

A systematic review and meta-analysis of miRNAs for the detection of cervical cancer

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Introduction

- miRNAs have been investigated as biomarkers for detection of cervical cancer (CC).
- The aim of study was to assess the ability of miRNAs to detect CC.

Methods

- This systematic review was registered with PROSPERO (Registration number: CRD42021234979).

Search strategy

- A primary search of PubMed, EMBASE and Web of Science was performed from inception to 13th December 2020. Search terms were designed to retrieve studies on epigenetic CC.
- A secondary search to capture relevant studies published after the date of the primary search was conducted on 13th November 2022.

Study eligibility

- Study abstracts were screened by two independent reviewers.
- Original studies were included if they reported diagnostic performance parameters (sensitivity, specificity, receiver operating characteristic (ROC), positive predictive value (PV+) and/or negative predictive value (PV-)) for screening cervical precancerous and/or cancerous lesions.

Data extraction

- Extraction and reporting of data followed the PRISMA guidelines.
- The main outcomes of interest were sensitivity, specificity, ROC, PV+ and PV-.
- 95% confidence intervals (CIs) were also extracted.

Risk of bias

- A validated tool (QUADAS-2) was utilised for assessing methodological quality.
- Data from poor quality studies were excluded from further analyses.

Meta-analysis of diagnostic performance

- Outlier data with a reported SE of 0 were excluded from all analyses.
- Meta-analysis of sensitivity, specificity, ROC, PV+ and PV- was performed.
- Heterogeneity was assessed using the inconsistency index (I²), with a Q-statistic for chi-squared significance for specific degrees of freedom (df).
- Individual biomarkers with a performance parameter (e.g. sensitivity) significantly greater than that of the umbrella meta-analysis (P<0.05) were deemed ‘excellent’.

GRADE assessment of evidence quality

- A Grading of Recommendations, Assessment, Development and Evaluations (GRADE) assessment was conducted to attribute a level of confidence to the overall evidence quality

Conclusion

- Moderate quality evidence suggested three miRNAs (miR199a-5p, miR21-5p and miR-141a) had excellent performance across all five diagnostic performance parameters.

Results

- A total of 52 miRNAs were included.
- Umbrella meta-analysis revealed significant heterogeneity in sensitivity, specificity, ROC, PV+, and PV-, which ranged from 0.53–0.96, 0.29–0.96, 0.28–0.99, 0.18–0.98 and 0.45–0.99, respectively.
- Umbrella effects were 0.76 (95% CI, 0.73–0.78), 0.78 (95% CI, 0.75–0.81), 0.77 (95% CI, 0.75–0.80), 0.75 (95% CI, 0.71–0.79) and 0.76 (95% CI, 0.74–0.79), respectively.

