Review Article

Serum mesothelin and other biomarkers: what have we learned in the last decade?

Alfonso Cristaudo[1], Alessandra Bonotti[2], Giovanni Guglielmi[2], Poupak Fallahi[1], Rudy Foddis[1]

[1]Department of Translational Research and of New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy; [2]Operative Unit of Preventive and Occupational Medicine, University Hospital of Pisa, Pisa, Italy

Contributions: (I) Conception and design: A Cristaudo, G Guglielmi, R Foddis; (II) Administrative support: A Cristaudo; (III) Provision of study materials or patients: G Giovanni, R Foddis; (IV) Collection and assembly of data: A Bonotti, P Fallahi; (V) Data analysis and interpretation: A Cristaudo, G Guglielmi, R Foddis, A Bonotti; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Alfonso Cristaudo. Professor, Department of Translational Research and of New Technologies in Medicine and Surgery, University of Pisa, via Paradisa 2, Pisa 56124, Italy. Email: alfonso.cristaudo@med.unipi.it.

Abstract: In the last decade there is been much interest in noninvasive, economic and well-accepted diagnostic tests for screening of subjects exposed to asbestos, and in patients with malignant pleuric mesothelioma (MPM) for diagnosis or monitoring response to treatment. Several biomarkers have been suggested as tools for screening and early diagnosis of MPM. Currently, in patients with MPM, have been reported high levels of soluble mesothelin-related peptides (SMRP), plasmatic osteopontin (pOPN), vimentin, fibulin-3 and many others as promising marker for diagnosis, even their use in prevention monitoring is still discussed. In this type of disease, a key role could be played by miRNAs, which expression has been investigated in a large series of MPM to examine new pathways useful in diagnosis, prognosis and therapy. An altered expression of some proteins has been reported, useful as biomarkers, in comparative proteomic analysis of malignant pleural mesothelioma. New promising markers are nowadays under study and alone or better in combination, they'll be very helpful in diagnosing, monitoring mesothelioma patients or for screening of risk groups.

Keywords: Mesothelin; mesothelioma; biomarkers

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The relevance of the malignant pleuric mesothelioma (MPM) biomarkers

MPM is a highly aggressive tumor with a poor survival rate (1).

It is characterized by a long latency period in spite of its rapid, aggressive clinical outcome.

Therefore, effective preventive protocols may include very frequent instrumental diagnostic tests performed over a long period of time, i.e., decades, which may be neither economic nor ethical. Consequently, the use of early high sensitivity/specificity diagnostic markers is strongly recommended.

For screening and early diagnosis of MPM, new tools are necessary, and several biomarkers have been suggested (2).

Presently, there are no useful tools for screening and early diagnosis of MPM, while clinical monitoring is based mainly on radiological tests. Moreover, evaluation of therapy response in MPM remains difficult, especially because of poor sensitivity and operator dependency of radiological assessment (3). In addition, in most cases relapse is characterized by a very rapid time course.

Several MPM biomarkers have been studied and some of them are still under investigation, these researches investigate serum, plasma and pleural effusions, especially using ELISA (4).

The value of tumor markers is more available to the clinician: it can only be useful if required and interpreted

taking into account the other information available to the clinical context.

An incorrect interpretation can trigger a series of diagnostic insights, even invasive, with stress and expenses that may not be justified.

Soluble mesothelin-related peptides (SMRP)

Mesothelin originates as a precursor of 71-kDa, then cutted into two mature proteins: megakaryocyte potentiating factor (MPF), secreted into the blood, and a cell surface glycoprotein (MW approximately 40 kDa) recognized by Chang and Pastan on 1992 in ovarian carcinomas (5), and then in malignant mesotheliomas, squamous-cell carcinomas and normal mesothelial cells (6).

SMRP are potentially a tumor marker for MPM. Many studies aimed to determine the differences in SMRP levels in patients with MPM versus patients with benign pleural disease or lung cancer (LC) or individuals formerly asbestos exposed; in other cases in patients with MPM before and after treatment.

Determination of serum SMRP has been proposed on 2003 by Robinson *et al.* as a marker for diagnosis of mesothelioma and monitoring disease progression on a relatively small group of subjects (7). Yet, SMRP dosage has been suggested to be a useful tool for screening asbestos-exposed individuals for early evidence of MPM and, possibly, LC.

Other studies (8-14) confirmed that serum SMRP was a promising marker for diagnosis, prognosis and clinical monitoring of MPM. High SMRP concentrations were detected in all the studies only in the epithelioid and mixed MPM.

Our data, in particular, provide the evidence that high SMRP dosage can be considered as an independent prognostic tool for patients with epithelioid MPM and suggest that this dosage could be useful both as a screening test for diagnosis (11), interpreted, of course, taking into account the other information available to the clinical context.

An important Individual patient data meta-analysis was performed by Hollevoet *et al.* (15). In symptomatic or high-risk individuals, this meta-analysis showed that a negative blood test for SMRP does not exclude MPM, even at a high-sensitivity threshold. On the contrary, a positive blood test for SMRP at a high specificity threshold leads to further diagnostic steps and could possibly help an earlier diagnosis.

