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REVIEW

The role of MicroRNAs as early biomarkers of asbestos-related lung cancer: A systematic review and meta-analysis

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Abstract

Background: Asbestos is still the leading cause of occupational cancer mortality worldwide. Asbestos-related lung cancer (LC) and malignant pleural mesothelioma (MPM) prognosis is still poor especially at advanced stage, so early diagnosis biomarkers are needed. MicroRNAs (miRNAs) have been proposed as potential early diagnostic biomarkers of asbestos-related LC and MPM.

Aim: To evaluate the role of miRNAs as diagnostic and prognostic biomarkers of asbestos-related LC and MPM by performing a literature systematic review and meta-analysis.

Methods: MEDLINE, EMBASE via Ovid, PUBMED and Cochrane library databases were systematically searched up to April 2023 to identify relevant articles. A grey literature search was also conducted using the Google Scholar platform. MeSH and free text terms for 'asbestos', 'occupational exposure', 'lung cancer', 'mesothelioma' and 'miRNAs' were used to search the literature. Our systematic review protocol was registered in the PROSPERO database. Study quality was assessed via the Newcastle-Ottawa Scale.

Results: From the search, 331 articles were retrieved, and, after applying our selection criteria, and exclusion of one study for poor quality, 27 studies were included in the review. Most of the studies were hospital-based case-control, conducted in Europe, and evaluated MPM among men only. MiRNAs expression was measured mainly in plasma or serum. MiR-126, miR-132–3p, and miR-103a-3p were the most promising diagnostic biomarkers for MPM, and we estimated a pooled

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area under the curve (AUC) of 85 %, 73 %, and 50 %, respectively. In relation to MPM prognosis, miR-197-3p resulted associated with increased survival time. MiR-126, alone and combined with miR-222, was confirmed associated also to LC diagnosis, together with miR-1254 and miR-574–5p; no miRNA was found associated to LC prognosis.

Conclusion: Based on our systematic literature review there is suggestive evidence that the expression of specific miRNAs in the blood serum or plasma are associated with asbestos-related LC and MPM diagnosis and prognosis. Further large longitudinal studies are urgently needed to validate these findings and elucidate the underlying mechanisms given the potential important implications for patients' survival.

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Introduction

Globally, it has been estimated that asbestos is still the leading cause of morbidity, disability, and mortality for occupational cancer accounting for 4120 (3060–5240) thousand DALYs (Disability-Adjusted Life Years) and 236 (176–296) thousand deaths. In relation to the specific cancer type, lung cancer (LC) is the most frequent, with 199 (140–257) thousand deaths, and malignant pleural mesothelioma (MPM) is the rarest, with 26.8 (24.3–28.6) thousand deaths, but it is virtually only caused by asbestos.¹ The International Agency for Research on Cancer (IARC) has classified asbestos as a known human carcinogen not only for LC and MPM, but also for all mesothelioma types, larynx, and ovarian cancer, and, with weaker evidence, for throat, stomach, and colorectum malignancies.² Moreover, chronic degenerative pleural and interstitial lung diseases, such as asbestosis are caused by asbestos exposure,³ so increasing the associated global morbidity and mortality burden.⁴ Of note, asbestos exposure is not only occupational, but it may occur in the home, and in surroundings of contaminated worksites with potential exposure of the most vulnerable, such as children and pregnant women.^{5,6} Regrettably, only 69 of the world's 195 countries have banned asbestos.⁷ The World Health Organization (WHO) estimated that 125 million people worldwide are still exposed to asbestos, and considering the long cancer latency (up to 60 years for MPM) the expected associated cancer burden won't decrease in the near future.⁸ Despite important advances in cancer therapy, both LC and MPM have poor prognosis, especially if diagnosed at a late stage. In addition, there is no agreed standard treatment for MPM whose median survival is less than one year from diagnosis.⁹ Cancer screening programs among exposed to asbestos using low-dose chest CT-scans have been proposed,¹⁰ but so far none has started yet due to uncertain cost-benefits and challenges in risk stratification to identify which subgroup of subjects would benefit the most. Therefore, non-invasive biomarkers for risk stratification, and earlier cancer detection are urgently needed to improve overall survival and quality of life, as was recently recommended by the European MPM guidelines.¹¹ MicroRNAs (miRNAs) are short, endogenous, non-coding ribonucleic acids that have been suggested as potential candidates. MiRNAs regulate key processes in cells and signaling pathways involved in lung tumorigenesis, such as cell proliferation, differentiation, angiogenesis, apoptosis, invasion, and metastasis by regulating gene expression at the post-

transcriptional level,¹² and are potential molecular targets for cancer therapies. Also, the availability of miRNAs in several accessible biological fluids and exhaled breath condensate (EBC) make them ideal candidates for liquid biopsies. Changes in miRNAs expression have been associated with diagnosis and prognosis of several chronic diseases and cancers,¹³ but the evidence for asbestos-related LC and MPM is still scarce and inconsistent. Therefore, the aim of our systematic literature review is to evaluate the role of miRNAs as diagnostic and prognostic biomarkers of asbestos-related LC and MPM.

Methods

We performed the systematic review according to the Cochrane Handbook for Systematic Reviews¹⁴ and the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.¹⁵ MeSH and free text terms for 'asbestos', 'occupational exposure', 'lung cancer', 'mesothelioma' and 'miRNAs' were used to search the literature in electronic databases: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (EMBASE) via Ovid platform, PubMed, and Cochrane Library (search period: January 1990 to April 2023) (see detailed search strategy in **supplementary Table 1s**). A grey literature search was conducted using the Google search engine platform to identify relevant studies not captured through database searches. Our systematic review protocol is registered in the PROSPERO database (registration Number: CRD42023414412 accessible at crd.york.ac.uk/prospero/display_record.php?ID=CRD42023414412). The studies retrieved from our electronic search were reviewed following the Population (P), Interventions (I), Comparators (C), Outcomes (O), Study Design (S), and Time Frame (T) model and screened for suitability according to our inclusion criteria (see PICOS-T criteria in **supplementary Table 2s**) by two reviewers independently (DM and SDM). A third reviewer was available in case of any disagreement (PC). Relevant data from each included study were extracted into an *ad hoc* Microsoft Excel (Microsoft Corp., Redmond, WA) table. Each study was appraised for quality using the Newcastle-Ottawa Scale (NOS) for observational studies.¹⁵ Studies of very poor quality were not included. For the miRNAs reported at least by two similar studies in association with diagnosis and/or prognosis of asbestos-related LC and/or MPM, a meta-analysis was performed to estimate a pooled

quantitative diagnostic and/or prognostic accuracy using the AUC (Area Under the Curve) and its 95 % Confidence Intervals (CIs). We extracted the AUCs and their standard errors (s.e.) from the studies. We displayed graphically in a forest plot the pooled AUCs and their asymptotic intervals (AUC \pm 1.96*s.e.) on a non-transformed scale. Random effect methods¹⁶ were applied in case of high heterogeneity ($I^2 > 50$ %). A potential small study effect bias was evaluated using Egger test and visualised using a funnel plot. The STATA v.17 (Stata Corp LP, College Station, TX) software was used for all analyses.

Results

The literature search retrieved a total of 331 citations. After duplicate removal and application of our selection criteria, 28 articles were included in the review. The quality of the included studies was scored between fair ($n = 14$), and high ($n = 13$); only one study¹⁷ was removed due to poor quality (see the New-Castle Ottawa quality of studies assessment scale in Table 1). Among the 27 studies included in the final review, only seven were selected as suitable for the meta-analysis (see PRISMA flow chart¹⁴ in Fig. 1). The characteristics of the 27 included studies are summarized in Table 2. Most studies were conducted in Europe, specifically in Italy ($n = 13$).^{18–30} Regarding the study design, all studies were hospital-based case-controls, but one study³¹ was a hospital-based retrospective cohort study. Most studies ($n = 18$) had low sample size. MiRNAs expression was evaluated mostly in blood serum or plasma^{19,20,22,26–30,32–37} and serum or plasma extracellular vesicles (EV).^{18,23,38,39} Some studies evaluated miRNA expression directly in the lung tumour tissue,^{23–25,31,40–42} and one in the EBC.²¹ The most frequently evaluated disease outcome was MPM, followed by non-small cell lung cancer (NSCLC)^{22,29,30} and lung adenocarcinoma.^{21,33} In most studies ($n = 15$), asbestos-exposed cancer-free hospital patients were used as controls. All but two studies^{19,26} were only among men. The age range was 52 – 73 years for MPM cases, 61 – 69 for LC cases, 58 – 74 years for non-asbestos-exposed controls and 55 – 76 for asbestos-exposed controls. Ten studies^{18–20,22,23,27,29,33,36,37} reported the asbestos exposure assessment method, either via personal interview or self-administered questionnaire and six studies^{20,22,27,36,41,43} calculated the asbestos exposure duration in years. The most frequent type of asbestos exposure was occupational. The majority of studies reported smoking status and some studies^{19,20,22–25,29,30,32–40} managed to include never smokers only; however seven studies^{18,26,28,31,41,42,44} did not report the smoking status. All included studies reported miRNAs diagnostic accuracy, and two studies reported the prognostic accuracy^{19,31} (Table 3). The miRNAs most frequently reported in association with MPM diagnosis were miR-126,^{22,25,27,29,40} miR-103a-3p,^{20,36–38} and miR-132–3p.^{35,37} Of note, miR-126 was confirmed alone,²⁹ and combined with miR-222²² also for LC diagnosis. Other miRNAs resulted associated with LC, but only by single studies, were miR-1254 and miR-574–5p,³⁰ and let-7f-5p, miR-518f-3p, miR-597–5p, miR-1260a.²¹ In relation to types of miRNAs perturbations, several miRNAs associated with MPM diagnosis resulted up-

regulated,^{18,19,22,26,30,32–34,41,42} others down-regulated.^{20,23–25,27,29,31,35–37,39} For LC, all miRNAs resulted up-regulated,^{21,30} but let-7f-5p.²¹ Most studies ($n = 16$)^{18,20–24,26,31–33,37,40–44} estimated miRNA expression difference between cases and controls as fold change (FC) using different cut-off thresholds. Some studies managed to adjust tests' p-values for multiple testing for MPM diagnosis^{18,19,23,30,31,40,41,44} and LC diagnosis.²¹ Eight studies.^{19,25,32,35–37,39,43} matched cases and controls by potential confounders (e.g. age, sex, smoking status, or asbestos exposure) while nine studies^{18,20–24,27,31,40} controlled for them in the statistical analysis. Ten studies^{20,21,25,28,30,32–34,40,41} reported also cancer stages and the most frequent was stage I. Twenty-two studies^{19–25,27,28,30,31,33–38,40–44} reported the histological subtypes; the most frequent type for asbestos-related LC was adenocarcinoma and for MPM was epithelioid. In relation to diagnostic accuracy (Table 4), the miRNAs with the highest values for MPM were: miR-103a-3p³⁸ with 86 % sensitivity, 63 % specificity and AUC of 0.76; miR-126²⁹ with 80 % sensitivity, 60 % specificity and AUC of 0.75(0.62–0.89) and miR-132–3p³⁵ with 86 % sensitivity, 61 % specificity and AUC of 0.91 (0.8–1.0). In relation to MPM prognosis, miR-197-3p¹⁹ was associated with an increased survival for epithelioid type of 13.5 (\pm 0.6) months, for sarcomatoid of 7.9 (\pm 0.7) months, and for biphasic of 12.4 (\pm 0.6) months. Also, six miRNAs combined (miR-21–5p, miR-23a-3p, miR-30e-5p, miR-221–3p, miR-222–3p, miR-31–5p)³¹ resulted associated to 57.2 (45.83–90.48) months to 6.4 (1.94–8.28) months increased survival. In relation to asbestos-related LC diagnosis, miR-126 was confirmed associated also to LC diagnosis, alone,²⁹ and in combination with miR-222.²² Also, miR-1254 and miR-574–5p³⁰ were found associated with early-stage NSCLC even months before clinical diagnosis. No miRNAs were reported in association to survival for asbestos-related LC.

Meta-analysis

We managed to perform a meta-analysis for miRNAs diagnostic accuracy by pooling the AUC reported by seven similar studies that found the same miRNAs associated to MPM diagnosis among men only.^{25,27,29,35–37,40} One study,³⁷ contributed twice to the meta-analysis for two different mi-RNAs. Random effect methods were used given the high heterogeneity detected (>50 %). We estimated for miR-126, miR-132–3p, and miR-103a-3p pooled diagnostic AUCs of 85 %, 73 %, and 50 %, respectively. The overall pooled accuracy resulted 73 % (Fig. 2). No small study effect bias was shown in the funnel plot (see supplementary file Fig. 1s) as confirmed by the Egger test (p-value=0.450).