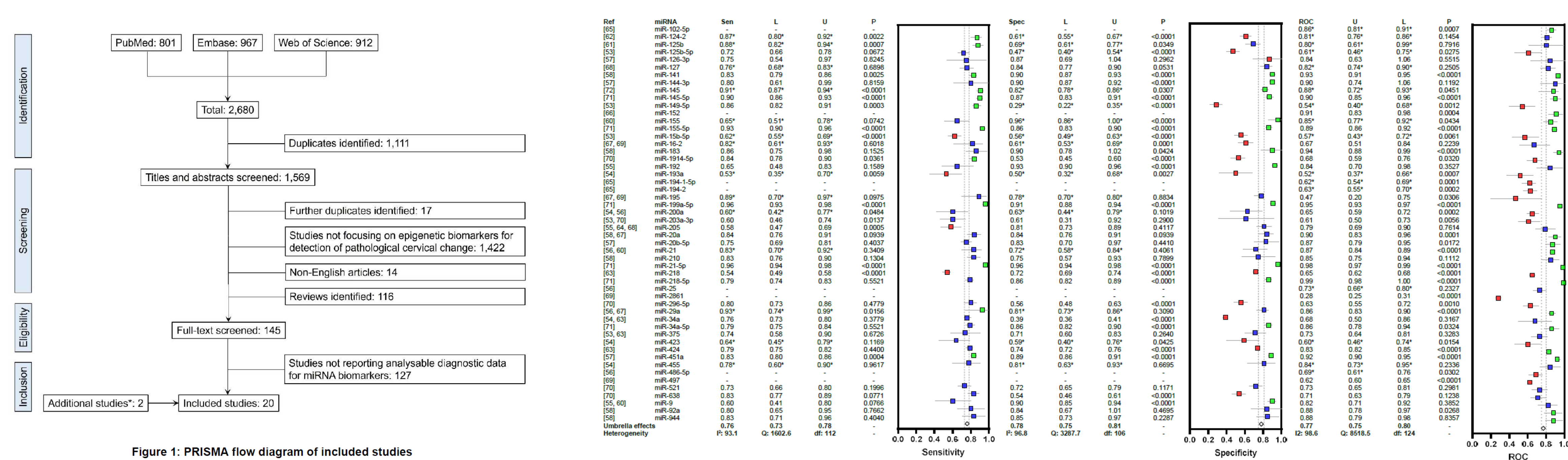


Figure 1: PRISMA flow diagram of included studies
*, additional studies identified from the secondary search

Ref	Author	Year	Risk of bias				Applicability concerns			Study quality
			Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard	
[71]	Attab	2021	?	?	?	?	+	?	+	Moderate
[53]	Babion	2018	?	?	?	+	?	?	+	Moderate
[54]	Bozgeyik	2020	?	?	?	+	?	?	+	Moderate
[55]	Farzanehpour	2019	?	?	?	+	?	?	+	Moderate
[56]	Jia	2015	?	?	?	+	?	?	?	Moderate
[57]	Kawal	2018	?	?	+	+	?	?	+	Moderate
[58]	Liu	2018	?	?	?	?	?	?	+	Moderate
[59]	Lv	2020	-	-	+	+	-	-	+	Poor
[60]	Park	2017	?	?	?	+	?	?	+	Moderate
[61]	Ribeiro	2015	+	?	?	+	+	?	+	High
[62]	Rogeri	2018	?	?	?	+	?	?	+	Moderate
[63]	Tian	2014	-	?	+	?	-	?	+	Moderate
[64]	Xie	2017	?	?	?	+	?	?	+	Moderate
[65]	Xu	2020	?	?	?	?	?	?	?	Moderate
[66]	Yang	2019	-	?	+	+	-	?	+	Moderate
[67]	Ye	2019	?	?	?	+	?	?	?	Moderate
[68]	You	2015	?	?	?	?	?	?	?	Moderate
[72]	Yu	2021	?	?	?	-	?	?	+	Moderate
[69]	Zhang	2015	?	?	+	+	?	?	+	Moderate
[70]	Zheng	2020	?	?	+	+	?	?	+	Moderate

