

ABSTRACT : The conventional cytology- based diagnosis for thyroid cancer is limited as more than 30-45% of nodules are categorized as indeterminate. Therefore, our aim is to systematically review the published literature and identify immunocytochemical markers that are effective in delineating benign from malignant thyroid lesions in Fine needle aspiration cytology (FNAC) samples. **Methodology:** The articles during the time period 2000-2020 were searched using the key words "thyroid" AND "immunocytochemistry" OR "ICC" in the electronic databases PubMed, Scopus, Web of Science and Cochrane Library. QUADAS-2 tool was used to assess risk of bias and applicability of studies. Review Manager 5.4.1 from Cochrane collaboration and MetaDisc Version 1.4 were used to conduct the meta-analysis. **Results:** Diagnostic accuracy analysis revealed that Gal-3 and HBME-1 show an optimal sensitivity and specificity of >80%. Forest plot analysis showed best association between the markers Galectin-3, HBME-1 and malignancy with Odds ratio of 50.09(29.43-85.25) and 41.78(24.28-71.87) respectively. **Conclusion:** This meta-analysis identified a panel of 5 immunocytochemical markers that could differentiate benign from malignant thyroid lesions in cytology samples. Of these, Gal-3 and HBME-1 are the effective markers that can reliably discriminate between benign and malignant thyroid lesions in FNAC samples with an accuracy >80%.

BACKGROUND

- Thyroid cancers constitute the most common tumor of endocrine system world-wide with incidence increasing annually (1).
- Histopathological diagnosis is the gold standard to distinguish between benign and malignant thyroid tumors (2)
- Conventional cytology based diagnosis is limited as more than 30-45% of nodules are categorized as indeterminate, which necessitates surgery for confirming or refuting the diagnosis of thyroid cancer. (3)

OBJECTIVES

- To identify the immunocytochemical markers that could differentiate benign from malignant thyroid lesions using ICC.
- To analyze the diagnostic accuracy of molecular cytology and, compare with histopathology, towards differentiating benign from malignant thyroid lesions.

INCLUSION CRITERIA

- Original research and full length articles
- Studies with reliability of marker in differentiating thyroid lesions from preoperative FNAC material using ICC
- Studies mentioning exact number of positive and negative cases/controls.
- Studies wherein histopathology of excised specimens was the gold standard of diagnosis.
- All histological types of thyroid malignancies

