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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.

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 ex-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 Reviews[14] 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 +/- 1.96*s.e.) on a non-transformed scale. Random effect methods[16] 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 study[17] 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 chart[14] 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 study[31] 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-222 [22] 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-3p [38] with 86 % sensitivity, 63 % specificity and AUC of 0.76; miR-126 [29] with 80 % sensitivity, 60 % specificity and AUC of 0.75(0.62−0.89) and miR-132−3p [35] with 86 % sensitivity, 61 % specificity and AUC of 0.91 (0.8−1.0). In relation to MPM prognosis, miR-197-3p [19] was associated with an increased survival for epithelioid type of 13.5 (±0.6) months, for sarcomatoid of 7.9 (±0.7) months, and for biphasic of 12.4 (±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-574−5p[30] 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

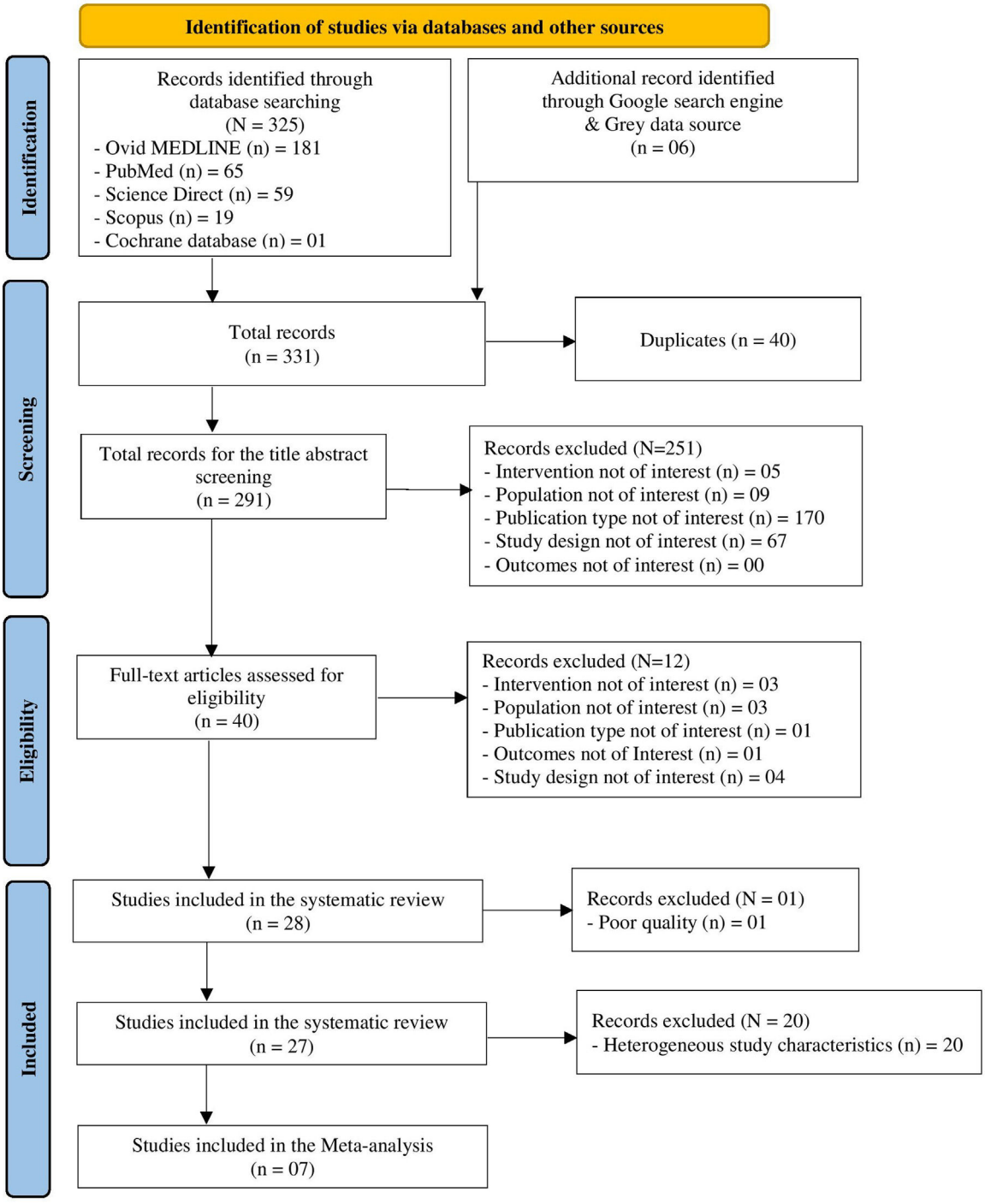

Fig. 1 PRISMA flow diagram showing screening and selection of articles related to miRNAs and asbestos-related lung cancer outcomes resulting from the search in electronic bibliographic databases.