Figure 2: Risk of bias assessment using the QUADAS-2 tool

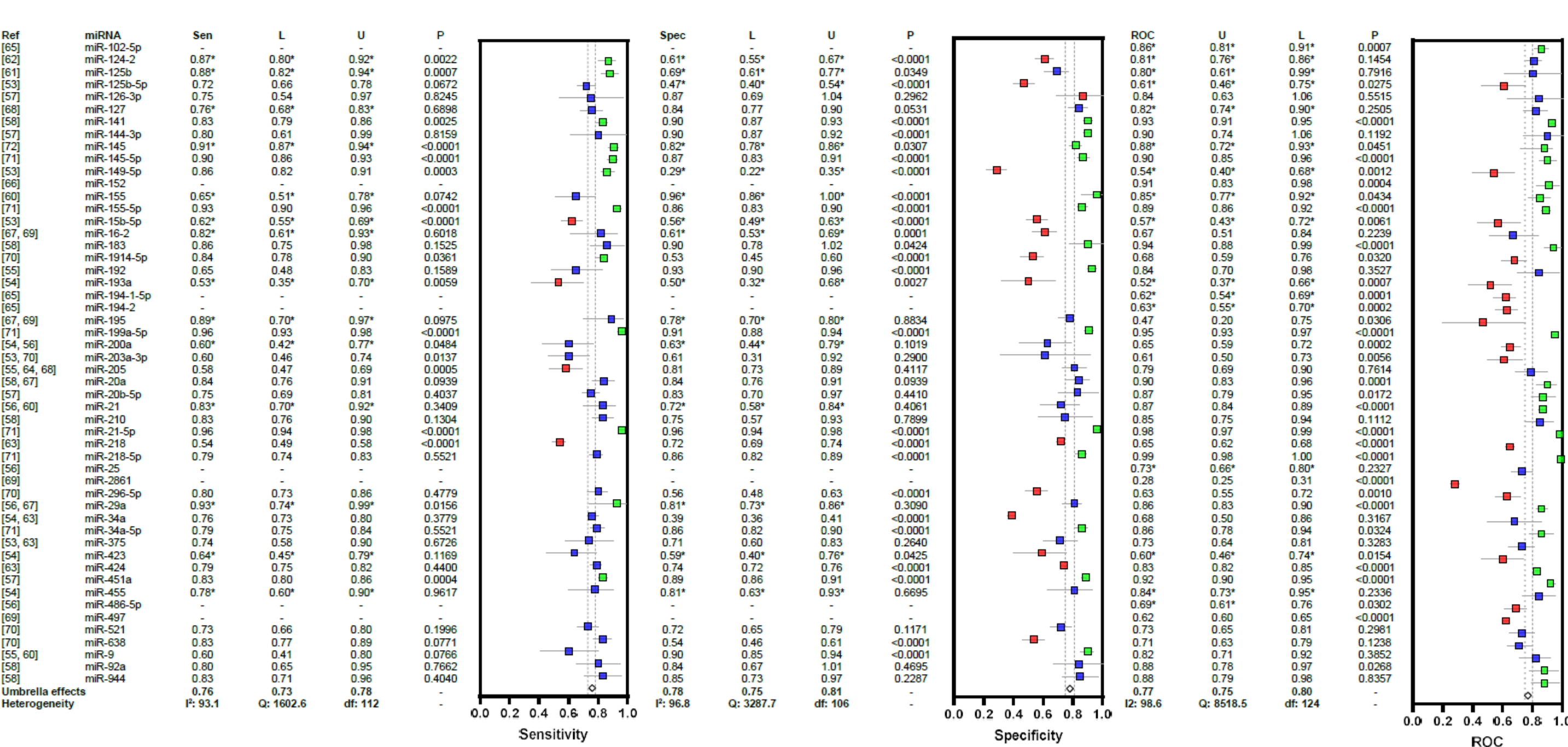


Figure 3: Umbrella meta-analysis of sensitivity, specificity and ROC of miRNA biomarkers
Sen, sensitivity; spec, specificity; ROC, receiver operating characteristic; L, lower limit of 95% CI; U, upper limit of 95% CI; P, p-value for comparison of diagnostic performance of individual miRNA biomarkers with umbrella effects (calculated as previously described [47]); green squares, 'excellent' diagnostic performance defined as significantly greater than umbrella effects; blue squares, 'moderate' diagnostic performance defined as not significantly different from umbrella effects; red squares, 'poor' diagnostic performance defined as significantly less than umbrella effects; diamond, umbrella effects; dashed lines, 95% confidence intervals of umbrella effects; *, single data set (i.e. not meta-analysis); I², inconsistency index; Q, qui-squared significance; df, degrees of freedom; P-values were calculated as described previously [47]