Discussion

In our systematic review and meta-analysis to evaluate the role of miRNAs as potential diagnostic and/or prognostic biomarkers of asbestos-related LC and MPM, we found that several miRNAs are promising candidates especially for MPM diagnosis. In particular, we managed to estimate for the

Table 1 Quality assessment of the included studies via Newcastle Ottawa Scale.

| New Castle Ottawa Scale Assessment for the Case Control Studies (n = 26) | | | | | | | | | | |
|--|--|---|-------------------------------|--|--|-------------------------------|---|--------------------------------------|---------------|---------------|
| References | Q1: Is the case definition adequate? | Q2: Representativeness of the cases | Q3: Selection of Controls | Q4: Definition of Controls | Q5: Comparability of cases and controls on the basis of the design or analysis | Q6: Ascertainment of exposure | Q7: Same method of ascertainment for cases and controls | Q8: Non-Response Rate | Overall Score | Study Quality |
| Casalone 2022 ¹⁸ | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 6 | High |
| Mauro 2023 ¹⁹ | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 0 | 7 | High |
| Jiménez-Ramírez 2022 ³⁶ | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 6 | High |
| Ferrari 2022 ²⁰ | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 6 | High |
| Faversani 2021 ²¹ | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 6 | High |
| Weber 2019 ³⁷ | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 0 | 7 | High |
| Matboli 2018 ¹⁷ | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 4 | Poor |
| Matboli 2018 ³² | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 5 | Fair |
| Santarelli 2019 ²² | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 4 | Fair |
| Cavalleri 2017 ²³ | 0 | 1 | 1 | 0 | 2 | 1 | 1 | 0 | 6 | High |
| Mozzoni 2017 ²⁵ | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 3 | Fair |
| Weber 2017 ³⁵ | 0 | 1 | 1 | 0 | 2 | 1 | 1 | 0 | 6 | High |
| Truini 2017 ²⁴ | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 5 | Fair |
| Bononi 2016 ²⁶ | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 3 | Fair |
| Ak 2015 ⁴¹ | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 4 | Fair |
| Santarelli 2015 ²⁷ | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 6 | High |
| Lamberti 2015 ²⁸ | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 5 | Fair |
| Andersen 2014 ⁴⁰ | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 3 | Fair |
| Weber 2014 ³⁸ | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 0 | 7 | High |
| Gayosso-Gómez 2014 ³³ | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 7 | High |
| Xu 2013 ⁴⁴ | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 3 | Fair |
| Muraoka 2013 ³⁴ | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 6 | High |
| Kirschner 2012 ⁴² | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 5 | Fair |
| Weber 2012 ³⁹ | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 0 | 7 | High |
| Tomasetti 2012 ²⁹ | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 5 | Fair |
| Foss 2011 ³⁰ | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 3 | Fair |
| Nymark 2011 ⁴³ | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 4 | Fair |
| New Castle Ottawa Scale Assessment for the Cohort Study (n = 01) | | | | | | | | | | |
| Reference | Q1: Representativeness of the exposed cohort | Q2: Selection of the non-exposed cohort | Q3: Ascertainment of exposure | Q4: Demonstration that outcome of interest was not present at start of study | Q5: Comparability of cohorts on the basis of the design or analysis controlled for confounders | Q6: Assessment of outcome | Q7: Was follow-up long enough for outcomes to occur | Q8: Adequacy of follow-up of cohorts | Overall Score | Study Quality |
| Kirschner 2015 ³¹ | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 5 | Fair |

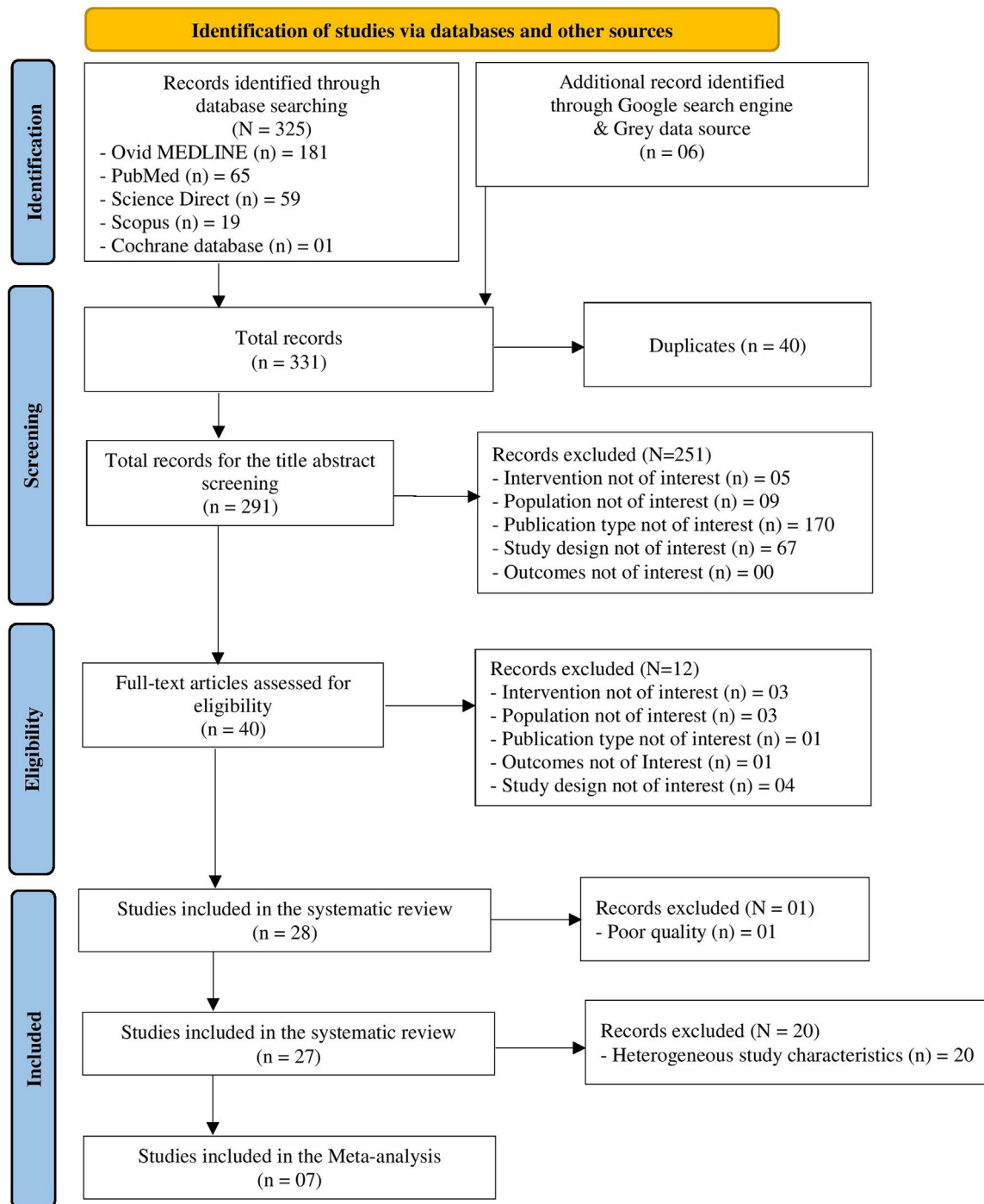


Fig. 1 PRISMA flow diagram showing screening and selection of articles related to miRNAs and asbestos-related lung cancer outcomes resulting from the search in electronic bibliographic databases.

three top miRNAs (miR-126, miR-132-3p, and miR-103a-3p) associated to MPM diagnosis a pooled accuracy of 73 % with the highest performance of 85 % for miR-126. In relation to MPM survival, miR-197-3p¹⁹ and six combined miRNAs (miR-21-5p, miR-23a-3p, miR-30e-5p, miR-221-3p, miR-222-3p, miR-31-5p)³¹ appeared associated to a better prognosis. In relation to asbestos-related LC, only single miRNAs were associated with diagnosis and/or survival, so

we were unable to perform a meta-analysis among the most frequently reported. Of note, miR-126, was confirmed also for LC diagnosis, alone,²⁹ and in association with miR-222.²² Also, miR-1254 and miR-574-5p³⁰ were found associated with early-stage NSCLC samples even months before clinical diagnosis, so potentially useful for LC screening programs. We did not find any promising miRNAs in relation to asbestos-related LC survival.

Table 2 Characteristics of the 27 studies included in the systematic review.

| Author, Year | Country | Study Design | Sample Size | Sex [n(%)] | Age [Mean(±SD)] | Smoking Status [n(%)] | Asbestos Exposure Assessment | Asbestos Exposure Duration | Asbestos Exposure types [n(%)] | miRNA Matrix | Outcome |
|------------------------------------|---|-------------------------------|--|--|---|--|---|---|---|----------------|--------------|
| Casalone 2022 ¹⁸ | Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, and The United Kingdom | Population based case-control | N: 164 CA: 82 CO_Non_Asb-Exp: 82 | M: 59(72) CO_Non_Asb-Exp: 59(72) F: 23(28) CO_Non_Asb-Exp: 23(28) | CA: 57.7(±8.1) CO_Non_Asb-Exp: 57.8(±8.1) | NR | Questionnaire administered via personal interview | NR | CA: Unexposed: 18(22) Exposed: 40(48.7) NA: 24(29.7) CO_Non_Asb-Exp: Unexposed: 18(22) Exposed: 40(48.7) NA: 24(29.7) Occupational: Documented: 17(22.7), Possible: 6(6.7) Domestic/Environmental: 14(18.7) No: 2(2.7) NA: 37(49.3) | Serum EV | MPM |
| Mauro 2023 ¹⁹ | Italy | Hospital based case-control | N: 225 CA: 75 CO_Asb-Exp: 75 CO_Non_Asb-Exp: 75 | N/A | CA: 69.3(±0.85) CO_Asb-Exp: 66.3(±0.78) CO_Non_Asb-Exp: 69.8(±0.92) | CA: 8(10.6) S: 13(17.3) Ex: 14(18.7) NS: 14(18.7) N/A: 40(53.3) | Questionnaire administered via personal interview | NR | CA: Occupational: 17(22.7), Possible: 6(6.7) Domestic/Environmental: 14(18.7) No: 2(2.7) NA: 37(49.3) | Blood serum | MPM |
| Ferrari 2022 ²⁰ | Italy | Hospital based case-control | N: 80 CA: 26 CO_Asb-Exp: 54 | CA: 20(77) F: 06(23) CO_Asb-Exp: 47(87) F: 07(13) | CA: 71.3(±7.8) CO_Asb-Exp: 64.8(±6.0) | CA: 8(31) NS: 15(58) S: 3(12) CO_Asb-Exp: NS: 25(46) Ex: 24(44) S: 5(9) | Questionnaire administered via personal interview | CA: 25(min: 1, Q1: 17, Q3: 32, max: 47) CO_Asb-Exp: 11 [min: 0, Q1: 6, Q3: 25, max: 40] | CA: Occupational: 14(53.8) Environmental: 1(3.8) Unknown: 11(42.3) CO_Asb-Exp: Occupational: 54(100) | Plasma | MPM |
| Jiménez-Ramírez 2022 ²⁶ | Mexico | Hospital based case control | N: 326 CA: 108 CO_Asb-Exp: 218 | CA: 90(33.5) F: 18(31.6) CO_Asb-Exp: M: 179(66.5) F: 39(68.4) | Total sample; CA: 62(55–71) CO_Asb-Exp: 62(55–71) ≤60 years; CA: 48(44.4) CO_Asb-Exp: 96(44.0) >60 years; CA: 60(55.6) CO_Asb-Exp: 122(56.0) | NS: 39(36.1) CO_Asb-Exp: 89(40.8) S: 69(63.9) CA: 48(44.4) CO_Asb-Exp: 129(59.2) | Self-administered questionnaire | Years of occupational exposure; CA: 11.5[2–28] CO_Asb-Exp: 17.5[5–27.5] Years of environmental exposure; CA: 30[18–42] CO: 35[20–46] | Asbestos; Yes; CA: 104(96.3) CO_Asb-Exp: 199(91.3) No; CA: 4(3.7) CO_Asb-Exp: 19(8.7) Occupational; Yes; CA: 82(75.9) CO_Asb-Exp: 128(58.7) No; CA: 26(24.1) CO_Asb-Exp: 90(41.3) Environmental; Yes; CA: 77(71.3) CO_Asb-Exp: 145(66.5) No; CA: 31(28.7) CO_Asb-Exp: 73(33.5) | Plasma | MPM |
| Faversani 2021 ²¹ | Italy | Hospital based case-control | N: 51 CA,MPM: 23 CO: 09 CA_Lung-Ad: 14 | CA,MPM: M: 23 F: N/A CO: M: 09 F: N/A CA_Lung-Ad: M: 14 F: N/A CO: 34(100) | CA_Lung-Ad: 69(±7) CO: 67(±7) CA,MPM: NR[55–90] | CA_Lung-Ad: Ex: 10(71) S: 2(14.3) NA: 2(14.3) CO: Ex: 6(66.7) Yes: 3(33.3) NA: 0(0) | NR | NR | CA: 31(28.7) CO_Asb-Exp: 73(33.5) | EBC and Plasma | MPM, Lung-Ad |
| Weber 2019 ²⁷ | Germany | Hospital based case-control | N: 51 CA: 17 CO: 34 | CA: 17(100) CO: 34(100) | CA: 73[64–83] CO: 74[63–84] | CA: S: 1 Ex: 13 NS: 3 CO: S: 4 Ex: 21 NS: 9 | Self-administered questionnaire | NR | Occupational: NR (100%) | Plasma | MPM |