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-197-3p[19] 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-574–5p[30] 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; CA: 59(72) CO_Non_Asb-Exp: 59 (72) F; CA: 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)	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; S: 8(10.6) Ex: 13(17.3) NS:14(18.7) N/A: 40(53.3)	Questionnaire administered via personal interview	NR	Occupational; Documented: 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; M: 20(77) F: 06(23) CO_Asb-Exp; M: 47(87) F: 07(13)	CA: 71.3(±7.8) CO_Asb-Exp: 64.8 (±6.0)	CA; NS: 8(31) Ex: 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[36]	Mexico	Hospital based case control	N: 326 CA: 108 CO_Asb-Exp: 218	CA; M: 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; CA: 39(36.1) CO_Asb-Exp: 89 (40.8) S; CA: 69(63.9) 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	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	NR	EBC and Plasma	MPM, Lung-Ad
Weber 2019[37]	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[32]	Egypt	Hospital based case-control	N: 100 CA: 60 CO_Asb-Exp: 20 CO_Non_Asb-Exp: 20	MPM; M: 35(58.3) 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; ≥55 years: 11(55) <55 years: 9(45) CO_Non_Asb-Exp; ≥55 years: 10(50) <55 years: 10(50)	CA; S: 24 (40) NS: 27 (45) Ex: 8 (13.3) PS: 1 (1.7) CO_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	Discovery; CA_NSCLC; NS: NR (25) S: NR (75) CA_NSCLC-Asb; NS: NR (25) S: NR (75) CA; NS: NR (25) Yes: NR (75) Serum Training; 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
Cavalieri 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	NR	Plasma and FFPE tissue samples	MPM
Weber 2017[75]	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; CA; S: 12(NR) NS: 9(NR) CO_Asb-Exp; S: 12(NR) NS: 9(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[24]	Italy	Hospital based case-control	N: 57 TS: 27 VS: 30	TS; M: 22(81) F: 5(19) VS; M: 25 (83) F: 5(17)	TS: 67.9(±6.5) VS: 69.5(±8.5)	TS; S: 18(67) NS: 9(33) Unknown: 0(0) VS; S: 19(63) NS: 9(30) NA: 2(7)	NR	NR	TS; Yes: 22(81) NA: 5(19) VS; 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	CA: 68.0(±7.5), NR [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)	Self-administered questionnaire	CA: 25(±12) CO_Asb-Exp: 28 (±11)	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)	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: 72[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
Gayoso-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; S: 09(NR) 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[34]	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) ≥69 years: 20(42) CO_B_Asb-Exp; <69 years: 4(20) ≥69 years: 17 (80) CO_Non_Asb-Exp; <69 years: 23(56) ≥69 years: 18(44)	CA; NS: 14(29) S: 34(71) CO_B_Asb-Exp; NS: 9(43) S: 12(57) CO_Non_Asb-Exp; NS: 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)	Plasma or Serum 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	NR	Plasma or serum and ting tissue	MPM