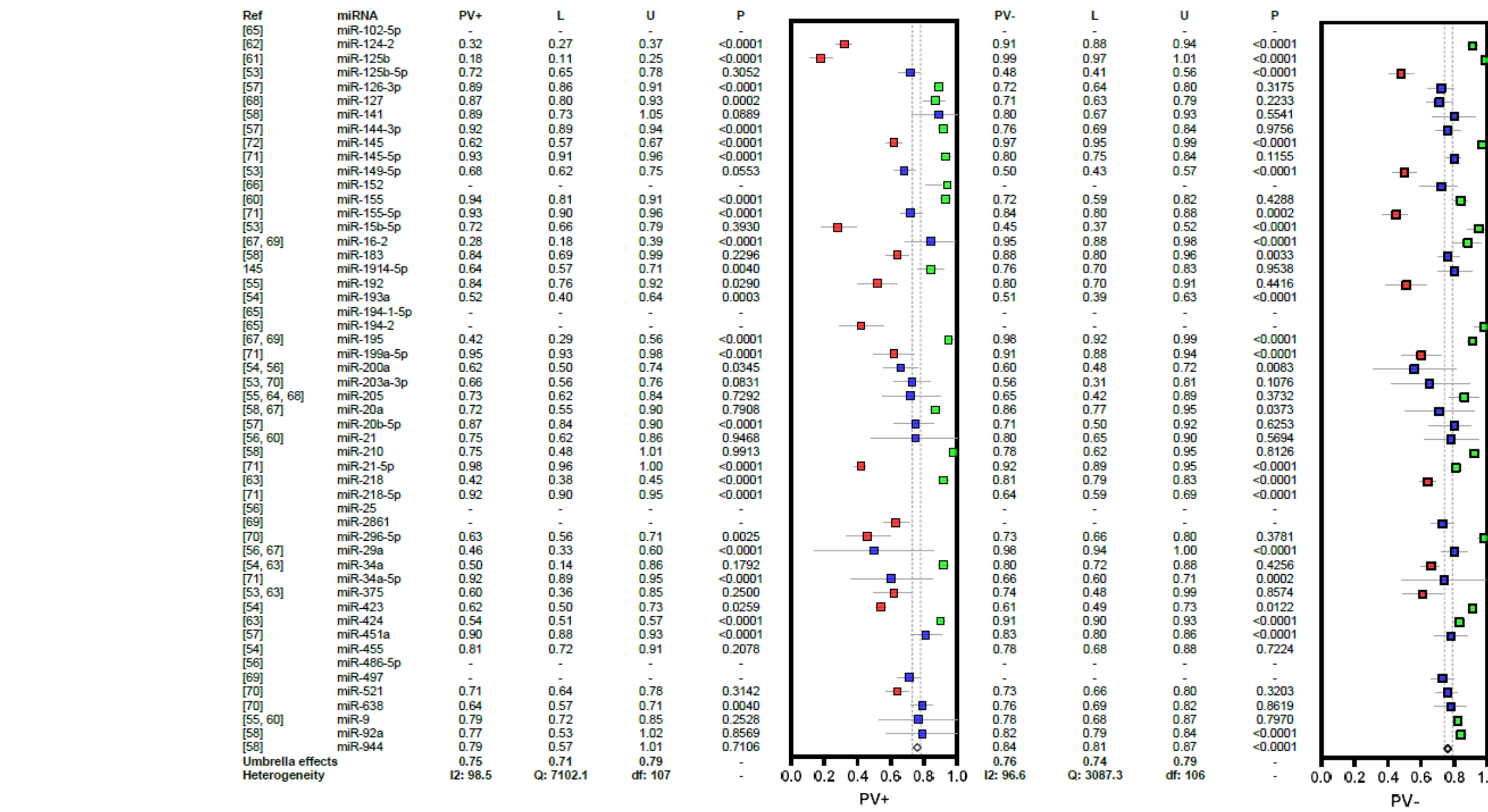


Figure 4: Umbrella meta-analysis of PV+ and PV- of miRNA biomarkers

PV+, positive predictive value; PV-, negative predictive value; L, lower limit of 95% CI; U, upper limit of 95% CI; P, p-value for comparison of diagnostic performance of individual miRNA biomarkers with umbrella effects (calculated as previously described [47]); green squares, 'excellent' diagnostic performance defined as significantly greater than umbrella effects; blue squares, 'moderate' diagnostic performance defined as not significantly different from umbrella effects; red squares, 'poor' diagnostic performance defined as significantly less than umbrella effects; diamond, umbrella effects; dashed lines, 95% confidence intervals of umbrella effects; *, single data set (i.e. not meta-analysis); I², inconsistency index; Q, qui-squared significance; df, degrees of freedom; P-values were calculated as described previously [47]