Table 2 (Continued)

| Author, Year | Country | Study Design | Sample Size | Sex, n(%) | Age [Mean(±SD)] | Smoking Status [n(%)] | Asbestos Exposure Assessment | Asbestos Exposure Duration | Asbestos Exposure types [n(%)] | miRNA Matrix | Outcome |
|-------------------------------|---------|-----------------------------|--|---|--|---|---|--|--|--------------|------------|
| Matboli 2018 ²² | Egypt | Hospital based case-control | N: 100 CA: 60 CO_Asb-Exp: 20 CO_Non_Asb-Exp: 20 | MPM: M: 35(98.3) F: 25(41.7) CO_Asb-Exp: M: 12(60) F: 8(40) CO_Non_Asb-Exp: M: 12(60) F: 8(40) | CA: ≥55 years: 33 (55) <55 years: 27(45) CO_Asb-Exp: M: 13(3.3) F: 1(1.7) ≥55 years: 11(55) CO_Non_Asb-Exp: M: 14(70) F: 1(5) CO_Non_Asb-Exp: S: 6 (30) NS: 13 (65) PS: 1 (5) | CA: S: 24 (40) NS: 27 (45) CO_Asb-Exp: M: 8 (13.3) F: 1 (1.7) CO_Non_Asb-Exp: S: 5 (25) NS: 14 (70) PS: 1 (5) CO_Non_Asb-Exp: S: 6 (30) NS: 13 (65) PS: 1 (5) | NR | NR | CA: -ve exp: 45(76.3) +ve exp: 14(23.7) CO_Asb-Exp: -ve exp: 20 (100) CO_Non_Asb-Exp: -ve exp: 20(100) | Blood serum | MPM |
| Santarelli 2019 ²² | Italy | Hospital based case-control | N: 397 CA, NSCLC-Asb: 105 CA, NSCLC: 60 CO_Asb-Exp: 80 CA, MPM: 74 CO: 78 | Discovery: CA, NSCLC: M: NR(100) F: 0(0) CA, NSCLC-Asb: M: NR(100) F: 0(0) CA, MPM: M: NR(100) F: 0(0) Serum Training: CO: M: NR(79) F: NR(21) CA, NSCLC: M: NR(60) F: NR(40) CA, NSCLC-Asb: M: NR(80) F: NR(20) CA, MPM: M: NR(83) F: NR(17) | Discovery: CA, NSCLC: 65±7 CA, NSCLC-Asb: 69±11 CA, MPM: 72±8 Serum Training: CO: 56±17 CA, NSCLC: 71±10 CA, NSCLC-Asb: 74±9 CA, MPM: 71±7 | CA, NSCLC-Asb: S: NR (25) CA, NSCLC: S: NR (75) CA, MPM: S: NR (75) CA: NS: NR (25) Yes: NR (75) CO: NS: NR (42) S: NR (26) Ex: NR (32) CA, NSCLC: NS: NR (29) S: NR (26) Ex: NR (45) CA, NSCLC-Asb: NS: NR (20) S: NR (35) Ex: NR (45) CA, MPM: NS: NR (38) S: NR (12) Ex: NR (50) | Self-administered questionnaire | Discovery set: NR Serum Training: CA, NSCLC-Asb: 6.4 (±3.7) CA, MPM: 4.2 (±3.3) | Discovery: CA, NSCLC: Not exposed: NR (100) CA, NSCLC-Asb: Occupational: NR (100) CA, MPM: Occupational: NR (100) Serum Training: CO: Not exposed: NR (100) CA, NSCLC: Not exposed: NR (100) CA, NSCLC-Asb: Occupational: NR (45), Environmental: NR (55) CA, MPM: Occupational: NR (59) Environmental: NR (41) | Blood serum | NSCLC, MPM |
| Cavalleri 2017 ²³ | Italy | Hospital based case-control | N: 42 CA: 23 CO_Asb-Exp: 19 | CA: M: 17(73.9) F: 6(26.1) CO_Asb-Exp: M: 15 (78.9) F: 4(21.1) | CA: 70.2(±7.8) CO_Asb-Exp: 66.5 (±6.4) | CA: S: 5(21.8) Ex: 12(52.1) NS: 6(26.1) CO_Asb-Exp: S: 3(15.8) Ex: 7(36.8) NS: 9(47.4) | Questionnaire administered via personal interview | NR | CA: Definite Occupational: 12(52.3) Possible Occupational: 2(4.3) Environmental: 2 (4.3) NA: 7(30.4) CO_Asb-Exp: Definite Occupational: 19(100) | Plasmatic EV | MPM |
| Mozzoni 2017 ²⁵ | Italy | Hospital based case-control | N: 61 CA: 32 CO_Asb-Exp: 14 CO_Non_Asb-Exp: 15 | CA: M: 24(NR) F: 3(NR) CO_Non_Asb-Exp: M: 12(NR) F: 3(NR) CO_Asb-Exp: M: 8(NR) F: 6(NR) | CA: 72.3(±15.6) CO_Asb-Exp: 75.9 (±9.9) CO_Non_Asb-Exp: 69.9(±7.0) | CA: NS: 12(NR) S: 20(NR) Ex: 00(NR) CO_Asb-Exp: NS: 8(NR) S: 4(NR) Ex: 2(NR) CO_Non_Asb-Exp: NS: 5(NR) S: 7(NR) Ex: 3(NR) | NR | NR | Plasma and FFPE tissue samples | MPM | |
| Weber 2017 ²⁵ | Germany | Hospital based case-control | N: 66 CA: 22 CO_Asb-Exp: 44 | Discovery: CA: M: 21 F: N/A CO_Asb-Exp: M: 21 F: N/A | Discovery: CA: 72[35–85] CO_Asb-Exp: 72 [43–82] | Discovery: NS: 5(NR) S: 7(NR) Ex: 3(NR) | NR | NR | NR | Plasma | MPM |

Table 2 (Continued)

| Author, Year | Country | Study Design | Sample Size | Sex, n(%) | Age [Mean(±SD)] | Smoking Status [n(%)] | Asbestos Exposure Assessment | Asbestos Exposure Duration | Asbestos Exposure types [n(%)] | miRNA Matrix | Outcome |
|-------------------------------|-----------|---|--|--|--|--|---------------------------------|---|---|---------------------------------|---------|
| Truini 2017 ⁴³ | Italy | Hospital based case-control | N: 57 CA: 10 CO_Asb-Exp: 10 CO_Non_Asb-Exp: 10 V: 27 NS: 9(33) S: 18(67) F: 5(19) V5: M: 25(83) F: 5(17) | TS: S: 18(67) NS: 9(33) Unknown: 0(0) V5: S: 19(63) NS: 9(30) NA: 2(7) NR | TS: 67.9(±6.5) V5: 69.5(±8.5) | TS: S: 18(67) NS: 9(33) Unknown: 0(0) V5: S: 19(63) NS: 9(30) NA: 2(7) NR | NR | NR | TS: Yes: 22(81) NA: 5(19) V5: Yes: 20(67) NA: 10(33) | FFPE biopsy tumour tissue | MPM |
| Bononi 2016 ²⁶ | Italy | Hospital based case-control | N: 30 CA: 10 CO_Asb-Exp: 10 CO_Non_Asb-Exp: 10 | NR | CA: 64(NR) CO_Asb-Exp: 64(NR) CO_Non_Asb-Exp: 64(NR) | NR | NR | NR | NR | Blood serum | MPM |
| AK 2015 ⁴¹ | Turkey | Hospital based case-control | N: 24 CA: 18 CO_B_Asb-Exp: 06 | MPM: M: 09 F: 09 CO_B_Asb-Exp: M: 5 F: 01 | [48–81] CO_B_Asb-Exp: 65.7(±12.3), NR [49–79] | NR | NR | CA: 33.1(±19.6), NR [0–81] CO_B_Asb-Exp: 28.2(±11.3), NR [20–49] | NR | Fresh frozen tissues | MPM |
| Santarelli 2015 ²⁷ | Italy | Hospital based case-control | N: 188 CA: 45 CO_Asb-Exp: 99 CO_Non_Asb-Exp: 44 | CA: M: 40(89) F: 5(11) CO_Asb-Exp: M: 90(91) F: 9(9) CO_Non_Asb-Exp: M: NR (80) F: NR (20) | CA: 69(±8) CO_Asb-Exp: 64(±10) CO_Non_Asb-Exp: 68(±6) | CA: S or Ex, No: 14 (31) Yes: 31(69) CO_Asb-Exp: S or Ex, No: 39 (39) Yes: 61(61) CO_Non_Asb-Exp: S or Ex, No: NR (41) Yes: NR(59) NR | Self-administered questionnaire | NR | NR | Blood serum | MPM |
| Kirschner 2015 ³¹ | Australia | Hospital based retrospective cohort study | N: 176 EPP: 85 P/D: 75 LS: 08 SS: 08 | EPP: M: 68(80) F: 17(20) P/D: M: 59(79) F: 16(21) LS: M: 6(NR) F: 2(NR) SS: M: 6(NR) F: 2(NR) CA: M: 13 F: 01 CO_Non_Asb-Exp: M: 09 F: 01 | EPP: 58[22–74] P/D: 66[42–83] LS: 51.5[37–64] SS: 62[47–70] | NR | NR | NR | NR | FFPE tumor specimens | MPM |
| Lamberti 2015 ²⁸ | Italy | Hospital based case-control | N: 24 CA: 14 CO_Non_Asb-Exp: 10 | CA: M: 13 F: 01 CO_Non_Asb-Exp: M: 09 F: 01 | CA: 70.3(±4.6) CO_Non_Asb-Exp: 68.2(±5) | NR | NR | NR | NR | Blood serum | MPM |
| Andersen 2014 ⁴⁰ | Denmark | Hospital based case-control | N: 71 CA: 40 CO: CO_DB: 12 CO_NNP: 14 CO_PTHX: 5 | CA: M: 32(80) F: 8(20) CO: CO_DB: M: 9(75), F: 3 (25) CO_NNP: M: 11(79), F: 3 (21) CO_PTHX: M: 5(100), F: 00 (00) | CA: 64[40–77] CO: DB: 58.5[43–70] NNP: 65.5[44–72] PTHX: 34[20–38] | CA: S: 26(65) NS: 14(35) CO: DB, S: 8(67), NS: 4(33) NNP, S: 10(71), NS: 4(29) PTHX, S: 1(20), NS: 4(80) | NR | NR | NR | FFPE tumor specimens | MPM |
| Weber 2014 ³⁸ | Germany | Hospital based case-control | N: 95 CA: 43 CO_Asb-Exp: 52 | CA: M: 43 F: N/A CO_Asb-Exp: M: 52 F: N/A | CA: 73[35–85] CO_Asb-Exp: 73 [43–85] | CA: S: 21(NR) NS: 20(NR) CO_Asb-Exp: S: 34(NR) NS: 18(NR) | NR | NR | NR | Blood - cellular blood fraction | MPM |