Weber 2012[39]	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	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) NS: 15(33) CA_NSCLC; S: 5(25) Ex: 6(30) NS: 9 (45) CO_Non_Asb-Exp; S: 27(48) Ex: 8(14) NS: 21(38)	Self-administered questionnaire	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)	NR	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)	NR	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, 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, 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_Non_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[36]	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	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[37]	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-Asb; 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 miR-222/miR-126: 0.047 (two-tailed Student t-test - adjusted p value)	MPM, NSCLC	Discovery, CA_NSCLC; Adenocarcinoma: NR(100) CA_NSCLC_Asb; 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_Asb; Squamous: NR (36) Large cell: NR(18) Adenocarcinoma: NR (46) CA; Epithelioid: NR (75) Sarcomatoid: NR(25)	NR
Cavalleri, 2017[23]	Plasmatic extracellular 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)	NR
Mozzoni 2017[25]	Blood plasma and FFPE tissue	miR-17 miR-126 miR-16 miR-486	↓	Two-sided, two-sample *t*-test NR	NR	NR	NR	MPM	Epithelioid: 26 (NR) Biphasic: 6(NR)	Stage I: 2(NR) Stage II: 9(NR) Stage III: 15(NR) Stage IV: 6(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)	NR
Truini 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) Biphasic: 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[26]	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	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: 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	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: 0.045 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	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[31]	Formalin-fixed paraffin embedded (FFPE) tumor specimens	miR-21−5p miR-23a-3p miR-30e-5p miR-221−3p miR-222−3p miR-31−5p	↓	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 RT-qPCR Results Microarray and RT-qPCR; miR-222−3p: −2.7 miR-221−3p: −2.49 miR-210−3p: −2.68 miR-21−5p: −1.76 miR-93−5p: −2.29 miR-106b-5p: −2.21 miR-17−5p: −2.23 miR-27a-3p: −1.79 miR-20a-5p: −1.82 miR-19b-3p: −1.49 miR-30e-5p: −2.34 miR-23a-3p: −1.73 miR-662: 1.14 RT-qPCR; miR-29c-5p: 1.03 miR-31−5p: 1.51 miR-106a-5p: −2.00 miR-126−3p: −1.75 miR-625−3p: −1.11 miR-92a-3p: −1.39 miR-24−3p: 1.51	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
Lamberti 2015[28]	Blood serum	miR-101 miR-25 miR26b miR335 miR433 miR191 miR-223	↑ ↓	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)

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 miR-365a miR-193a-3p miR-193b miR-210 let-7c miR-99a miR-126 miR143 miR-145 miR-144−5p miR-451a miR-486−5p miR-652	↑ ↓	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: −2.91 miR-143: −2.62 miR-145: −6.95 miR-193a-3p: 2.38 miR-193b: −1.90 miR-652: −3.06	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)
Weber 2014[38]	Blood - cellular blood fraction	miR-103a-3p	NR	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
Gayosso-Gómez 2014[33]	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_Non_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	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	↑ ↓	NR	NR	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	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 Correction for FDR − adjusted p value)	MPM	Epithelial: 18 (NR) Biphasic: 4(NR) Sarcomatoid: 3 (NR)	NR
