

Abstract: **Background:** Non-invasive (NI) imaging systems have been developed to overcome the limitations of invasive biopsy procedures, which is the gold standard in diagnosis of Oral dysplasia and Oral Squamous Cell Carcinoma(OSCC). This systematic review and meta- analysis was carried out with an aim to investigate the efficacy of the NI-imaging systems in the detection of dysplastic oral potentially malignant disorders (OPMDs) and OSCC. **Methods:** Records concerned in the detection of OPMDs, Oral Cancer (OC) were identified through search in PubMed, Science direct, Cochrane Library electronic database (January 2000 to October 2020) and additional manual search. **Results:** Out of 527 articles evaluated for eligibility, 54 studies satisfied the pre-determined inclusion criteria. Our final data set for the meta-analysis contained 40 studies, including 13 different NI-imaging systems and majority of the imaging systems studied included autofluorescence (AFI-45%) followed by chemiluminescence (CHEM-17.5%), diffuse reflectance spectroscopy(DRS-15%, SEN:79%, SPEC:86% ,SAUC=0.91),Narrow Band Imaging(NBI-15%) and 5-aminolevulinic acid (ALA) induced protoporphyrin IX (PPIX) fluorescence (5ALA-7%, SEN:91%, SPEC:78% ,SAUC=0.98) in the detection of dysplastic OPMDs from non-dysplastic lesions (NDLs).Analyzed NI imaging systems AFI, DRS, NBI showed higher sensitivities and SAUC (>90%) in differentiating OSCC from NDLs. **Conclusion:** Analysed NI-imaging systems suggests the higher accuracy levels in the diagnosis of OSCC when compared to dysplastic OPMDs. 5 ALA induced PPIX and DRS showed evidence of superior accuracy levels in differentiation of dysplastic OPMDs from NDLs, however more number of studies to be included.

Introduction

- Oral cancer (OC) is mostly preceded by precursors referred as oral potentially malignant Disorders (OPMDs).
- Early detection is important in downstaging OC, improving survival rate, limiting comorbidities, preserving oral functions and maintaining the quality of life.
- Biopsy and histopathological grading of dysplasia is the gold-standard for diagnosis and management.
- Multiple new, non-invasive (NI) imaging systems have been used as adjuncts
- This systematic review and meta-analysis was carried out with the following objectives:

Objectives

To identify and evaluate the evidence of NI-imaging systems in detection of:

- 1 Dysplastic OPMDs from Non dysplastic lesions
- 2 OSCC from Non dysplastic lesions

Methods

Registered at PROSPERO: (CRD42021229122; JAN 4, 2021)

Record search: PubMed, Science direct, Cochrane Library electronic database (JAN 2000 to OCT 2020), with keywords

PRISMA and QUADAS-2 Questionnaire followed

Inclusion Criteria

- Disease condition either OPMDs or OC
- Histopathology, as the gold standard of diagnosis
- NI-imaging system on humans, human tissue bio specimens for diagnosis , follow up, surgical margin assessment
- Study with exact number of cases/controls, where statistical values can be calculated

Exclusion criteria

- Case reports, case series, review articles, editorials, letters, comments, conference proceedings, non-original articles
- Sample size -Normal/Benign <10 and dysplastic OPMD /OSCC < 10
- Animal studies
- Sites other than oral cavity
- Non-English language

Statistical Analysis

Pooled index values : Sensitivity(SEN, Specificity(SPE), Positive & Negative predictive value (PLR &NLR)

Summary estimates: Diagnostic odds ratio (DOR) & area under curve (SAUC)

Forest plot analysis

Funnel plot

Heterogeneity Chi square (p<0.10) and (I² >50%)

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Results

- 40 studies of meta-analysis included
- Auto fluorescence (AFI-45%), chemiluminescence (CHEM-17.5%), diffuse reflectance spectroscopy(DRS-15%),Narrow Band Imaging(NBI-15%, 5-aminolevulinic acid (ALA) induced protoporphyrin IX (PPIX) fluorescence (5ALA-7%). (Fig 1),
- Quality methodology evaluated using Quadas 2 (Fig 2); bias risk , low applicability related to patient selection.
- 5ALA induced PPIX showed high accuracy (Fig 3, Table 1 and 2).