Ref	miRNA	Sen	Spec	ROC	PV+	PV-	Evidence quality	Risk of bias	GRADE assessment			
									Inconsistency	Indirectness	Imprecision	Other factors
[65]	miR-102-5p	-	-	Excellent	-	-	Poor	Moderate	-	-	-	Single dataset
[62]	miR-124-2	Excellent	Poor	Moderate	Poor	Excellent	Poor	Moderate	-	-	-	Single dataset
[61]	miR-125b	Excellent	Poor	Moderate	Poor	Excellent	Moderate	Low	-	-	-	Single dataset
[53]	miR-125b-5p	Moderate	Poor	Poor	Moderate	Poor	Moderate	Moderate	-	-	-	-
[57]	miR-126-3p	Moderate	Moderate	Moderate	Moderate	Moderate	Poor	Moderate	Sen, spec, ROC, PV-	-	-	-
[68]	miR-127	Moderate	Moderate	Moderate	Excellent	Moderate	Poor	Moderate	-	-	-	Single dataset
[58]	miR-141	Excellent	Excellent	Excellent	Moderate	Moderate	Poor	Moderate	PV+, PV-	-	-	-
[57]	miR-144-3p	Moderate	Excellent	Moderate	Excellent	Moderate	Poor	Moderate	Sen, ROC, PV-	-	-	-
[72]	miR-145	Excellent	Excellent	Excellent	Poor	Excellent	Poor	Moderate	-	-	-	Single dataset
[71]	miR-145-5p	Excellent	Excellent	Excellent	Excellent	Moderate	Poor	Moderate	PV+, PV-	-	-	-
[53]	miR-149-5p	Excellent	Poor	Poor	Moderate	Poor	Moderate	Moderate	-	-	-	-
[63]	miR-152	-	-	Moderate	-	-	Moderate	Moderate	-	-	-	-
[60]	miR-155	Poor	Poor	Poor	Poor	Poor	Poor	Moderate	-	-	-	Single dataset
[70]	miR-155-5p	Excellent	Excellent	Moderate	Moderate	Excellent	Excellent	Moderate	-	-	-	-
[53]	miR-15b-5p	Poor	Poor	Moderate	Moderate	Poor	Moderate	Moderate	-	-	-	-
[67, 69]	miR-16-2	Moderate	Poor	Moderate	Poor	Excellent	Excellent	Moderate	ROC	-	-	-
[58]	miR-183	Moderate	Excellent	Excellent	Moderate	Excellent	Poor	Moderate	Sen, spec, ROC, PV+, PV-	-	-	-
[70]	miR-1914-5p	Excellent	Poor	Poor	Poor	Moderate	Moderate	Moderate	-	-	-	-
[55]	miR-192	Moderate	Excellent	Moderate	Excellent	Moderate	Poor	Moderate	Sen, ROC, PV+, PV-	-	-	-
[54]	miR-193a	Poor	Poor	Poor	Poor	Poor	Poor	Moderate	-	-	-	Single dataset
[65]	miR-194-1-5p	-	-	Poor	-	-	Very poor	Moderate	PV+, PV-	-	-	Single dataset
[65]	miR-194-2	Moderate	Moderate	Poor	-	-	Poor	Moderate	-	-	-	Single dataset
[67, 69]	miR-195	Moderate	Moderate	Poor	Poor	-	ROC	Moderate	-	-	-	Single dataset
[71]	miR-199a-5p	Excellent	Excellent	Excellent	Excellent	Excellent	Moderate	Moderate	-	-	-	-
[54, 56]	miR-200a	Moderate	Moderate	Poor	Poor	Poor	Moderate	Moderate	-	-	-	-
[53, 70]	miR-203a-3p	Moderate	Moderate	Poor	Moderate	Moderate	Very poor	Moderate	Sen, spec, ROC, PV+, PV-	-	-	Spec
[55, 64, 68]	miR-205	Poor	Moderate	Moderate	Moderate	Moderate	Poor	Moderate	Sen, spec, ROC, PV+, PV-	-	-	-
[58, 67]	miR-20a	Moderate	Moderate	Excellent	Moderate	Excellent	Poor	Moderate	Sen, spec, ROC, PV+, PV-	-	-	-