Muraoka 2013[34]	Serum	miR-34b/c	↑	NR	NR	NR	NR	Advanced MPM	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)
Kirschner 2012[42]	Blood plasma	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	MPM	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
Weber 2012[39]	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[30]	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 I/II: 0 Stage II: 6 Unavailable: 1 MPM Stage I: 1 Stage I/II: 0 Stage II: 2 Unavailable: 0
Nymark 2011[43]	Tissues	miR-148b miR-374a miR-24–1* let-7d let-7e miR-199b-5p miR-331–3p miR-96	↑	NR Age, sex, nationality, smoking history and distribution of histological types were matched	NR	miR-148b: 0.325 miR-374a: 0.5335714 miR-24–1*: 0.19904763	miR-148b: 0.028543 miR-374a: 0.028543 miR-24–1*: 0.047273	MPM	Exposed Patients LCLC: 03 AC: 06 SCC: 03 SCLC: 02 Non-exposed patients LCLC: 01 AC: 05 SCC: 06 SCLC: 02	NR
		miR-939 miR-671–5p miR-605 miR-1224–5p miR-202	↓			CO_Asb-Exp; miR-939: −1.2571429 miR-671–5p: −0.42619047 miR-605: −0.21642858 miR-1224–5p: −0.52761906 miR-202: −0.632619 Lung-Adenocarcinoma CO_Asb-Exp; miR-202: −1.142	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-7d: 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)			

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, 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, OR: Odds ratio, HR: Hazard ratio, (β): β, 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	M; FP: 8 FN: 86 F; FP: 0 FN: 18	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)	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 specified: 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	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 (%)	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
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; Adenocarcinoma: NR (100) CA_N-SCLC_Asb; 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_N-SCLC_Asb; Squamous: NR(36) Large cell: NR(18) Adenocarcinoma: NR(46) CA; Epithelioid: NR(75) Sarcomatoid: NR (25)	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: 10(NR) Biphasic: 11 (NR) Sarcomatoid: 01(NR) Not specified: 01(NR)	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 (%)	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
Weber 2017[35]	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-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: $10\times^{10-3}$ (relative exp) Met-TM: 1 (relative exp)	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 (%)	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
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)
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)
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 (%)	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
Weber 2012[39]	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, 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.

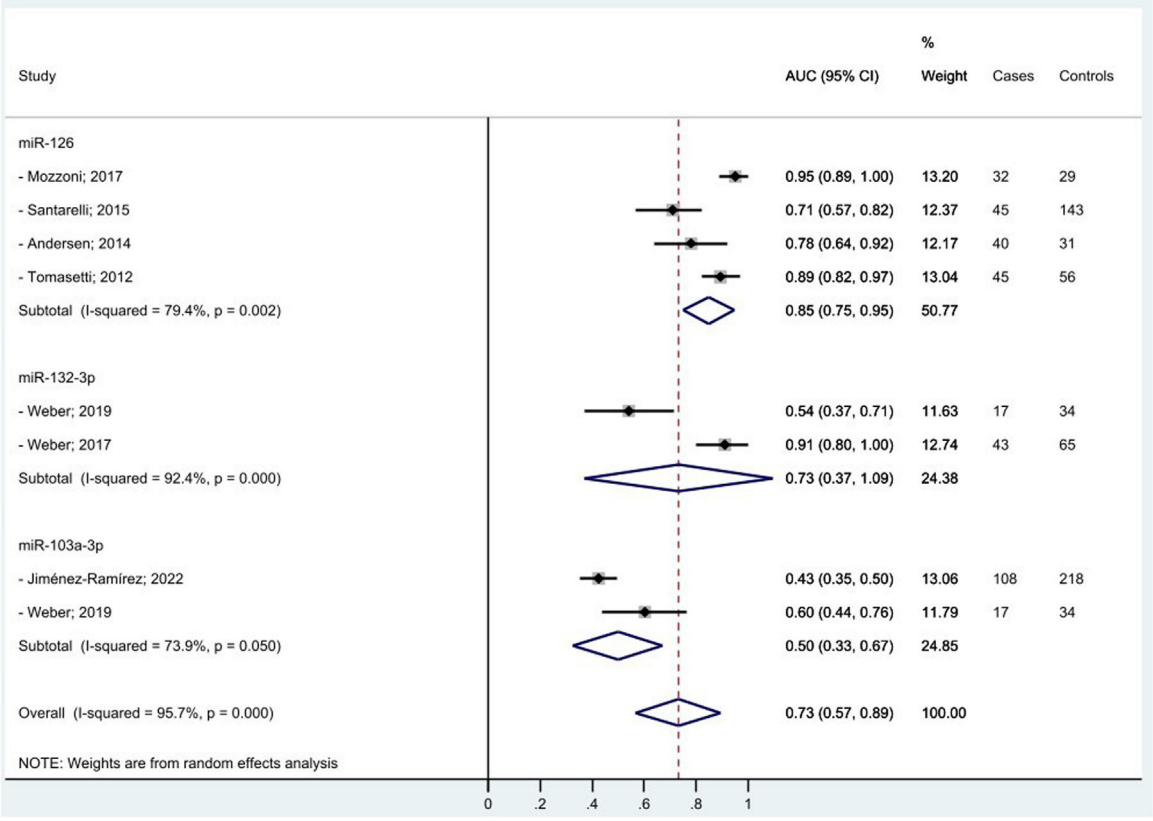

Fig. 2 Meta-analysis of selected studies evaluating the diagnostic accuracy expressed as Area Under the Curve (AUC) and 95 % Confidence Intervals (CIs) of specific miRNAs for MPM among men only.