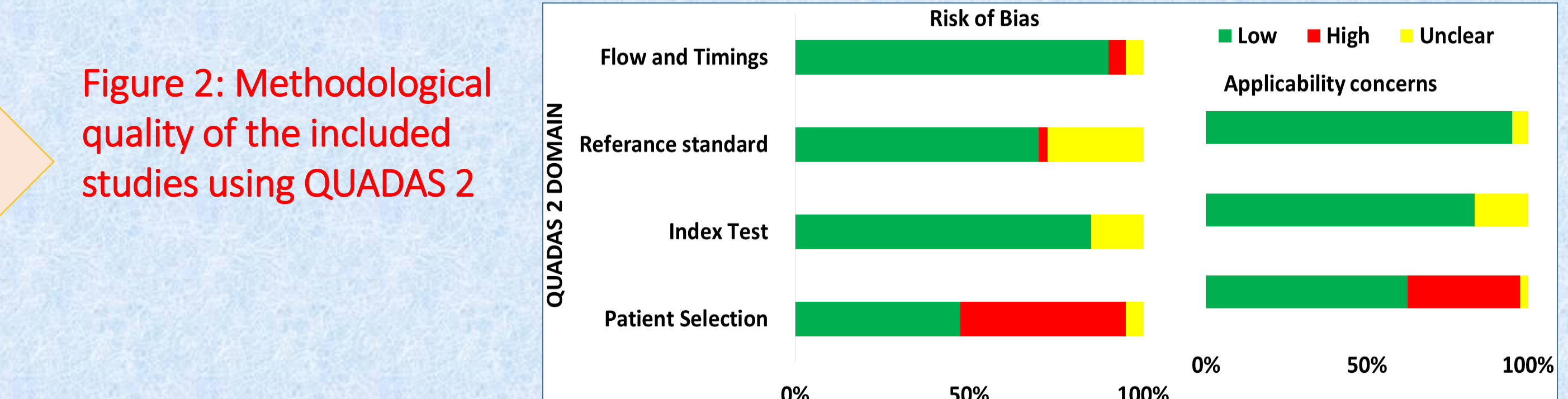