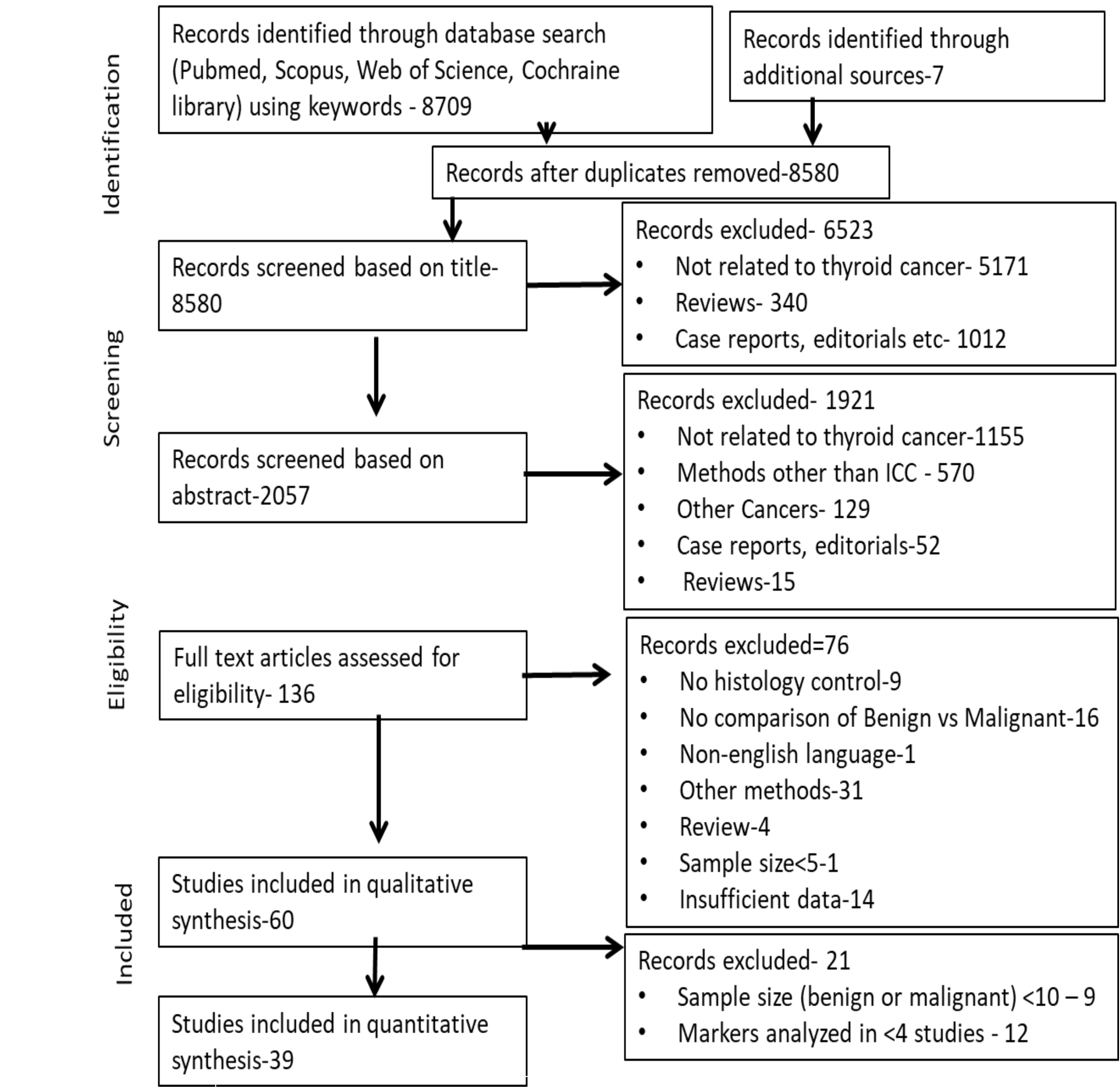
EXCLUSION CRITERIA

- Case reports, case series, review articles, editorials, letters, comments, conference proceedings, or non-original articles
- Non-English language publications
- Studies performed in non-human thyroid tissue.
- Absence of surgical histopathology results
- Studies with lower sample size (benign < 5 cases, malignant < 5 cases)

SEARCH STRATEGY

"thyroid" AND "immunocytochemistry" OR "ICC" [2000-2020]