Footnote: AUC: Area Under the Curve; s.e.: standard error.

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.

References

1. GBD 2019 Risk Factors Collaborators. The global burden of cancer attributable to risk factors, 2010-19: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2022;400 (10352):563–91.
2. IARC. Working Group on the Evaluation of Carcinogenic Risks to Humans. Arsenic, metals, fibres, and dusts. IARC Monogr Eval Carcinog Risks Hum. 2012;100:11–465.
3. Wolff H, Vehmas T, Oksa P, Rantanen J, Vainio H. Asbestos, asbestosis, and cancer, the Helsinki criteria for diagnosis and attribution 2014: recommendations. Scand J Work Environ Health. 2015;41:5–15.
4. Stanaway JD, Afshin A, Gakidou E, Lim SS, Abate D, Abate KH, et al. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1923–94.
5. Goldberg M, Luce D. The health impact of nonoccupational exposure to asbestos: what do we know? Eur J Cancer Prev. 2009;18(6):489.
6. Marinaccio A, Binazzi A, Bonafede M, Corfiati M, Di Marzio D, Scarselli A, et al. Malignant mesothelioma due to non-occupational asbestos exposure from the Italian national surveillance system (ReNaM): epidemiology and public health issues. Occup Environ Med. 2015;72(9):648–55.
7. International Ban Asbestos Secretariat. Available at: (http://www.ibasecretariat.org/alpha_ban_list.php2023).
8. WHO. Asbestos: elimination of asbestos-related diseases. Available at: (https://www.who.int/en/news-room/fact-sheets/detail/asbestos-elimination-of-asbestos-related-diseases2023).
9. The Lancet Respiratory M. Pleural mesothelioma: tackling a deadly cancer. Lancet Respir Med. 2019;7(2):99.
10. Markowitz SB. Lung cancer screening in asbestos-exposed populations. Int J Environ Res Public Health. 2022;19(5):2688.
11. Scherpereel A, Opitz I, Berghmans T, Psallidas I, Glatzer M, Rigau D, et al. ERS/ESTS/EACTS/ESTRO guidelines for the management of malignant pleural mesothelioma. Eur Respir J. 2020;55(6):1900953.
12. Peng Y, Croce CM. The role of MicroRNAs in human cancer. Signal Transduct Target Ther. 2016;1:15004.
13. Condrat CE, Thompson DC, Barbu MG, Bugnar OL, Boboc A, Cretoiu D, et al. miRNAs as biomarkers in disease: latest findings regarding their role in diagnosis and prognosis. Cells. 2020;9(2):276.
14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Int Surg J. 2021;88:105906.
15. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. Ottawa: Ottawa Hospital Research Institute; 2000. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
16. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–88.