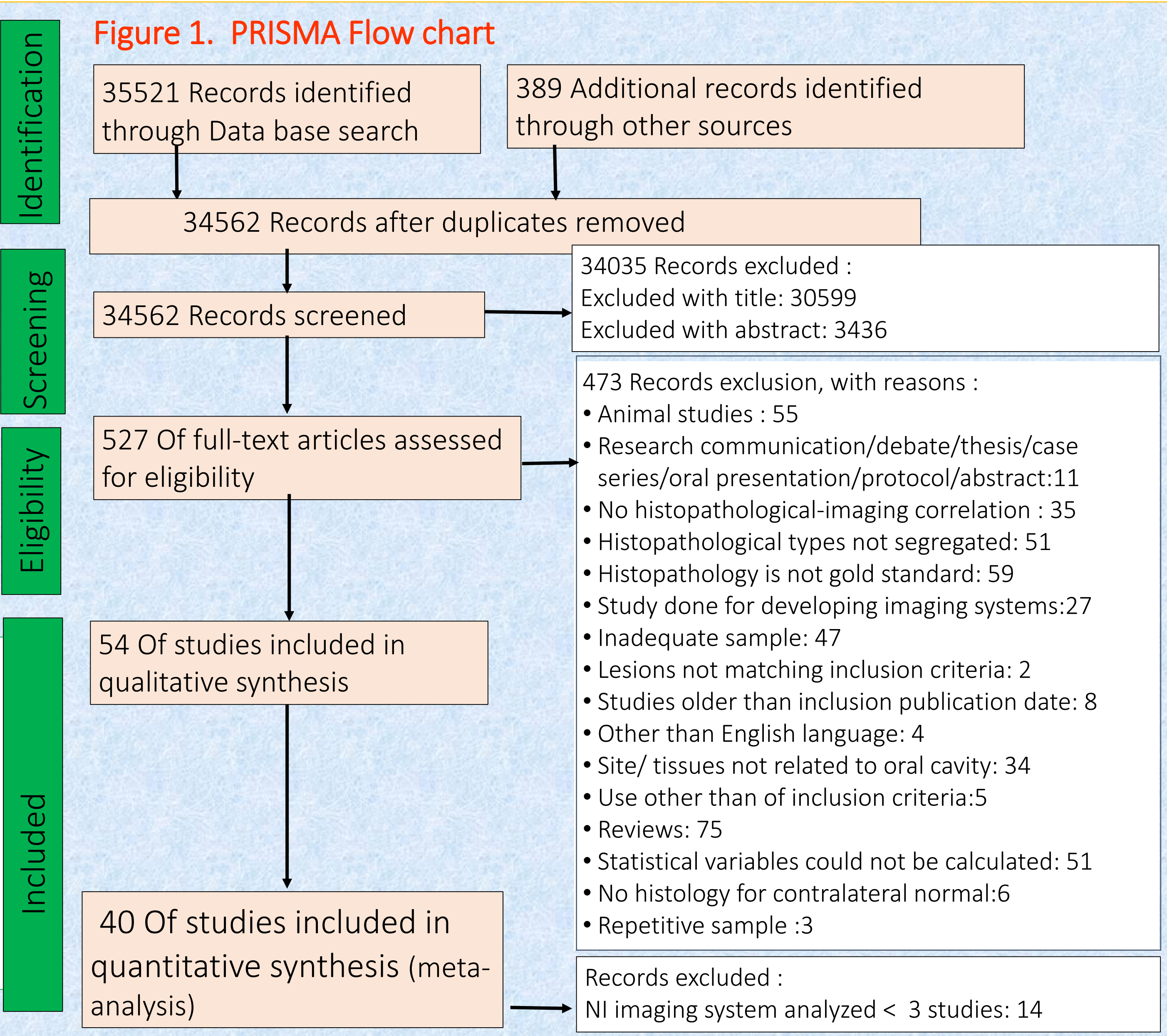