The low false positivity indicated a high specificity as well. The detection of elevated SMRP levels in asbestos-exposed subjects should induce the clinical consideration of the presence of MPM denotes. A lower probability of the presence of MPM in patients with normal SMRP levels can be considered due to the high negative predictive value of the method, but the limiting lower sensitivity cannot entirely excluded the presence of disease (16).

Several findings suggest that SMRP may be a useful tumor marker for detecting the progression of malignant mesothelioma and evaluating tumor response to treatment (17).

However, the poor sensitivity of mesothelin (35–50%) limits its value for diagnosis (18).

Osteopontin (OPN)

OPN is a secreted glycoprotein that plays key roles in different biological processes, such as immunological regulation, cell-matrix interaction, cell migration and tumor development (19,20). The circulating OPN levels in serum are increased in several cancers, including MPM (21), in which serum OPN has been considered as a potential biomarker for early detection of the disease (22,23).

Our data suggest that confounding factors such as age, smoking habits and asbestos exposure do not influence plasma OPN and serum OPN. In addition to traditional radiological exams, plasma and serum OPN may be useful markers in the diagnosis of epithelial MPM. Furthermore, plasma OPN is more stable than serum OPN, and measurements of OPN in plasma are more reliable (23,24).

Other authors confirmed OPN as an effective marker for MPM diagnosis (22,25-28) and the utility as biological markers for the health surveillance of past-exposed patients (28). Nevertheless, further studies with a larger sample size and better design are needed to carefully assess the diagnostic power of this biomarker (25).

Fibulin-3

Human fibulin-3 is a secreted glycoprotein encoded by the epidermal growth factor (EGF)-containing fibulin-like extracellular matrix protein-1 (EFEMP-1) gene (29), and it could play a role in the regulation of MPM cell proliferation and migration. Fibulin-3 is produced in MPM but its role remains uncertain (30).

Several studies have investigated the diagnostic value of fibulin-3 for MPM and based on these fibulin-3 results a useful diagnostic marker for MPM (30-34).

Plasma fibulin-3 levels can distinguish healthy persons with exposure to asbestos from patients with mesothelioma. In conjunction with effusion fibulin-3 levels, plasma fibulin-3 levels can further differentiate mesothelioma effusions from other malignant and benign effusions (31).

Creaney *et al.* determined that fibulin-3 is increased in the plasma of MPM patients but at a lower diagnostic sensitivity than previously reported and inferior to that of SMRP in both plasma and effusions (32).

Other authors considered that the real use for serum fibulin-3 was for diagnosis in MPM but not for prognosis (30).

MicroRNAs (MiRNAs)

MiRNAs are short RNA no-codifing sequences. In recent years, miRNAs expression involved in post-transcriptional regulation of gene expression-in mesothelioma biology was found dysregulated both in cancer cells and sera, in patients affected by tumors of different histotypes, including MPM (35).

MiRNA are recently considered as diagnostic markers in different types of cancer. Preliminary analysis evidence miRNAs as possible markers for diagnosis and prognosis of MPM, and hypothesize new mechanisms for the therapy of this malignancy (35-48).

The histopathological subtypes were associated with the expression of miR-17-5p, miR-21, miR-29a, miR-30c, miR-30e-5p, miR-106a, and miR-143 and the reduction of the expression of two miRNAs (miR-17-5p and miR-30c) correlated with better survival of patients with sarcomatoid subtype (37).

Gee *et al.* studied the molecular differences between mesothelioma and lung adenocarcinoma by using miRNA microarrays (36).

Santarelli *et al.* proposed miR-126 as useful marker because significantly remained down-regulated in the malignant tissues compared with the normal tissues (38) and in serum (41) while Kirschner *et al.* confirmed the potential of miR-29c and miR-92a as candidate tumor markers and revealed that miR-625-3p was a promising novel diagnostic marker for MPM (39).

Bononi *et al.*, on the base of their studies, proposed as potential new MPM biomarkers three circulating up-regulated microRNAs, i.e., miR-197-3p, miR-1281 and miR-32-3p (35).

Micolucci *et al.* designated as "mesomiRs" (MM-associated miRNAs), a pool of deregulated circulating and tissue miRNAs; identified as biomarker useful for MPM.

Data from previously exposed to asbestos and MPM subjects showed that the most promising candidates for a multimarker signature were circulating miR-126-3p, miR-103a-3p, and miR-625-3p in combination with SMRP (44).

De Santi *et al.* showed that in MPM the pattern of miRNAs expression is highly deregulated and that a 2-miRNA signature (Let-7c-5p and miR-151a-5p) can be considered as a useful tool for prognosis of MPM (45). Also miRNA-16 was directly related to MPM patient prognosis, suggesting its possible use as a prognostic marker in MPM patients (47).

The study of Cavalleri *et al.* suggests that plasmatic extracellular vesicles (EV)-associated miR-103a-3p and miR-30e-3p are able to discriminate MPM from subjects with past asbestos exposure (46).