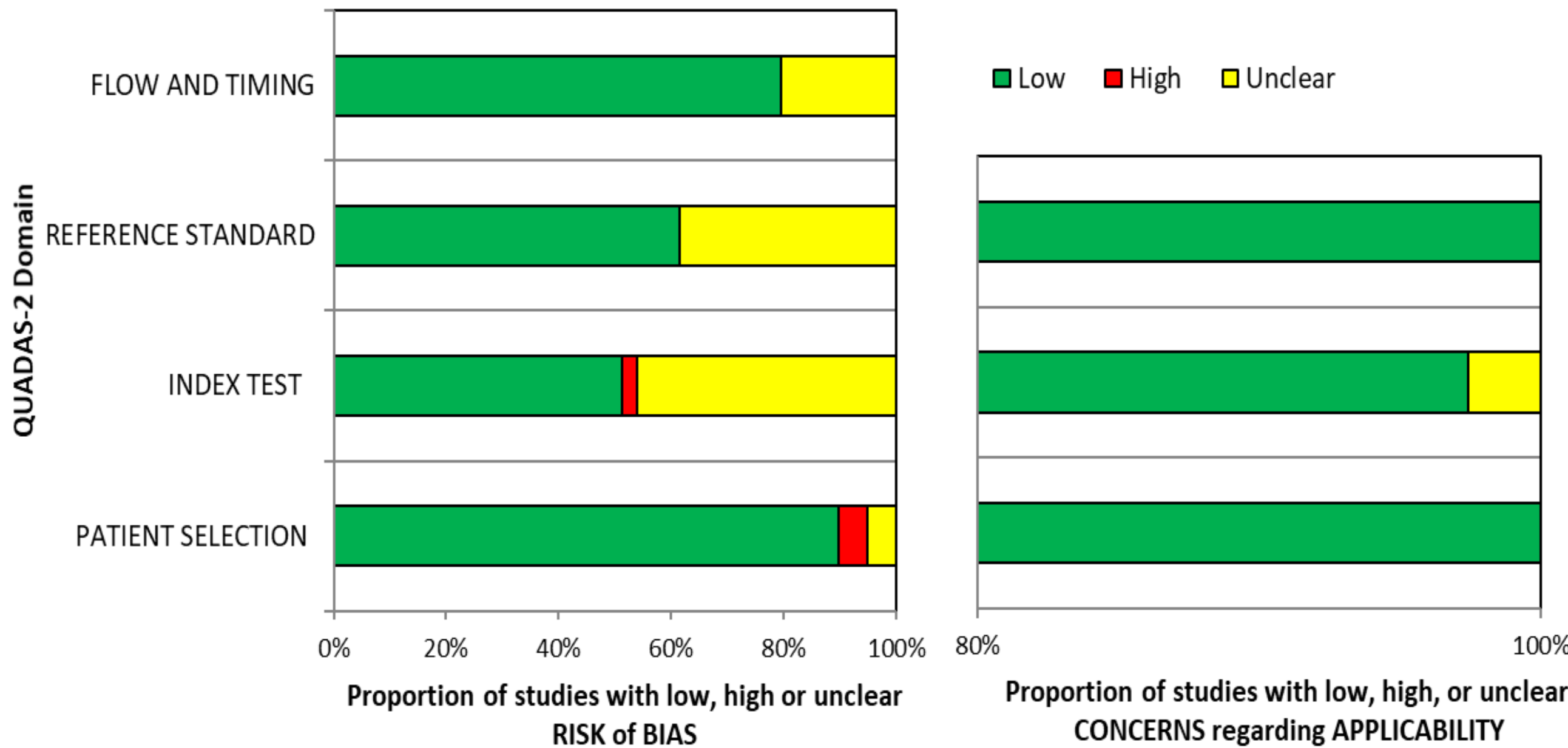
METHODOLOGY



Markers included in Meta-analysis

(1) Galectin – 3 (2) HBME-1 (3) Cytokeratin – 19 (4) CD 56 (5) TPO

Quality assessment of included studies(QUADAS-2)