Table 2 (Continued)

| Author, Year | Country | Study Design | Sample Size | Sex [n(%)] | Age [Mean(±SD)] | Smoking Status [n(%)] | Asbestos Exposure Assessment | Asbestos Exposure Duration | Asbestos Exposure types [n(%)] | miRNA Matrix | Outcome |
|----------------------------------|-----------|-----------------------------|---|--|---|--|---|----------------------------|---|--|--------------|
| Gayosso-Gómez 2014 ³³ | Mexico | Hospital based case-control | N: 92 CA_MPM: 11 CO_Non_Asb-Exp_1: 23 CO_Non_Asb-Exp_2: 22 CA_Lung-Ad_1: 15 CA_Lung-Ad_2: 21 | CA_MPM; M: 10(NR) F: 1(NR) CA_Lung-Ad_1; M: 04(NR) F: 11(NR) CA_Lung-Ad_2; M: 13(NR) F: 8(NR) CO_Non_Asb-Exp_1; M: 23(NR) F: 00(00) CO_Non_Asb-Exp_2; M: 00(00) F: 22(NR) | CA_MPM: 65.8 (±13.4) CA_Lung-Ad_1: 61.7 (±11.4) CA_Lung-Ad_2: 60.9 (±15.4) CO_Non_Asb-Exp_1: 47.25(±5.8) CO_Non_Asb-Exp_2: 57.0 (±10.0) | CA_MPM; NS: 02(NR) CA_Lung-Ad_1; NS: 15(NR) CA_Lung-Ad_2; S: 21(NR) CO_Non_Asb-Exp_1; S: 23(NR) CO_Non_Asb-Exp_2; S: 22(NR) | Questionnaire administered via personal interview | NR | NR | Blood serum | MPM, Lung-Ad |
| Xu 2013 ⁴⁴ | USA | Hospital based case-control | N: 31 CA: 25 CO_Non_Asb-Exp: 06 | CA; M: 14(NR) F: 11(NR) CO_Non_Asb-Exp; M: 04(NR) F: 02(NR) | CA: NR [35–70] CO_Non_Asb-Exp: NR [58–71] | NR | NR | NR | NR | Tumor samples specimens and Normal parietal pleura | MPM |
| Muraoka 2013 ⁴⁴ | Japan | Hospital based case-control | N: 110 CA: 48 CO_B_Asb-Exp: 21 CO_Non_Asb-Exp: 41 | CA; M: 45(94) F: 3(6) CO_B_Asb-Exp; M: 15(71) F: 6(29) CO_Non_Asb-Exp; M: 23(56) F: 18(44) | Overall: 69[38–91] CA; <69 years: 28(58) S: 34(71) CO_B_Asb-Exp; >69 years: 20(42) NS: 9(43) S: 12(57) <69 years: 4(20) >69 years: 17 (80) CO_Non_Asb-Exp; M: 23(56) S: 18(44) | NR | NR | NR | Serum | MPM | |
| Kirschner 2012 ⁴² | Australia | Hospital based case-control | N: 94 Plasma or serum; CA: 15 CO_Non_Asb-Exp: 14 Tissue; CA: 18 CO_Non_Asb-Exp: 7 | Plasma or Serum CA; M: 13(NR) F: 02(NR) CO_Non_Asb-Exp; M: 09(NR) F: 05(NR) Tissue CA; M: 14(NR) F: 04(NR) CO_Non_Asb-Exp; M: 05(NR) F: 02(NR) | CA: 68[51–83] CO_Non_Asb-Exp: 58.5[21–78] Tissue Samples CA: 55[37–66] CO_Non_Asb-Exp: 68[57–76] | NR | NR | NR | Plasma or serum and ling tissue | | MPM |
| Weber 2012 ⁴⁹ | Germany | Hospital based case-control | N: 65 CA: 23 CO_Asb-Exp: 17 CO_Non_Asb-Exp: 25 | CA; M: 18(NR) F: 5(NR) CO_Asb-Exp; M: 16(NR) F: 01(NR) CO_Non_Asb-Exp; M: 18(NR) F: 7(NR) | CA: 66[34–84] CO_Asb-Exp: 68 [47–80] CO_Non_Asb-Exp: 70 [56–84] | CA; Ex: 10(NR) NS: 12(NR) NA: 01(NR) CO_Asb-Exp; S: 06(NR) Ex: 05(NR) NS: 06(NR) CO_Non_Asb-Exp; S: 05(NR) Ex: 15(NR) NS: 05(NR) | NR | NR | Cellular fraction of human peripheral blood | MPM | |

Table 2 (Continued)

| Author, Year | Country | Study Design | Sample Size | Sex, [n(%)] | Age [Mean(±SD)] | Smoking Status [n(%)] | Asbestos Exposure Assessment | Asbestos Exposure Duration | Asbestos Exposure types [n(%)] | miRNA Matrix | Outcome |
|------------------------------|---------|-----------------------------|--|---|---|--|---|----------------------------|--------------------------------|--------------|---------|
| Tomasetti 2012 ²⁹ | Italy | Hospital based case-control | N: 121 CA_MPM: 45 CA_NSCLC: 20 CO_Non_Asb-Exp: 56 | CA_MPM; M: 31(NR) F: 14(NR) CA_NSCLC; M: 15(NR) F: 5(NR) CO_Non_Asb-Exp; M: 34(NR) F: 22(NR) | CA_MPM: 67.7(± 8.9) CA_NSCLC: 69.6(± 8.1) CO_Non_Asb-Exp: 66.0(± 6.8) | CA_MPM; S: 21(47) Ex: 9(20) CA_NSCLC; NS: 15(33) S: 5(25) Ex: 6(30) NS: 9(45) CO_Non_Asb-Exp; S: 27(48) Ex: 8(14) NS: 21(38) Discovery Cohort CO; NS: 1(NR) S: 5(NR) Ex: 5(NR) CA_NSCLC; S: 6(NR) Ex: 5(NR) CA; S: NR(38) Ex: NR(62) CO_Asb-Exp; S: NR(54) Ex: NR(46) CO_Non_Asb-Exp; S: NR(57) Ex: NR(43) | NR | NR | Blood serum | MPM, NSCLC | |
| Foss 2011 ³⁰ | Italy | Hospital based case-control | N: 78 CA: 03 CA_NSCLC: 33 CO_Non_Asb-Exp: 42 | Discovery; CO; M: 11 F: 00 CA_NSCLC; M: 10 F: 01 | Discovery; CO: 64[60–74] CA_NSCLC: 65[50–72] | Discovery Cohort CO; NS: 1(NR) S: 5(NR) Ex: 5(NR) CA_NSCLC; S: 6(NR) Ex: 5(NR) CA; S: NR(38) Ex: NR(62) CO_Asb-Exp; S: NR(54) Ex: NR(46) CO_Non_Asb-Exp; S: NR(57) Ex: NR(43) | NR | NR | Blood serum | NSCLC, MPM | |
| Nymark 2011 ⁴³ | Finland | Hospital based case-control | N: 34 CA: 13 CO_Asb-Exp: 13 CO_Non_Asb-Exp: 8 | CA; M: 13 F: 00 CO_Asb-Exp; M: 13 F: 00 CO_Non_Asb-Exp; M: 08 F: 00 | CA: 62.5(NR) CO_Asb-Exp: 62.6(NR) CO_Non_Asb-Exp: NR | CA; S: NR(38) Ex: NR(62) CO_Asb-Exp; S: NR(54) Ex: NR(46) CO_Non_Asb-Exp; S: NR(57) Ex: NR(43) | CA: 33.4(NR) CO_Asb-Exp: 0.04(NR) CO_Non_Asb-Exp: 0.7(NR) | NR | FFPE biopsy tumour tissue | MPM | |

Abbreviations: CA: cases, CO_Non_Asb-Exp: controls non-exposed to asbestos, CO_Asb-Exp: controls exposed to asbestos, exp: exposure, +ve exp: positive exposure, -ve exp: negative exposure, EV: extracellular vesicles, Lung-Ad: lung adenocarcinoma, N: total sample size, SD: Standard deviation, M: male, F: female, S: smoker, NS: non-smoker, Ex: former smoker, NA: data not available, N/A: not applicable, EBC: exhaled breathe condensate, NR: data not reported, NSCLC: non-small cell lung cancer, NSCLC_Asb: Asbestos exposed non-small cell lung cancer, TS: training set, VS: validation set, FFPE: formalin-fixed paraffin embedded, EPP: extra pleural pneumonectomy, P/D: pleurectomy ± decortication, LS: long survivor, SS: short survivor, NNP: patient-matched non-neoplastic pleura, PTHX: non neoplastic reactive mesothelial proliferation due to pneumothorax, BAsb-Exp: Benign pleural asbestosis, Y: years.

Table 3 MicroRNAs found associated with diagnosis and/or prognosis of asbestos-related LC and/or MPM in the studies included in the systematic review.

| Author, Year | Matrix of miRNA | miRNAs | miRNA Expression change | Statistical model and adjustment for confounders | Effect estimates (95 % CI) of miRNAs expression change | miRNAs expression changes in Fold change (FC) | Adjustment for multiple tests | Cancer type | Cancer Histology | Cancer Stage |
|------------------------------------|------------------------------|---|----------------------------|--|---|---|--|-------------------------------|--|--|
| Casalone 2022 ¹⁸ | Serum Extracellular Vesicles | miR-11,400 miR-148a-3p miR-409-3p | ↑ ↓ | Multivariable logistic regression model adjusted for age, batch effect, country and asbestos exposure | NR | miR-11,400: 1.4 (0.69–2.0) miR-148a-3p: 0.6 (0.2–0.82) miR-409-3p: 0.7 (0.02–1.3) | miR-11,400: 0.01 (FDR - adjusted p value) | MPM | NR | NR |
| Mauro 2023 ¹⁹ | Blood serum | miR-197-3p | ↑ | ANOVA test matching by age | NR | NR | CA vs. CO_Asb-Exp: 0.0036 CO_Asb-Exp vs. CO_No_Asb-Exp: 0.0001 (Tukey test – adjusted p value) | MPM | Epithelioid: 27 (36.0) Sarcomatoid: 20 (26.7) Biphasic: 28 (37.3) | NR |
| Jiménez-Ramírez 2022 ²⁶ | Plasma | miR-103a-3p | ↓ | Mann-Whitney U, Chi-squared or Fisher's exact test Matching by sex and age | NR | NR | NR | MPM | Epithelioid: 102 (94.4) Biphasic: 2(1.9) Sarcomatoid: 4 (3.7) | NR |
| Ferrari 2022 ²⁰ | Plasma samples | miR-103a-3p miR-30e-3p | ↓ | Multivariable logistic regression model adjusted for sex, age, BMI, and smoking | OR; miR-103a-3p: 0.99996 (0.99970–1.000) miR-30e-3p: 1.00004 (0.99950–1.001) | miR-103a-3p: 0.57 miR-30e-3p: 0.76 | NR | MPM | Epithelioid: 14 (54) Biphasic: 10(38) Sarcomatoid: 2 (8) | Stage I: 8(31) Stage II: 6(23) Stage III: 7 (27) Stage IV: 5 (19) |
| Faversani 2021 ²¹ | Blood plasma EBC | miR-597-5p miR-1260a miR-130b-3p miR-302b-3p miR-518f-3p let-7f-5p miR-345-5p miR-362-5p miR-1260a miR-1260a | ↑ ↓ ↓ ↓ ↑ ↑ | Multivariable logistic regression model adjusted for age, BMI and smoking habits | OR; miR-597-5p: 0.852 miR-1260a: 1.615 miR-130b-3p: 0.410 miR-302b-3p: 2.849 miR-518f-3p: 1.030 let-7f-5p: 0.301 miR-345-5p: 0.406 miR-362-5p: 0.390 miR-1260a: 1.615 | Blood plasma; miR-597-5p: 2.4 miR-1260a: 9.9 Let-7f-5p: 0.39 miR-1260a: 21.5 miR-130b-3p: 0.98 miR-302b-3p: 0.06 miR-345-5p: 2.68 miR-362-5p: 2.04 miR-518f-3p: 4.0 miR-597-5p: 2.57 EBC; miR-1260a: 1.26 miR-597-5p: 1.42 NR | let-7f-5p: 0.399 miR-1260a: 0.999 miR-130b-3p: 0.999 miR-302b-3p: NR miR-345-5p: 0.936 miR-362-5p: 0.999 miR-518f-3p: 0.200 (FDR - adjusted p value) | MPM Lung-Ad MPM | Lung_Ad: NR (100) | Stage I - II: NR (100) |
| Weber 2019 ¹⁷ | Plasma | miR-132-3p miR-126-3p miR-103a-3p Combination of three miRNAs | ↓ | Mann-Whitney U tests and Kruskal-Wallis tests Matching by age, sex, smoking status, and date of blood collection | NR | NR | NR | MPM | Epithelioid: 10 (58.8) Biphasic: 2 (11.8) Sarcomatoid: 3 (17.6) Not specified: 2 (11.8) | NR |
| Matboli 2018 ³² | Blood serum | miR-548a-3p miR-20a | ↑ | Kruskal-Wallis tests and one way analysis Matching by sex, age, history of smoking and asbestos exposure | Standardized coefficients (β) Linear regression analysis miRNA-2053 after cutoff: 0.303 (0.072–0.522) | CA; miR-250,053: 19.3729 CO_Asb-Exp; miR-250,053: 0.8450 CO_Non_Asb-Exp; miR-250,053: 0.7492 | NR | MPM | NR | Stage I: 46 (76.7) Stage II: 13 (21.7) Stage III: 1 (1.7) |