17. Matboli M, Shafei AE, Ali MA, Gaber AI, Galal A, Tarek O, et al. Clinical significance of serum DRAM1 mRNA, ARSA mRNA, hsa-miR-2053 and lncRNA-RP1-86D1. 3 axis expression in malignant pleural mesothelioma. J Cell Biochem. 2019;120(3):3203–11.
18. Casalone E, Birolo G, Pardini B, Allione A, Russo A, Catalano C, et al. Serum extracellular vesicle-derived microRNAs as potential biomarkers for pleural mesothelioma in a European prospective study. Cancers. 2022;15(1):125.
19. Di Mauro G, Frontini F, Torreggiani E, Iaquinta MR, Caselli A, Mazziotta C, et al. Epigenetic investigation into circulating microRNA 197-3p in sera from patients affected by malignant pleural mesothelioma and workers ex-exposed to asbestos. Sci Rep. 2023;13(1):6501.
20. Ferrari L, Iodice S, Cantone L, Dallari B, Dioni L, Bordini L, et al. Identification of a new potential plasmatic biomarker panel for the diagnosis of malignant pleural mesothelioma. Med Lav. 2022;113(6):e2022052.
21. Faversani A, Favero C, Dioni L, Pesatori AC, Bollati V, Montoli M, et al. An EBC/plasma miRNA signature discriminates lung adenocarcinomas from pleural mesothelioma and healthy controls. Front Oncol. 2021;11:643280.
22. Santarelli L, Gaetani S, Monaco F, Bracci M, Valentino M, Amati M, et al. Four-miRNA signature to identify asbestos-related lung malignancies. Cancer Epidemiol Biomarkers Prev. 2019;28 (1):119–26.
23. Cavalleri T, Angelici L, Favero C, Dioni L, Mensi C, Bareggi C, et al. Plasmatic extracellular vesicle microRNAs in malignant pleural mesothelioma and asbestos-exposed subjects suggest a 2-miRNA signature as potential biomarker of disease. PLoS One. 2017;12(5):e0176680.
24. Truini A, Coco S, Nadal E, Genova C, Mora M, Dal Bello MG, et al. Downregulation of miR-99a/let-7c/miR-125b miRNA cluster predicts clinical outcome in patients with unresected malignant pleural mesothelioma. Oncotarget. 2017;8(40):68627.
25. Mozzoni P, Ampollini L, Goldoni M, Alinovi R, Tiseo M, Gnetti L, et al. MicroRNA expression in malignant pleural mesothelioma and asbestosis: a pilot study. Dis Markers. 2017;2017:9645940.
26. Bononi I, Comar M, Puozzo A, Stendardo M, Boschetto P, Orecchia S, et al. Circulating microRNAs found dysregulated in ex-exposed asbestos workers and pleural mesothelioma patients as potential new biomarkers. Oncotarget. 2016;7(50):82700.
27. Santarelli L, Staffolani S, Strafella E, Nocchi L, Manzella N, Grossi P, et al. Combined circulating epigenetic markers to improve mesothelin performance in the diagnosis of malignant mesothelioma. Lung Cancer. 2015;90(3):457–64.
28. Lamberti M, Capasso R, Lombardi A, Di Domenico M, Fiorelli A, Feola A, et al. Two different serum MiRNA signatures correlate with the clinical outcome and histological subtype in pleural malignant mesothelioma patients. PLoS One. 2015;10(8): e0135331.
29. Tomasetti M, Staffolani S, Nocchi L, Neuzil J, Strafella E, Manzella N, et al. Clinical significance of circulating miR-126 quantification in malignant mesothelioma patients. Clin Biochem. 2012;45(7–8):575–81.

30. Foss KM, Sima C, Ugolini D, Neri M, Allen KE, Weiss GJ. miR-1254 and miR-574-5p: serum-based microRNA biomarkers for early-stage non-small cell lung cancer. J Thorac Oncol. 2011;6 (3):482—8.
