
Cost per screening (Assuming for laboratory processing, consumables, and sample collection) (As per CGHS 2014)	430.00		
Human Resources			
Salary of ANM (INR)	12,000		
Total working days for ANM in a month (days)		26	
Working hours for ANM per day (hours)		6	
Total working hours for ANM in a mouth (hours)		156	
Total earnings of ANM per hour (INR)	77		
People over 30 years in a 5000 (sub-centre) level population as per census			925
Time is taken to conduct screening of 1 person (minutes)		20	
Time is taken to conduct screening of 925 people (minutes)		18500	
The amount the ANM gets for conducting the screening of 925 people	23,742		
The amount the ANM gets for conducting one screening	25.67		
Support activities (8)	235.00		
Total costs per screening using oral cytology	**690.67**		

Light-based detection			
Cost for screening	142.08		
Human Resources			
Salary of ANM (INR)	12,000		
Total working days for ANM in a month (days)		26	
Working hours for ANM per day (hours)		6	
Total working hours for ANM in a mouth (hours)		156	
Total earnings of ANM per hour (INR)	77		
People over 30 years in a 5000(sub-centre) level population as per census			925
Time is taken to conduct screening of 1 person(minutes)		20	
Time is taken to conduct screening of 925 people(minutes)		18500	
The amount the ANM gets for conducting the screening of 925 people	23,742		
The amount the ANM gets for conducting one screening	25.67		
Support activities (8)	235.00		
Total costs per screening with LBD	**402.75**		

Table 5 (A) (Detailed stage-wise treatment cost in a public facility)

STAGES	Treatment	Resource used per patient	CGHS cost (INR)	Total cost per patient (INR)	Source of data
Pre-cancer lesion					
1	Excision Biopsy Grade I surgery fees	1	5000	8700	Estimated cost (as per CGHS rates, 2014& 2015) (5), (6).
	Anaesthesia fees		2700		
	Minor OT charges		1000		
2	Follow up visits	2	302	604	
3	Hospital bed days (3096 per day)	2	3096	6192	
	Total cost			**15,496**	
Stage I/II					
1	Resection of primary ± ipsilateral neck dissection Grade III surgery	1	44098	44098	Chauhan et al. Prinja et al.
2	Diagnostic charges	1	4108	4108	
3	Hospital bed charges	4	3096	12384	
4	Outpatient follow-up	12	302	3624	
5	Out-of-pocket expenditure	1	4788	4788	
	Total cost			67987	

Table 5 (B) (Detailed stage-wise treatment cost in a public facility)

Stage III/IV A	Treatment	Resource used per patient	Cost (INR)	Total cost per patient (INR)	Source of Data
1	Primary resection Grade IV surgery	1	47,911	47,911	**Chauhan et al. Prinja et al.**
2	Adjuvant RT	1	35150	35150	
3	Adjuvant CT	1	992	992	
3	Hospital bed charges	4	3096	12384	
4	Outpatient follow-up	12	538	6456	
5	Out-of-pocket expenditure	1		12328	
	Total cost			1,20,693	

Table 5 (C) (Detailed stage-wise treatment cost in a public facility)

Stage IV B	**Treatment**	**Resource used per patient**	**Cost (INR)**	**Total cost per patient (INR)**	**Source of Data**
1	Palliative RT treatment	1	39,345	39,345	Estimated cost (as per CGHS rates, 2014 & 2015).
2	Adjuvant CT (Cisplatin 30-40mg weekly for six weeks	1	992	992	
3	Outpatient visit-Follow- up	12	538	6456	
	Total costs			**46,793**	

Results

The cumulative cost combining the public facility and private facility cost was estimated based on the utilisation pattern in public and private hospitals derived from the NSS 75th Report 2017-2018 (12). The utilisation pattern showed 35% in public facilities and 65% in private ones. The stage-wise cumulative cost was then used as the model input parameter in the further analysis to estimate lifetime cost for the hypothetical cohort of one lakh population (Table 6).

Table 6: Stage-wise cumulative cost

Stages	**Cumulative Cost**
Pre-cancer	12,280.00
Stage I	93,051.65
Stage II	93,051.65
Stage III	1,11,498.58
Stage IV	95,979.68

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