Table 3 (Continued)

| Author, Year | Matrix of miRNA | miRNAs | miRNA Expression change | Statistical model and adjustment for confounders | Effect estimates (95% CI) of miRNAs expression change | miRNAs expression changes in Fold change (FC) | Adjustment for multiple tests | Cancer type | Cancer Histology | Cancer Stage |
|-------------------------------|---|---|-------------------------|--|---|--|---|-------------|--|---|
| Santarelli 2019 ²² | Blood serum | miR-126 miR-222 | ↑ | Multivariable logistic regression model adjusted for age, sex, and smoking | OR; miR-222: 1.501 (1.148–1.958) miR-222/miR-126: 0.138 (0.019–0.076) | CA, NSCLC; miR-126: 0.90 miR-205: 2.93 miR-222: 1.84 miR-520 g: 1.09 CA, NSCLC, A5b; miR-126: 1.18 miR-205: 2.91 miR-222: 4.14 miR-520 g: 0.63 CA; miR-126: 0.45 miR-205: 0.61 miR-222: 0.85 miR-520 g: 0.65 | miR-222: 0.003 (two-tailed Student t-test - adjusted p value) | MPM, NSCLC | Discovery, CA, NSCLC, Adenocarcinoma: NR(100) CA, NSCLC, A5b; Squamous: NR (25) Adenocarcinoma: NR(75) CA; Epithelioid: NR (90) Biphasic: NR(10) Serum_Training CA, NSCLC; Squamous: NR (35) Large cell: NR(10) Adenocarcinoma: NR (55) CA, NSCLC, A5b; Squamous: NR (36) Large cell: NR(18) Adenocarcinoma: NR (46) CA; Epithelioid: NR (75) Sarcomatoid: NR(25) Epithelioid: 10 (NR) Biphasic: 11(NR) Sarcomatoid: 01 (NR) Not specified: 01(NR) Epithelioid: 26 (NR) Biphasic: 6(NR) Sarcomatoid: 3 (NR) Not specified: 0 (NR) Epithelioid: 20 (74) Sarcomatoid: 3 (11) Not typified: 1 (4) | NR |
| Cavalleri, 2017 ²³ | Plasmatic extra-cellular vesicles (EVs) | miR-103a miR-98 miR-148b miR-744 miR-30e-3p | ↓ | Cox multivariable regression model adjusted for age, sex, BMI and smoking. | HR; miR-103a: 0.37 (0.13–1.13) miR-30e-3p: 0.51 (0.17 - 1.52) | miR-103: 0.25 miR-98: 0.23 miR-148b: 0.29 miR-744: 0.31 miR-30e-3p: 0.37 | miR-103: 0.056 miR-98: 0.056 miR-148b: 0.056 miR-744: 0.056 miR-30e-3p: 0.056 (FDR - adjusted p value) | MPM | Epithelioid: 10 (NR) Biphasic: 11(NR) Sarcomatoid: 01 (NR) Not specified: 01(NR) Epithelioid: 26 (NR) Biphasic: 6(NR) Sarcomatoid: 3 (NR) Not specified: 0 (NR) Epithelioid: 20 (74) Sarcomatoid: 3 (11) Not typified: 1 (4) | NR |
| Mozzoni 2017 ²⁵ | Blood plasma and FFPE tissue | miR-17 miR-126 miR-16 miR-486 miR-132-3p | ↓ | Two-sided, two-sample t-test NR | NR | NR | NR | MPM | Epithelioid: 26 (NR) Biphasic: 6(NR) Sarcomatoid: 3 (NR) Not specified: 0 (NR) Epithelioid: 20 (74) Sarcomatoid: 3 (11) Not typified: 1 (4) | Stage I: 2(NR) Stage II: 9(NR) Stage III: 15(NR) Stage IV: 6(NR) NR |
| Weber 2017 ³⁵ | Plasma | miR-132-3p | ↓ | Wilcoxon rank-sum tests Matching by age and smoking | NR | NR | NR | MPM | Discovery; Epithelioid: 14 (NR) Biphasic: 4(NR) Sarcomatoid: 3 (NR) Not specified: 0 (NR) Epithelioid: 20 (74) Sarcomatoid: 3 (11) Not typified: 1 (4) | NR |
| Tuini 2017 ²⁴ | FFPE biopsy tumor | miR-99a let-7c miR-125b | ↓ | Cox multivariable regression model adjusted for age and histological subtype | HR; Training set miR-99a: 0.42 (NR) let-7c: 0.32 (NR) miR-125b: 0.41 (NR) TCGA MPM dataset miR-99a-5p: 0.75 (NR) let-7c: 0.79 (NR) miR-125b-5p: 0.63 (NR) | miR-99a-5p: 0.14 let-7c: 0.18 miR-125b-5p: 0.31 | Training set; miR-99a: 0.0014 let-7c: 0.0014 miR-125b: 0.0010 TCGA MPM dataset miR-99a-5p: 0.0040 let-7c: 0.0240 miR-125b-5p: 0.0010 (Cox proportional hazard - adjusted p value) | MPM | Epithelioid: 20 (74) Sarcomatoid: 3 (11) Not typified: 1 (4) | NR |

Table 3 (Continued)

| Author, Year | Matrix of miRNA | miRNAs | miRNA Expression change | Statistical model and adjustment for confounders | Effect estimates (95 % CI) of miRNAs expression change | miRNAs expression changes in Fold change (FC) | Adjustment for multiple tests | Cancer type | Cancer Histology | Cancer Stage |
|-------------------------------|----------------------|--|-------------------------|---|---|---|-------------------------------|--|---|--------------|
| Bononi 2016 ⁴⁶ | Blood serum | miR-197-3p miR-1281 miR-32-3p miR-197-3p miR-32-3p miR-1281 | ↑ | NR | NR | miR-1281: 3.7 miR-32-3p: 18 miR-197-3p; CA vs. CO_Non_Asb-Exp: 4.4 CA vs. CO_Asb-Exp: 5.5 miR-1281; CA vs. CO_Non_Asb-Exp: 3.7 CO_Asb-Exp vs. CO_Non_Asb-Exp: 3.3 miR-32-3p; CA vs. CO_Non_Asb-Exp: 17.6 CO_Asb-Exp vs. CO_Non_Asb-Exp: 61.5 miR-197-3p; CA vs. CO_Non_Asb-Exp: 1.8 CA vs. CO_Asb-Exp: 2.5 miR-1281; CA vs. CO_Non_Asb-Exp: 2.5 CA vs. CO_Asb-Exp: 3.5 miR-484: 5.58 miR-320: 2.87 let-7a: 13.93 miR-744: 4.26 miR-20a: 5.7 miR-193b: 3.03 let-7d: 5.82 miR-125a-5p: 8.17 miR-92a: 2.39 miR-155: 3.16 miR-152: 2.93 | NR | MPM | NR | NR |
| Ak 2015 ⁴¹ | Fresh frozen tissues | miR-484 miR-320 let-7a miR-744 miR-20a miR-193b let-7d miR-125a-5p miR-92a miR-155 miR-152 | ↑ | NR | NR | miR-484: 0.010 miR-320: 0.017 let-7a: 0.019 miR-744: 0.019 miR-20a: 0.019 miR-193b: 0.019 let-7d: 0.046 miR-125a-5p: 0.045 miR-92a: 0.045 miR-155: 0.045 miR-152: 0.047 (Multiple hypothesis testing, q value function – adjusted p value) | MPM | Epithelial: 10 (55.6) Mixed: 4 (22.2) Sarcomatoid: 4 (22.2) | Stage I - II: 4 (22.2) Stage III - IV: 14 (77.8) | |
| Santarelli 2015 ²⁷ | Blood serum | miR-126 | ↓ | Multivariable regression model adjusted for age, sex, smoking and asbestos exposure | CO_Non_Asb-Exp vs CO_Asb-Exp: miR-126: 1.23 (1.0–1.6) (p = 0.056) CO_Asb-Exp vs. CA: miR-126: 1.13 (0.9–1.4) (p = 0.259) CA vs. CO_Non_Asb-Exp: miR-126: 1.34 (1.0–1.8) (p = 0.05) | NR | MPM | Epithelioid: 33 (73 %) Biphasic: 9 (20 %) Sarcomatoid: 3 (7 %) | NR | |

Table 3 (Continued)

| Author, Year | Matrix of miRNA | miRNAs | miRNA Expression change | Statistical model and adjustment for confounders | Effect estimates (95% CI) of miRNAs expression change | miRNAs expression changes in Fold change (FC) | Adjustment for multiple tests | Cancer type | Cancer Histology | Cancer Stage | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|------------------------------|---|-----------------------------|-------------------------|---|--|---|--|-------------|--|--------------|-------------|------------|-----------|-----------|-------------|-----------|------------|------------|--|---|------------|---------|----------|----------|---------|------------|-----------|-------------|------------|------------|------------|-----------|------------|------------|------------|-----------|-----------|-------------|-----------|------------|------------|------------|------------|------------|---------|----------|----------|---------|------------|-----------|-------------|------------|------------|------------|-----------|
| Kirschner 2015 ¹¹ | Formalin-fixed paraffin embedded (FFPE) tumor specimens | miR-21-5p | ↓ | Multivariable logistic regression model adjusted for histological subtype, age, and sex | OR: miR-21-5p: 0.87 miR-23a-3p: 1.20 miR-30e-5p: 0.79 miR-221-3p: 0.79 miR-222-3p: 0.90 miR-31-5p: 1.06 HR from Cox regression model: Univariable model: miR-21-5p: 2.84 (1.48–5.45) Multivariable model: hsa-miR-21-5p: 3.35 (1.66–6.75) | miR-222-3p: -4.43 miR-221-3p: -3.51 miR-210-3p: -3.46 miR-21-5p: -2.76 miR-93-5p: -2.67 miR-106b-5p: -2.51 miR-17-5p: -2.50 miR-27a-3p: -2.16 miR-20a-5p: -2.12 miR-19b-3p: -2.02 miR-30e-5p: -2.02 miR-23a-3p: -1.81 miR-662: 2.88 Microarray only: miR-1469: 2.02 miR-1826: 2.29 miR-298: 15.39 RT-qPCR only: miR-29c-5p: NA miR-31-5p: NA miR-106a-5p: NA miR-126-3p: NA miR-625-3p: NA miR-92a-3p: NA miR-24-3p: NA | miR-221-3p: 0.0147 miR-210-3p: 0.0465 miR-21-5p: 0.0465 miR-93-5p: 0.0495 miR-27a-3p: 0.0465 (Benjamini-Hochberg Correction for FDR – adjusted p value) | MPM | EPP- Complete cohort; Epithelioid: 65(76) Biphasic: 20(24) Sarcomatoid: 0 (0) P/D- Complete cohort; Epithelioid: 37(49) Biphasic: 26(35) Sarcomatoid: 12 (16) | NR | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | miR-221-3p | | | | | | | | | miR-222-3p | miR-210-3p | miR-21-5p | miR-93-5p | miR-106b-5p | miR-17-5p | miR-27a-3p | miR-20a-5p | miR-19b-3p | miR-30e-5p | miR-23a-3p | miR-662 | miR-1469 | miR-1826 | miR-298 | miR-29c-5p | miR-31-5p | miR-106a-5p | miR-126-3p | miR-625-3p | miR-92a-3p | miR-24-3p | miR-221-3p | miR-222-3p | miR-210-3p | miR-21-5p | miR-93-5p | miR-106b-5p | miR-17-5p | miR-27a-3p | miR-20a-5p | miR-19b-3p | miR-30e-5p | miR-23a-3p | miR-662 | miR-1469 | miR-1826 | miR-298 | miR-29c-5p | miR-31-5p | miR-106a-5p | miR-126-3p | miR-625-3p | miR-92a-3p | miR-24-3p |
| | | Lamberti 2015 ²⁸ | | | | | | | | | Blood serum | miR-101 | ↑ | NR | NR | NR | NR | MPM | Epithelial: 07 (NR) Sarcomatoid: 03 (NR) Mixed: 04(NR) | Stage I: 05 (NR) Stage II: 03 (NR) Stage III: 06 (NR) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | miR-25 | | | | | | | | | miR-26b | miR-335 | miR-433 | miR191 | miR-223 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | miR-25 | | | | | | | | | miR-26b | miR-335 | miR-433 | miR191 | miR-223 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | miR-25 | | | | | | | | | miR-26b | miR-335 | miR-433 | miR191 | miR-223 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | miR-25 | | | | | | | | | miR-26b | miR-335 | miR-433 | miR191 | miR-223 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | miR-25 | | | | | | | | | miR-26b | miR-335 | miR-433 | miR191 | miR-223 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | miR-25 | | | | | | | | | miR-26b | miR-335 | miR-433 | miR191 | miR-223 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | miR-25 | | | | | | | | | miR-26b | miR-335 | miR-433 | miR191 | miR-223 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | miR-25 | | | | | | | | | miR-26b | miR-335 | miR-433 | miR191 | miR-223 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | miR-25 | | | | | | | | | miR-26b | miR-335 | miR-433 | miR191 | miR-223 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | miR-25 | | | | | | | | | miR-26b | miR-335 | miR-433 | miR191 | miR-223 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