31. Kirschner MB, Cheng YY, Armstrong NJ, Lin RC, Kao SC, Linton A, et al. MiR-score: a novel 6-microRNA signature that predicts survival outcomes in patients with malignant pleural mesothelioma. Mol Oncol. 2015;9(3):715—26.
32. Matboli M, Shafei AE, Azazy AE, Reda M, El-Khazragy N, Nagy AA, et al. Clinical evaluation of circulating miR-548a-3p and-20a expression in malignant pleural mesothelioma patients. Biomark Med. 2018;12(2):129—39.
33. Gayosso-Gómez L, Zárraga-Granados G, Paredes-Garcia P, Falfán-Valencia R, Vazquez-Manríquez M, Martinez-Barrera L, et al. Identification of circulating miRNAs profiles that distinguish malignant pleural mesothelioma from lung adenocarcinoma. EXCLI J. 2014;13:740.
34. Muraoka T, Soh J, Toyooka S, Aoe K, Fujimoto N, Hashida S, et al. The degree of microRNA-34b/c methylation in serum-circulating DNA is associated with malignant pleural mesothelioma. Lung Cancer. 2013;82(3):485—90.
35. Weber DG, Gawrych K, Casjens S, Brik A, Lehnert M, Taeger D, et al. Circulating miR-132-3p as a candidate diagnostic biomarker for malignant mesothelioma. Dis Markers. 2017;2017:9280170.
36. Jiménez-Ramírez C, Gilbert Weber D, Aguilar-Madrid G, Brik A, Juárez-Pérez CA, Casjens S, et al. Assessment of miR-103a-3p in leukocytes—No diagnostic benefit in combination with the blood-based biomarkers mesothelin and calretinin for malignant pleural mesothelioma diagnosis. PLoS One. 2022;17(10): e0275936.
37. Weber DG, Brik A, Casjens S, Burek K, Lehnert M, Pesch B, et al. Are circulating microRNAs suitable for the early detection of malignant mesothelioma? Results from a nested case—control study. BMC Res Notes. 2019;12:1—6.
38. Weber DG, Casjens S, Johnen G, Bryk O, Raiko I, Pesch B, et al. Combination of MiR-103a-3p and mesothelin improves the biomarker performance of malignant mesothelioma diagnosis. PLoS One. 2014;9(12):e114483.
39. Weber DG, Johnen G, Bryk O, Jöckel K-H, Brüning T. Identification of miRNA-103 in the cellular fraction of human peripheral blood as a potential biomarker for malignant mesothelioma—a pilot study. PLoS One. 2012;7(1):e30221.
40. Andersen M, Grauslund M, Ravn J, Sørensen JB, Andersen CB, Santoni-Rugiu E. Diagnostic potential of miR-126, miR-143, miR-145, and miR-652 in malignant pleural mesothelioma. J Mol Diagn. 2014;16(4):418—30.
41. Ak G, Tomaszek SC, Kosari F, Metintas M, Jett JR, Metintas S, et al. MicroRNA and mRNA features of malignant pleural mesothelioma and benign asbestos-related pleural effusion. Biomed Res Int. 2015;2015:635748.
42. Kirschner MB, Cheng YY, Badrian B, Kao SC, Creaney J, Edelman JJB, et al. Increased circulating miR-625-3p: a potential biomarker for patients with malignant pleural mesothelioma. J Thorac Oncol. 2012;7(7):1184—91.
43. Nymark P, Guled M, Borze I, Faisal A, Lahti L, Salmenkivi K, et al. Integrative analysis of microRNA, mRNA and aCGH data reveals asbestos-and histology-related changes in lung cancer. Genes Chrom Cancer. 2011;50(8):585—97.
44. Xu Y, Zheng M, Merritt RE, Shrager JB, Wakelee HA, Kratzke RA, et al. miR-1 induces growth arrest and apoptosis in malignant mesothelioma. Chest. 2013;144(5):1632—43.