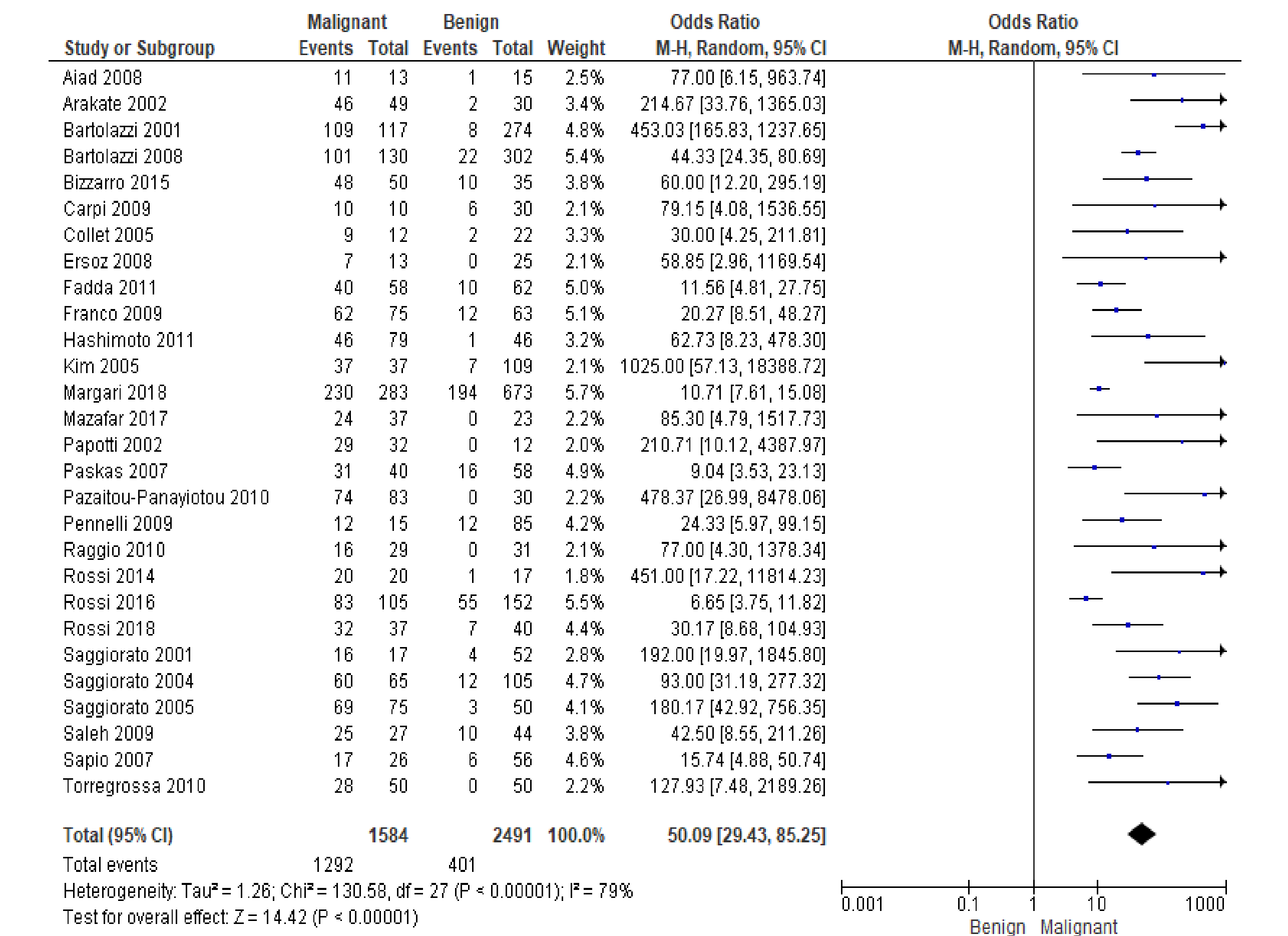
RESULTS

- Meta-analysis carried out for 5 markers (39 studies); Galectin-3, HBME-1, Cytokeratin-19, CD56 and TPO. (**Table 1**).
- Diagnostic accuracy analysis (**Table 2**):
 - CD56 showed the highest pooled sensitivity of 97%
 - CK-19 and TPO showed the highest pooled specificity of 92%.
 - Considering the number of studies , Gal-3 and HBME-1 show an optimal sensitivity and specificity of >80%.
- Diagnostic accuracy analysis in indeterminate categories; Bethesda Category III, IV and V (**Table 3**)
 - HBME-1 is the most sensitive marker(sensitivity-84%)
 - Gal-3 is the most specific marker (specificity-88%)

ICC	Studies	Patients	TP	FP	FN	TN
Gal- 3	28	4075	1292	401	292	2090
HBME 1	17	2657	980	221	158	1298
CK 19	9	1627	582	79	86	880
CD 56	4	319	174	41	6	98
TPO	4	589	200	28	20	341

ICC Marker	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)	AUC
Gal 3	0.82(0.80 - 0.83)	0.84(0.82- 0.85)	50.09(29.43- 85.25)	0.94
HBME 1	0.86(0.84- 0.88)	0.85(0.84- 0.87)	41.78(24.28- 71.87)	0.93
CK 19	0.87(0.85- 0.90)	0.92(0.90- 0.93)	59.87(21.92- 163.51)	0.94
CD 56	0.97(0.93- 0.99)	0.71(0.62- 0.78)	121.64(15.15- 976.56)	0.99
TPO	0.91(0.86- 0.94)	0.92(0.89- 0.95)	258.24(31.73- 2102.01)	0.98

ICC Marker	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)	AUC
Gal 3	0.76(0.71- 0.80)	0.88(0.85- 0.90)	19.75 (10.61- 36.74)	0.88
HBME 1	0.84(0.78- 0.89)	0.81(0.76- 0.86)	22.97(13.34- 39.55)	0.897



CONCLUSION

- Gal-3 and HBME-1 are the effective markers that can reliably discriminate between benign and malignant thyroid lesions in FNAC samples with an accuracy >80%,
- The panel of 5 markers identified from this meta-analysis should be evaluated later in large scale for their clinical application.
- Further work is needed in this field to find new molecular markers that can improve the diagnostic accuracy of thyroid FNAC.

FUTURE PERSPECTIVES

- Gal-3 and HBME-1 will be validated in cytology samples of thyroid tissue using immunocytochemistry in our center, to determine their clinical efficacy
- Large scale validation in combination with assessment in cytology samples will enable their implementation as a point of care assay.

ACKNOWLEDGMENT

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