Figure 3. Forest plot analysis of 5ALA induced PPIX fluorescence

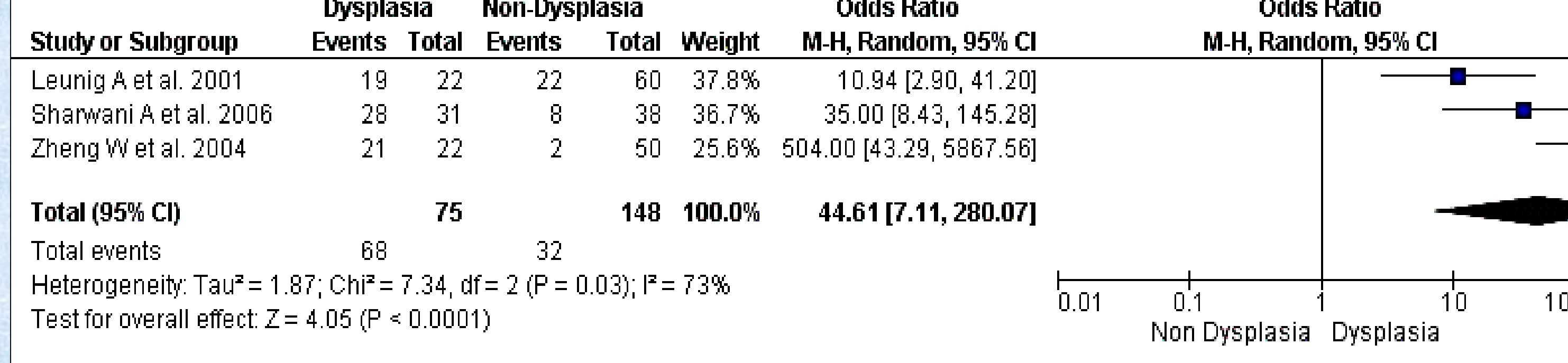


Table 1:Pooled estimates in detection of dysplastic OPMDs from NDLs

TEST	No of studies	Samples		Pooled estimates (95% CI)				
		Dysplasia	NDLs	SEN	SPE	I ² (%)	DOR	AUC
AFI	16	876	1196	0.75 (0.72-0.78)	0.51 (0.48-0.54)	84	4.40 (2.08, 9.2)	0.77
VELSCOPE	6	439	547	0.72 (0.67-0.76)	0.38 (0.34-0.42)	46	1.02 (0.56, 1.8)	0.46
CHEM	7	247	248	0.74 (0.68-0.79)	0.47 (0.40-0.53)	89	5.10 (0.90,28.9)	0.95
DRS	3	63	177	0.79 (0.67-0.89)	0.86 (0.80-0.91)	91	40.47 (0.80,2047)	0.91
NBI	6	269	324	0.31 (0.25-0.37)	0.90 (0.86-0.93)	27	4.12 (1.89,8.9)	0.67
5-ALA	3	75	148	0.91 (0.82-0.96)	0.78 (0.71-0.85)	73	44.61 (7.1, 280)	0.98

Table 2. Pooled estimates in differentiating OSCC from NDLs

Test	No of studies	Samples		Pooled estimates(95% CI)				
		OSCC	NDLs	SEN	SPE	I ² (%)	DOR	AUC
AFI	11	343	972	0.97 (0.94-0.98)	0.58 (0.55-0.62)	72	35.1 (10,118)	0.97
VELSCOPE	4	104	204	0.95 (0.90-0.98)	0.54 (0.49-0.58)	26	16.3 (4.7,56.3)	0.78
DRS	6	123	288	0.93 (0.88-0.97)	0.90 (0.85-0.93)	75	134.2 (21,844)	0.96
DRS, subgroup	5	111	234	0.96 (0.91-0.99)	0.93 (0.89-0.96)	0	286.7 (94,866)	0.98
NBI	4	72	157	0.97 (0.90-1.00)	0.89 (0.82-0.93)	36	309.7 (45,2101)	0.98

Discussion

- Differentiation of dysplastic OPMDs from NDLs
 - 5-ALA showed higher sensitivity (SEN:91%,SPEC:78%, SAUC :0.98), DRS showed higher specificity (SEN :79%,SPEC:86%, SAUC: 0.911).
 - AFI, Velscope, CHEM showed moderate sensitivity (SEN:72%-75%), with low specificity (SPEC: 38% to 51%) in differentiating dysplastic OPMDs.
- Higher sensitivities (SEN >90%) in OSCC diagnosis.
- DRS, NBI differentiated OSCC from NDLs with higher sensitivity/specificity (SEN:>90%, SPEC: 89%-90%).

Conclusion & Future Implications

- NI-imaging systems suggests a higher accuracy level in the diagnosis of OSCC when compared to dysplastic OPMDs.
- 5 ALA induced PPIX & DRS showed evidence of superior accuracy levels in differentiation of dysplastic OPMDs, however larger number of studies required
- Clinical examinations followed by biopsy, will remain the gold standard, wherein these NI imaging can be used as adjuncts.
- Further studies are required with superior evidence, technological advancements, diagnostic accuracy, objective interpretation, cost effectiveness, community application & with minimal training.