Table 3 (Continued)

| Author, Year | Matrix of miRNA | miRNAs | miRNA Expression change | Statistical model and adjustment for confounders | Effect estimates (95% CI) of miRNAs expression change | miRNAs expression changes in Fold change (FC) | Adjustment for multiple tests | Cancer type | Cancer Histology | Cancer Stage |
|-----------------------------|--|-------------|-------------------------|--|---|--|---|--|--|---|
| Andersen 2014 ⁴⁰ | Formalin-fixed, paraffin-embedded tissue specimens | miR-378 | ↑ | Multivariable logistic regression model used to estimate the performance of each miRNA (i.e., miR-143, miR-145, and miR-652) adjusted for the effect of the other 2 miRNAs | Estimate (where $p < 0.001$) Intercept: 4.38 (4.22–4.54) miR-126: 0.53 (0.49–0.57) miR-143: 0.98 (0.94–1.02) miR-145: –2.34 [–2.27] – (–2.39)] miR-652: –1.45 [–1.40] – (–1.50)] | CO_DB vs CA miR-126: 1.95 miR-143: 2.44 miR-145: 1.54 miR-193a-3p: 2.49 miR-193b: 1.31 miR-652: 1.20 CA vs CO_NNP miR-126: –4.42 (1.53) miR-143: –4.00 (1.64) miR-145: –5.33 (1.30) miR-193a-3p: –2.36 (1.32) miR-193b: 0.95 (1.12) miR-652: –0.27 (1.11) CA; miR-126: –2.87 (1.28) miR-143: –2.61 (1.27) miR-145: –2.53 (1.42) miR-193a-3p: –1.11 (1.13) miR-193b: 0.02 (1.24) miR-652: 1.34 (0.87) CO_PTHX; miR-126: –5.50 (1.40) miR-143: –4.13 (1.49) miR-145: –4.79 (1.27) miR-193a-3p: –2.38 (0.76) miR-193b: –1.14 (0.74) miR-652: 0.30 (1.17) turky-kramer post hoc test – adjusted p value | CO_DB; miR-126: –1.91 (1.53) miR-143: –1.32 (1.11) miR-145: –1.91 (1.33) miR-193a-3p: –2.43 (1.20) miR-193b: –0.37 (0.66) miR-652: 1.60 (1.12) CO_NNP; miR-126: –4.42 (1.53) miR-143: –4.00 (1.64) miR-145: –5.33 (1.30) miR-193a-3p: –2.36 (1.32) miR-193b: 0.95 (1.12) miR-652: –0.27 (1.11) CA; miR-126: –2.87 (1.28) miR-143: –2.61 (1.27) miR-145: –2.53 (1.42) miR-193a-3p: –1.11 (1.13) miR-193b: 0.02 (1.24) miR-652: 1.34 (0.87) CO_PTHX; miR-126: –5.50 (1.40) miR-143: –4.13 (1.49) miR-145: –4.79 (1.27) miR-193a-3p: –2.38 (0.76) miR-193b: –1.14 (0.74) miR-652: 0.30 (1.17) turky-kramer post hoc test – adjusted p value | MPM | MPM; Epithelioid: 18 (45), Biphasic: 22 (55) CO_DB; Epithelioid: 9 (75), Biphasic: 3 (25) | CA, Stage I: 1 (3) Stage II: 6 (15) Stage III: 23 (58) Stage IV: 10 (25) CO_DB; Stage I: 1 (8) Stage II: 8 (67) Stage III: 3 (25) |
| | | miR-365a | | | | | | | | |
| | | miR-193a-3p | | | | | | | | |
| | | miR-193b | | | | | | | | |
| | | miR-210 | | | | | | | | |
| | | let-7c | | | | | | | | |
| | | miR-99a | | | | | | | | |
| | | miR-126 | | | | | | | | |
| | | miR-143 | | | | | | | | |
| | | miR-145 | | | | | | | | |
| | | miR-144-5p | | | | | | | | |
| | | miR-451a | | | | | | | | |
| | | miR-466-5p | | | | | | | | |
| | | miR-652 | | | | | | | | |
| Weber 2014 ³⁸ | Blood - cellular blood fraction | miR-103a-3p | NR | NR | NR | NR | MPM | Epithelioid: 28 (NR), Biphasic: 6 (NR), Sarcomatoid: 5 (NR), Not specified: 4 (NR) | NR | |
| | | | | | | | | | | |

Table 3 (Continued)

| Author, Year | Matrix of miRNA | miRNAs | miRNA Expression change | Statistical model and adjustment for confounders | Effect estimates (95 % CI) of miRNAs expression change | miRNAs expression changes in Fold change (FC) | Adjustment for multiple tests | Cancer type | Cancer Histology | Cancer Stage |
|----------------------------------|---|---|-------------------------|---|--|--|-------------------------------|--------------|---|---|
| Goyasso-Gómez 2014 ²³ | Blood serum | miR-1292-5p miR-409-5p miR-92b-5p miR-4791 miR-185-5p miR-96-5p miR-1271-5p | ↑ | NR | NR | CA vs. CO_Non_Asb-Exp miR-4791: 8.93 miR-185-5p: 3.995 miR-96-5p: 4.453 miR-1271-5p: Inf miR-1292-5p: Inf miR-409-5p: Inf miR-92b-5p: 6.33 CA_Lung-Ad vs CO_No- n_Asb-Exp miR-4791: 10.1449 miR-185-5p: 5.1217 miR-1271-5p: Inf CA vs. CA_Lung-Ad miR-1292-5p: 2.345 miR-409-5p: 2.603 miR-363: 23.8 miR-130b: 3.5 miR-221: 3.7 miR-155: 3.8 miR-21: 3.9 miR-379: 4.1 miR-629: 7.6 | NR | MPM | CA; Epithelioid: 11 (NR) | CA, IIIA: 01(NR), IIIB: 03(NR), IV: 04(NR), IIA: 04(NR), IIA: 01(NR), NR: 03(NR) CA_Lung-Ad; IIIB: 05; IV: 31 |
| Xu 2013 ⁴⁴ | Tumor | miR-551b miR-483-5p miR-206 miR-363 miR-323-3p miR-34b miR-514 miR-130b miR-221 miR-155 miR-21 miR-34b/c | ↑ ↓ | NR | NR | miR-363: 9.3E-06 miR-130b: 1.9E-04 miR-221: 4.1E-03 miR-155: 1.0E-03 miR-21: 1.7E-03 miR-379: 1.8E-02 miR-629: 9.7E-05 (Benjamini-Hochberg Cor- rection for FDR – adjusted p value) | NR | MPM | Epithelioid: 18 (NR) Biphasic: 4(NR) Sarcomatoid: 3 (NR) | NR |
| Muraoka 2013 ³⁴ | Serum | miR-29c* miR-92a miR-625-3p | ↑ | NR | NR | Plasma; miR-29c: 1.64 In tumors; miR-625-3p: 4.35 miR-29c: -2.65 miR-92a: -1.8 | NR | Advanced MPM | Epithelioid: 36 (75) Biphasic: 8(17) Sarcomatoid: 4 (8) Test Cohort – CA: Epithelioid: 9 (60) Biphasic: 3(20) Sarcomatoid: 2 (13, 33) Unspecified: 1 (0.07) Tissue samples; Epithelioid: 15 (83, 33) Biphasic: 3 (16, 66) Sarcomatoid: 0 NR | Stage I: 12(25) Stage II: 5(10) Stage III: 16(33) Stage IV: 12(25) Unknown: 3(7) NR |
| Kirschner 2012 ⁴² | Blood plasma | miR-103 miR-20a | ↓ | NR | NR | NR | NR | MPM | CA; Epithelioid: 9 (60) Biphasic: 3(20) Sarcomatoid: 2 (13, 33) Unspecified: 1 (0.07) Tissue samples; Epithelioid: 15 (83, 33) Biphasic: 3 (16, 66) Sarcomatoid: 0 NR | NR |
| Weber 2012 ²⁹ | Cellular fraction of human peripheral blood | miR-103 miR-20a | ↓ | Mann-Whitney unpaired test Age, sex, and smoking status were matched | NR | NR | NR | MPM | NR | NR |
| Tomasetti 2012 ²⁹ | Blood serum | miR-126 | ↓ | One-way ANOVA to evaluate differences among MM and NSCLC patients and healthy controls. | NR | NR | Post-hoc Bonferroni test | MPM NSCLC | NR | NR |

Table 3 (Continued)

| Author, Year | Matrix of miRNA | miRNAs | miRNA Expression change | Statistical model and adjustment for confounders | Effect estimates (95% CI) of miRNAs expression change | miRNAs expression changes in Fold change (FC) | Adjustment for multiple tests | Cancer type | Cancer Histology | Cancer Stage |
|---------------------------|-----------------|--|--|--|---|---|--|-------------------|--|--|
| Foss 2011 ¹⁰ | Blood serum | miR-1254 miR-574-5p | ↑ | NR | NR | NR | miR-574-5p: 0.22 miR-1254: 0.42 (FDR – adjusted p value) | Early-stage NSCLC | CA, NSCLC, Adenocarcinoma: 6(NR), Bronchioloalveolar carcinoma: 1(NR), Squamous cell carcinoma: 1(NR), Large cell carcinoma: 1(NR), Other: 1(NR), Unavailable: 1(NR) | Discovery, NSCLC, Stage I: 4, Stage II: 0, Stage III: 6, Unavailable: 1, MPM |
| Nymark 2011 ⁴³ | Tissues | miR-148b miR-374a miR-24-1* let-7e miR-199b-5p miR-331-3p miR-96 miR-939 miR-671-5p miR-605 miR-1224-5p miR-202 | ↑ ↓ | NR Age, sex, nationality, smoking history and distribution of histological types were matched | NR | miR-148b: 0.325 miR-374a: 0.535714 miR-24-1*: 0.19904763 CO_Asb-Exp: miR-939: -1.2571429 miR-671-5p: -0.42619047 miR-605: -0.2164288 miR-1224-5p: -0.52761906 miR-202: -0.632619 Lung-Adenocarcinoma CO_Asb-Exp: miR-202: -1.142 | miR-148b: 0.028543 miR-374a: 0.028543 miR-24-1*: 0.047273 miR-939: 0.018745 miR-671-5p: 0.018745 miR-605: 0.018745 miR-1224-5p: 0.018745 miR-202: 0.047273 Lung-Ad CO_Asb-Exp: miR-199b-5p: 0.049309 miR-374a: 0.057633 let-7e: 0.067007 let-7e: 0.067007 miR-331-3p: 0.067007 miR-96: 0.067007 miR-24-1: 0.067007 Lung-Ad CO_Asb-Exp: miR-202: 0.049309 (Benjamini-Hochberg test, FDR – adjusted p value) | MPM | Exposed Patients LCLC: 03 AC: 06 SCC: 03 SCLC: 02 Non-exposed patients LCLC: 01 AC: 05 SCC: 06 SCLC: 02 | NR |

Abbreviations: CA: cases, CO: Non-Asb-Exp: controls non-exposed to asbestos, MPM: malignant pleural mesothelioma, CO_Asb-Exp: controls exposed to asbestos, exp: exposure, +ve exp: positive exposure, -ve exp: negative exposure, EV: extracellular vesicles, Lung-Ad: lung adenocarcinoma, N: total sample size, M: male, F: female, S: smoker, NS: non-smoker, Ex: former smoker, NA: data not available, N/A: not applicable, EBC: exhaled breathe condensate, NR: data not reported, NSCLC: non-small cell lung cancer, NSCLC_Asb: Asbestos exposed non-small cell lung cancer, TS: training set, VS: validation set, FFPPE: formalin-fixed paraffin embedded, EPP: extra pleural pneumonectomy, P/D: pleurectomy ± decortication, LS: long survivor, SS: short survivor, INP: patient-matched non-neoplastic pleura, PTHX: non neoplastic reactive mesothelial proliferation due to pneumothorax, BAsb-Exp: Benign pleural asbestosis, Y: years, OR: Odds ratio, (f): f, standard co-efficient.