[57]	miR-20b-5p	Moderate	Moderate	Excellent	Excellent	Moderate	Poor	Moderate	Sen, spec, ROC, PV-	-	-	-
[56, 60]	miR-21	Moderate	Moderate	Excellent	Moderate	Moderate	Moderate	Moderate	-	-	-	-
[58]	miR-210	Moderate	Moderate	Moderate	Moderate	Moderate	Poor	Moderate	Sen, spec, ROC, PV+, PV-	-	-	-
[71]	miR-21-5p	Excellent	Excellent	Excellent	Excellent	Excellent	Moderate	Moderate	-	-	-	-
[63]	miR-218	Poor	Poor	Poor	Poor	Excellent	Moderate	Moderate	-	-	-	-
[71]	miR-218-5p	Moderate	Excellent	Excellent	Excellent	Poor	Poor	Moderate	PV+, PV-	-	-	-
[56]	miR-25	-	-	Excellent	-	-	Poor	Moderate	-	-	-	Single dataset
[69]	miR-2861	-	-	Poor	-	-	Moderate	Moderate	-	-	-	-
[70]	miR-296-5p	Moderate	Poor	Poor	Poor	Moderate	Poor	Moderate	PV+, PV-	-	-	-
[56, 67]	miR-29a	Excellent	Moderate	Excellent	Poor	Excellent	Moderate	Moderate	-	-	-	-
[54, 63]	miR-34a	Moderate	Poor	Moderate	Moderate	Moderate	Poor	Moderate	ROC, PV+, PV-	-	-	-
[71]	miR-34a-5p	Moderate	Excellent	Excellent	Excellent	Poor	Moderate	Moderate	-	-	-	-
[53, 63]	miR-375	Moderate	Moderate	Moderate	Moderate	Moderate	Poor	Moderate	Sen, spec, ROC	-	-	-
[54]	miR-423	Moderate	Poor	Poor	Poor	Poor	Poor	Moderate	-	-	-	Single dataset
[63]	miR-424	Moderate	Poor	Excellent	Poor	Excellent	Moderate	Moderate	-	-	-	-
[57]	miR-451a	Excellent	Excellent	Excellent	Excellent	Excellent	Moderate	Moderate	-	-	-	-
[54]	miR-455	Moderate	Moderate	Moderate	Moderate	Moderate	Poor	Moderate	-	-	-	Single dataset
[56]	miR-466-5p	-	-	Poor	-	-	Poor	Moderate	-	-	-	Single dataset
[69]	miR-467	-	-	Poor	-	-	Moderate	Moderate	-	-	-	-
[70]	miR-521	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	-	-	-	-
[70]	miR-638	Moderate	Poor	Moderate	Poor	Moderate	Moderate	Moderate	-	-	-	-
[55, 60]	miR-9	Moderate	Excellent	Moderate	Moderate	Moderate	Poor	Moderate	Sen, spec, ROC, PV+, PV-	-	-	-
[58]	miR-92a	Moderate	Moderate	Excellent	Moderate	Excellent	Poor	Moderate	Sen, spec, ROC, PV+, PV-	-	-	-
[58]	miR-944	Moderate	Moderate	Excellent	Moderate	Excellent	Poor	Moderate	Sen, spec, ROC, PV+, PV-	-	-	-

Table 1: GRADE assessment of evidence quality
Evidence quality for each biomarker was based on the risk of bias assessment from QUADAS-2. From this starting point, evidence quality was down-graded if biomarkers scored adversely in any of the other GRADE domains, e.g. miR126-3p, which has a QUADAS-2 assessment for risk of bias of moderate quality, was down-graded to poor quality due to significant inconsistency (I² ≥50.0%); sen, sensitivity; spec, specificity; ROC, receiver operating characteristic; PV+, positive predictive value; PV-, negative predictive value