Table 4 Diagnostic and prognostic accuracy of the miRNAs significantly associated with increased lung cancer risk in the included studies.

| Author, Year | miRNA(s) | Sensitivity (%) | Specificity (%) | Sensibility specificity at cut-off | Cut off Value | Positive predictive value (PPV) | Negative predictive value (NPV) | Areas under the curve (AUC) and (95 % CI) for diagnosis | Areas under the curve (AUC) and (95 % CI) for survival (months) | Cancer Histology | Cancer Stage |
|------------------------------------|---|--|--|------------------------------------|--|--|--|--|--|---|--------------|
| Casalone 2022 ¹⁸ | miR-11,400 miR-148a-3p miR-409-3p | miR-11,400 miR-148-3p and miR-409 Discovery set (Prospective): 75 % Validation (Retrospective): 53 % | miR-11,400 miR-148-3p and miR-409 Discovery set (Prospective): 70 % Validation (Retrospective): 95 % | NR | NR | miR-11,400 miR-148-3p and miR-409 Discovery set (Prospective): 71 % Validation (Retrospective): 94 % | miR-11,400 miR-148-3p and miR-409 Discovery set (Prospective): 74 % Validation (Retrospective): 57 % | miR-11,400 miR-148-3p and miR-409 Discovery set (Prospective): 81 % Validation (Retrospective): 86 % | NR | NR | NR |
| Mauro 2023 ¹⁹ | miR-197-3p | NR | NR | NR | NR | NR | NR | ddPCR analyses; miR-197-3p, CA vs. CO_Asb- Exp: 0.65 (0.563-0.739) CA vs CO_No- n_Asb-Exp: 0.55 (0.454-0.640) RT-qPCR analyses; miR-197-3p, CA vs. CO_Asb- Exp: 0.62 (0.525-0.708) CA vs CO_No- n_Asb-Exp: 0.56 (0.472-0.657) | Epithelioid: 13.5(±0.6) Sarcomatoid: 7.9(±0.7) Biphasic: 12.4 (±0.6) TOT: 11.5 (±0.6) | Epithelioid: 27 (36.0) Sarcomatoid: 20 (26.7) Biphasic: 28 (37.3) | NR |
| Jiménez-Ramírez 2022 ³⁶ | miR-103a-3p | miR-103a-3p; M: 4.4 % F: 0 % | miR-103a-3p; M: 95.5 % F: 97.4 % | NR | miR-103a-3p; M: 1782 F: 3082 | M; TP: 4 TN: 171 F; TP: 00 TN: 39 NR | M; FP: 8 FN: 86 F; FP: 0 FN: 18 NR | miR-103a-3p; M: 0.426 (0.355-0.497) F: 0.437 (0.284-0.589) | NR | Epithelioid: 102(94.4) Biphasic: 2 (1.9) Sarcomatoid: 4 (3.7) Epithelioid: 10(58.8) Biphasic: 2 (11.8) Sarcomatoid: 3(17.6) Not speci- fied: 2(11.8) | NR |
| Weber 2019 ³⁷ | miR-132-3p miR-126-3p miR-103a-3p Combination of three miRNAs | miR-132-3p: 71 % miR-126-3p: 59 % miR-103a-3p: 82 % Combination of three miRNAs: 82 % | miR-132-3p: 47 % miR-126-3p: 72 % miR-103a-3p: 42 % Combination of three miRNAs: 47 % | NR | NR | NR | NR | miR-132-3p: 0.542 (0.370-0.713) miR-126-3p: 0.614 (0.439-0.789) miR-103a-3p: 0.603 (0.440-0.765) Combination of three miRNA (s): 0.605 (0.445-0.765) | NR | Epithelioid: 10(58.8) Biphasic: 2 (11.8) Sarcomatoid: 3(17.6) Not speci- fied: 2(11.8) | NR |
| Matboli 2018 ³² | miR-548a-3p miR-20a Combination miRNAs | miR 548a-3p: 91.7 % mir-20a: 96.7 % Combined (mir20a + miR- 548a-3p): 100 % | miR 548a-3p: 97.5 % mir-20a: 95.0 % Combined (mir20a + miR- 548a-3p): 87.5 % | NR | miRNA-548a- 3p: 1.69 miRNA-20a: 1.2 Combind miRNAs: 1.7 | miR 548a-3p: 98.2 % mir20a: 96.7 % Combined (mir20a + miR- 548a-3p): 100 % | miR 548a-3p: 88.6 % mir20a: 95.0 % Combined (mir20a + miR- 548a-3p): 92.3 % | miR-548a-3p: 0.922 (0.855-0.982) miR-20a: 0.98 (0.927-0.992) Combind miRNAs: 0.96 (0.917-0.996) | NR | Stage I: 46 (76.7) Stage II: 13 (21.7) Stage III: 1 (1.7) | |

Table 4 (Continued)

| Author, Year | miRNA(s) | Sensitivity (%) | Specificity (%) | Sensitivity specificity at cut-off | Cut off Value | Positive predictive value (PPV) | Negative predictive value (NPV) | Areas under the curve (AUC) and (95 % CI) for diagnosis | Areas under the curve (AUC) and (95 % CI) for survival (months) | Cancer Histology | Cancer Stage |
|-------------------------------|---|--|--|--|---|---------------------------------|---------------------------------|---|---|---|---|
| Santarelli 2019 ²² | miR-126 miR-205 miR-222 miR-520 g | miR-222: 80 % | miR-222: 70 % | NR | miR-222: 0.466 | NR | NR | miR-222: 0.767 (0.675–0.858) | NR | Discovery, CA_NSCLC; Adenocarci- noma: NR (100) CA_N- SCLC_Asb; Squamous: NR(25) Ade- nocarcinoma: NR(75) CA; Epithelioid: NR(90) Biphasic: NR (10) Serum_Train- ing CA_NSCLC; Squamous: NR(35) Large cell: NR(10) Adenocarci- noma: NR(55) CA_N- SCLC_Asb; Squamous: NR(36) Large cell: NR(18) Adenocarci- noma: NR(46) CA; Epithelioid: NR(75) Sarco- matoid: NR (25) Epithelioid: 10(NR) Biphasic: 11 (NR) Sarcomatoid: 01 (NR) Not speci- fied: 01(NR) | NR |
| Cavalleri 2017 ²³ | miR-103a miR-98 miR-148b miR-744 miR-30e-3p | miR-103: 1.000 miR-98: 1.000 miR-148b: 1.000 miR-744: 0.727 miR-30e-3p: 0.636 | miR-103: 0.667 miR-98: 0.667 miR-148b: 0.733 miR-744: 0.867 miR-30e-3p: 0.933 | NR | NR | NR | NR | miR-103: 0.864 (0.724–1.000) miR-98: 0.864 (0.727–1.000) miR-148b: 0.852 (0.699–1.000) miR-744: 0.845 (0.705–0.986) miR-30e-3p: 0.827 (0.679–0.976) | NR | Epithelioid: 26(NR) Biphasic: 6 (NR) | Stage I: 2(NR) Stage II: 9 (NR) Stage III: 15 (NR) Stage IV: 6 (NR) |
| Mozzoni 2017 ²⁵ | miR-17 miR-126 miR-16 miR-486 | NR | NR | miR-17: 80.0–84.4 miR-126: 80.0–97.8 miR-486: 80.0–89.1 miR-16: 86.7–82.2 | miR-17: 5.9 miR-126: 5.4 miR-486: 9.2 miR-16: 77.5 | NR | NR | miR-17: 0.88 (0.78–0.98) miR-126: 0.95 (0.89–1.00) miR-486: 0.88 (0.79–0.96) miR-16: 0.89 (0.81–0.97) | NR | Epithelioid: 26(NR) Biphasic: 6 (NR) | Stage I: 2(NR) Stage II: 9 (NR) Stage III: 15 (NR) Stage IV: 6 (NR) |

Table 4 (Continued)

| Author, Year | miRNA(s) | Sensitivity (%) | Specificity (%) | Sensitivity specificity at cut-off | Cut off Value | Positive predictive value (PPV) | Negative predictive value (NPV) | Areas under the curve (AUC) and (95 % CI) for diagnosis | Areas under the curve (AUC) and (95 % CI) for survival (months) | Cancer Histology | Cancer Stage |
|-------------------------------|---|--|--|------------------------------------|--|---------------------------------|---------------------------------|--|--|---|---|
| Weber 2017 ²⁵ | miR-132-3p | miR-132-3p: 86 % Combination of miR-132-3p with the previously described miR-126; sensitivity: 77 % | miR-132-3p: 61 % Combination of miR-132-3p with the previously described miR-126; specificity: 77 % | NR | NR | NR | NR | Discovery group; miR-132-3p: 0.91 (0.80-1.00) Verification group; miR-132-3p: 0.75 (0.63-0.88) | NR | Discovery; Epithelioid: 14(NR) Biphasic: 4 (NR) Sarcomatoid: 3(NR) Not specified: 0(NR) | NR |
| Ak 2015 ⁴¹ | miR-484 miR-320 let-7a miR-744 miR-20a miR-193b let-7d miR-125a-5p miR-92a miR-155 miR-152 miR-126 | miR-320: ≤ 7.27 let-7a: ≤ 11 miR-125a-5p: ≤ 9.36 | miR-320: 78 % - 100 % let-7a: 94 % - 83 % miR-125a-5p: 89 % - 100 % | NR | NR | NR | NR | miR-484: ≥ 0.90 (NR) miR-320: ≥ 0.90 (NR) let-7a: ≥ 0.90 (NR) miR-125a-5p: ≥ 0.90 (NR) miR-484: ≤ 8.15 (NR) | NR | Epithelial: 10 (55.6) Mixed: 4 (22.2) Sarcomatoid: 4(22.2) | Stage I - II: 4 (22.2) Stage III - IV: 14 (77.8) |
| Santarelli 2015 ²⁷ | miR-126 | miR-126: 75 % Met-TM: 60 % SMRPs: 60 % | miR-126: 54 % Met-TM: 82 % SMRPs: 89 % | NR | SMRPs: 1 (nmol/L) miR-126: 10×10^{-3} (relative exp) Met-TM: 1 (relative exp) NR | NR | NR | SMRPs: 0.818(0.723-0.914) miR-126: 0.710(0.568-0.822) Met-TM: 0.750 (0.641-0.858) | NR | Epithelioid: 33 (73 %) Biphasic: 9 (20 %) Sarcomatoid: 3 (7 %) | NR |
| Kirschner 2015 ³¹ | miR-21-5p miR-23a-3p miR-30e-5p miR-221-3p miR-222-3p miR-31-5 | Combined 6 miR-Score: 82.4 % | Combined 6 miR-Score: 80.6 % | NR | NR | NR | NR | Combined 6 miR-Score: 0.867(0.76-0.96) | EPP (median): 18.86 [0.07-122.41] P/D(median): 7.62 [0.33-224.82] LS (median): 57.2 [45.83-90.48] SS (median): 6.4[1.94-8.28] | EPP - Complete cohort; Epithelioid: 65(76) Biphasic: 20 (24) Sarcomatoid: 0(0) P/D - Complete cohort; Epithelioid: 37(49) Biphasic: 26 (35) Sarcomatoid: 12 (16) | NR |

Table 4 (Continued)

| Author, Year | miRNA(s) | Sensitivity (%) | Specificity (%) | Sensitivity specificity at cut-off | Cut off Value | Positive predictive value (PPV) | Negative predictive value (NPV) | Areas under the curve (AUC) and (95 % CI) for diagnosis | Areas under the curve (AUC) and (95 % CI) for survival (months) | Cancer Histology | Cancer Stage |
|------------------------------|---|--|---|--|----------------------------------|---|--|---|---|---|---|
| Andersen 2014 ⁴⁰ | miR-126 miR-143 miR-145 miR-193a-3p miR-193b miR-652 | All miRNAs (not individual): 0.95 (95 % CI, 0.89 - 1.00) | All miRNAs (not individual): 0.93 (95 % CI, 0.87 - 1.00) | NR | NR | NR | NR | miR-126: 0.78 (0.64 - 0.92) miR-143: 0.76 (0.61 - 0.90) miR-145: 0.93 (0.85 - 1.00) miR-193a-3p: NA miR-193b: NA miR-652: 0.89 (0.80 - 0.90) | NR | MPM; Epithelioid: 18(45), Biphasic: 22 (55) CO_DB; Epithelioid: 9 (75), Biphasic: 3 (25) | CA, Stage I: 1(3) Stage II: 6 (15) Stage III: 23 (58) Stage IV: 10 (25) CO_DB, Stage I: 1(8) Stage II: 8 (67) Stage III: 3 (25) NR |
| Weber 2014 ³⁸ | miR-103a-3p | All subjects; miR-103a-3p: 86 % Epithelioid mesothelioma; miR-103a-3p: 74 % Biphasic mesothelioma; miR-103a-3p: 89 % | All subjects miR-103a-3p: 63 % Epithelioid mesothelioma; miR-103a-3p: 85 % Biphasic mesothelioma; miR-103a-3p: 63 % | miR-103a-3p FPR = 4 %, Cut-off = 2.01 nmol/l Maximum YI: 749.61 FPR = 4 %, Cut off = 99.73 Without sarcomatoid mesothelioma, Maximum YI, Cut off = 749.61 | All subjects miR-103a-3p: 749.61 | All subjects, miR-103a-3p TP: 37 TN: 33 | All subjects, miR-103a-3p FP: 19 FN: 6 | miR-103a-3p: 0.76 (NR) | NR | Epithelioid: 28(NR), Biphasic: 6 (NR), Sarcomatoid: 5 (NR), Not specified: 4(NR) | NR |
| Muraoka 2013 ³⁴ | miR-34b/c | miR-34b/c: 67 % | miR-34b/c: 77 % | NR | NR | NR | NR | miR-34b/c: 0.77 | NR | Epithelioid: 36(75) Biphasic: 8 (17) Sarcomatoid: 4(8) | Stage I: 12 (25) Stage II: 5 (10) Stage III: 16 (33) Stage IV: 12 (25) Unknown: 3 (7) NR |
| Kirschner 2012 ⁴² | miR-29c* miR-92a miR-625-3p | CA; miR-625-3p: 73.33 % CO; miR-625-3p: 70 % | CA; miR-625-3p: 78.57 % CO; miR-625-3p: 90 % | NR | NR | NR | NR | CA; miR-625-3p: 0.824 (0.669 - 0.979) CO; miR-625-3p: 0.793 (0.657 - 0.930) | NR | Test Cohort – CA; Epithelioid: 9 (60) Biphasic: 3 (20) Sarcomatoid: 2(13.33) Unspecified: 1(0.07) Tissue samples; Epithelioid: 15(83.33) Biphasic: 3 (16.66) Sarcomatoid: 0 | NR |

Table 4 (Continued)

| Author, Year | miRNA(s) | Sensitivity (%) | Specificity (%) | Sensitivity specificity at cut-off | Cut off Value | Positive predictive value (PPV) | Negative predictive value (NPV) | Areas under the curve (AUC) and (95 % CI) for diagnosis | Areas under the curve (AUC) and (95 % CI) for survival (months) | Cancer Histology | Cancer Stage |
|------------------------------|--|---|---|------------------------------------|----------------|---------------------------------|---------------------------------|---|---|---|---|
| Weber 2012 ²⁹ | miR-103, miR-20a | CO_Asb-Exp: 83 % CO_Non_Asb-Exp: 78 % | CO_Asb-Exp: 71 % CO_Non_Asb-Exp: 76 % | NR | miR-103: 0.621 | NR | NR | miR-103, CA vs. CO_Asb-Exp: 0.757 (95 % CI: 0.586–0.929) miR-103, CA vs. CO_Non_Asb-Exp: 0.871 (95 % CI: 0.766–0.977) | NR | NR | NR |
| Tomasetti 2012 ²⁹ | miR-126 | miR-126: 80 % | miR-126: 60 % | NR | NR | NR | NR | CO_Non_Asb-Exp Vs. CA: 0.894 (0.821–0.968) CO_Non_Asb-Exp Vs. CA_NSCLC: 0.675 (0.503–0.847) CA Vs. CA_NSCLC: 0.751 (0.616–0.886) | NR | NR | NR |
| Foss 2011 ³⁰ | miR-1268, miR-574–5p, miR-1254, miR-1258 | NSCLC, miR-1254: 82 % miR-574–5p: 82 % Discovery cohort, miR-1254: 73 % miR-574–5p: 73 % | NSCLC, miR-1254: 77 % miR-574–5p: 77 % Discovery cohort, miR-1254: 71 % miR-574–5p: 71 % | NR | NR | NR | NR | Discovery cohort, miR-1254 and miR-574–5p [miR-1254 + miR-574–5p] = 0.77 Validation cohort, miR-1254 and miR-574–5p [miR-1254 + miR-574–5p] = 0.75 | NR | CA_NSCLC, Adenocarcinoma: 6(NR), Bronchioloalveolar carcinoma: 1(NR), Squamous cell carcinoma: 1(NR), Large cell carcinoma: 1(NR), Other: 1(NR), Unavailable: 1(NR) | Discovery, NSCLC, Stage I: 4 Stage I/II: 0 Stage II: 6 Unavailable: 1 MPM Stage I: 1 Stage I/II: 0 Stage II: 2 Unavailable: 0 |

Abbreviations: CA: cases, CO_Non_Asb-Exp: controls non-exposed to asbestos, MPM: malignant pleural mesothelioma, CO_Asb-Exp: controls exposed to asbestos, exp: exposure, +ve exp: positive exposure, -ve exp: negative exposure, EV: extracellular vesicles, Lung-Ad: lung adenocarcinoma, N: total sample size, M: male, F: female, S: smoker, NS: non-smoker, Ex: former smoker, NA: data not available, N/A: not applicable, EBC: exhaled breathe condensate, NR: data not reported, NSCLC: non-small cell lung cancer, NSCLC_Asb: Asbestos exposed non-small cell lung cancer, TS: training set, VS: validation set, FFPPE: formalin-fixed paraffin embedded, EPP: extra pleural pneumonectomy, P/D: pleurectomy ± decortication, LS: long survivor, SS: short survivor, NNP: patient-matched non-neoplastic pleura, PTHX: non neoplastic reactive mesothelial proliferation due to pneumothorax, BAsb-Exp: Benign pleural asbestosis, Y: years.

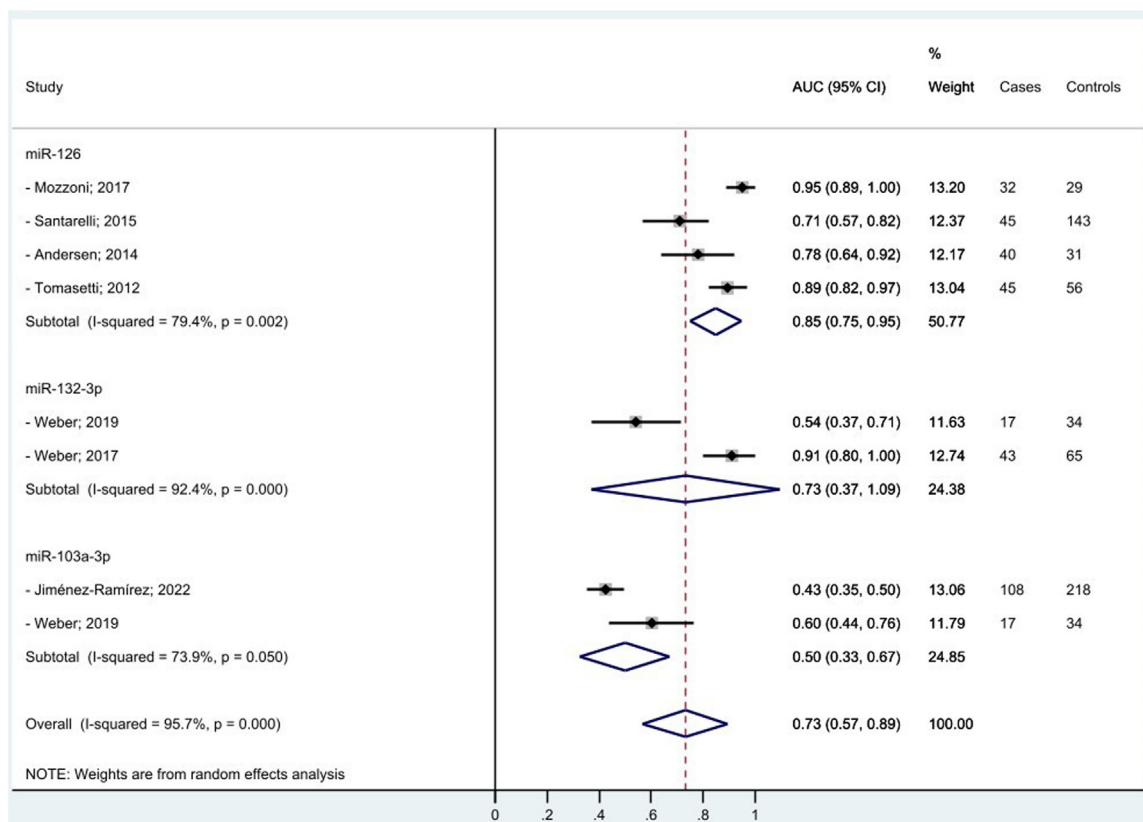


Fig. 2 Meta-analysis of selected studies evaluating the diagnostic accuracy expressed as Area Under the Curve (AUC) and 95 % Confidence Intervals (CIs) of specific miRNAs for MPM among men only.

Footnote: AUC: Area Under the Curve; s.e.: standard error.

The strength of our systematic review is the comprehensive search strategy including also the so-called grey literature, as also confirmed by the absence of publication bias in the Egger test for the studies included in the meta-analysis. Also, we used a standard tool to assess study quality. Further, we evaluated both diagnosis and prognosis for both asbestos-related LC and MPM. Finally, we managed to quantify the diagnostic performance of the top miRNAs associated with MPM using a meta-analytic approach, so quantifying their potential role as cancer biomarkers.

We acknowledge several limitations. Almost all studies were case-controls, so subject to reverse causation bias. Almost all studies included men only, and had small sample size, so preventing generalizability of the findings to women. Also, asbestos exposure was usually self-reported and without information on type and duration of exposure, so vulnerable to exposure misclassification; there is even no evidence this was a differential between cases and hospital controls. The studies were also heterogeneous in methodology, and this allowed us to perform a meta-analysis only on a small selected sub-sample of more comparable studies. In addition, given that we pooled AUCs estimated also from multivariable models or studies matched by design, we cannot rule out a certain degree of overestimation.

Several knowledge gaps on this topic remain to be addressed: the accuracy of miRNAs to predict asbestos-related LC and MPM in prospective longitudinal studies of

healthy ex-asbestos-exposed subjects, especially among women; the exposure-response relationship between asbestos and miRNA changes; the underlying biological mechanisms, and the influence of internal (e.g. age, sex, genes) and external (e.g. smoking, co-exposure to other occupational agents, therapies) factors on miRNA expression perturbations. Future research addressing these shortcomings in large prospective studies is warranted to shed some light on these issues.

Conclusion

To conclude, in this comprehensive systematic review and meta-analysis we identified some promising miRNA candidates to predict diagnosis and survival of asbestos-related LC and MPM. Future large longitudinal standardized validation studies are needed to confirm these findings, assess their clinical relevance, and address present knowledge gaps. The current poor survival and quality of life for patients affected by asbestos-related lung cancers, especially MPM, urge the identification of accurate and reliable, non-invasive, early diagnostic biomarkers to be included in cancer screening protocols among ex asbestos-exposed subjects, as well as to provide molecular targets for new therapies. However, the best prevention remains to ban asbestos globally to avoid the associated important death toll for the long-term future.

Conflicts of interest

None.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.pulmoe.2024.02.002](https://doi.org/10.1016/j.pulmoe.2024.02.002).

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