Standardized validation studies are needed to assess clinical relevance of the MiRNAs, so as to move from the workbench to the clinic (44).

For screening use as biomarkers for monitoring of workers exposed to asbestos a better knowledge of miRNA signatures in MPM is still necessary to verify the contribution of specific miRNAs as early diagnostic biomarkers, also compared to different asbestos forms, exposure and subject work history (42).

Other biomarkers proposed

Many other indicators have been evaluated as biomarker for MPM [cytokines, serum thioredoxin-1 (TRX-1), CA125, CYFRA 21-1, IL6, HGF, desmin, IP10, vimentin, THSP2, circulating fibrinogen, etc.].

MPF is a 31-kDa secreted cytokine, originated from mesothelin cutting. When evaluated in serum of MPM patients and control subjects by ELISA, MPF levels were higher in MPM cases, with respect to healthy subjects, individuals with benign asbestos-related diseases, or LC patients (49,50).

C-C chemokine RANTES were found significantly associated with workers formerly asbestos exposed and MPM patients compared with healthy controls. Increased immune mediator concentrations were observed in the sera of the workers previously exposed to asbestos compared to controls for human fibroblast growth factor (FGF-b), vascular endothelial growth factor (VEGF), CCL5 (RANTES), CXCL10 (IP-10), CLEC11A (SCGF-b), CCL27 (CTACK), CCL11 (EOTAXIN), IL-5 and IL-6

(P<0.001). Levels of chemokines IP-10 and RANTES were associated with the severity of asbestos-related diseases. The immune proteins secreted by mesothelioma biopsies showed detectable levels of RANTES, VEGF, and IP-10 in MPM patients. A significant relationship between serum and pleural fluid concentrations was found for RANTES alone in the MPM cases (51).

In the progression of asbestos-related diseases some chemokines may have a prognostic role and can be useful for the health surveillance of workers with an occupational history of asbestos exposure, and patients affected by non-malignant asbestos-related diseases (52).

To differentiate patients with MPM from SPE, also serum sCD26 and DPPIV enzyme activity appear to be useful biomarkers. The prognosis of patients with MPM can be predicted by DPPIV activity in serum or pleural fluid (53).

The relationship between interleukin 6 (IL-6) levels and clinical parameters was studied by Nakano *et al.* in 25 patients with MPM (54).

IL-6 mRNA expression in the tumors and serum IL-6 levels was described also by Bielefeldt-Ohmann *et al.* (55).

Quite recently among some new serum markers differentially expressed in MPM and healthy subjects, have been found levels of IL6 statistically different between the studied groups (56).

Fitzpatrick *et al.* suggest involvement of the expression of cytokines and cytokine receptors *in situ* in MMP (57).

Serum TRX-1 (58) and circulating fibrinogen (59) are other reported serum biomarkers.

Combination or panel of serum biomarkers

The combination of multiple markers could be very useful to increase sensitivity and specificity in early diagnosis, monitoring e screening of MPM rather than the use of single markers.

Several panels of biomarkers have been suggested as tools for screening and early diagnosis, clinical monitoring, prognosis and screening of MPM (60-68). The combinations studied are multiple: 80HdG, VEGFbeta and SMRPs (60), miR-126, in association with SMRPs (61), serum concentrations of SMRP, CA125, and CYFRA21-1 (62), combination of serum SMRP and pOPN (27), combination of SMRP and miR-103a-3p (63,64), SMRPs, miR-126 and methylated thrombomodulin promoter, Met-TM (65), fibulin-3 and SMRP (66), combination of miR-132-3 and miR-126 (48), combination of six biomarkers (SMRP-pOPN-IL6-vimentin-desmin-HGF) (56).

Conclusions

For diagnostic and prognostic purposes, to date, SMRP is the only biomarker approved by the FDA and suggested by several consensuses (66).

In accordance with the most advanced scientific papers and the most authoritative guidelines, this biomarker can be used, some sensitivity limits, as a diagnostic marker for evaluating follow-up therapy and as a prognostic indicator, at least in epithelioid mesotheliomas.

Helsinki criteria suggest that SMRP, pOPN, MPF, fibulin-3, quantitative miRNA expression and other may be useful as a follow-up tool in the treatment of malignancies and could be helpful in early clinical diagnosis. A major debate is whether early detection can improve treatment outcome. Actually no specific recommendations were made regarding these biomarkers for screening or other purposes (67).

Studies in recent years show that the use of markers panel, using also markers obtained evaluated by different approaches based on proteomics technology, greatly improves clinical diagnostic performance.

New promising markers are in the study and alone or better in combination and will be very helpful in diagnosing and monitoring mesothelioma patients.

Recently, a proteomic approach, screening of a large number of biomarkers, improves the diagnostic accuracy in different types of cancer, including MPM (68-70).

There are needed additional studies with more enrolled patients and better drawing to scrupulously assess the diagnostic power of all these biomarkers.

Probably the ongoing studies will allow, in the near future, more accurate MPM diagnosis and prognosis, earlier detection of MPM and helpful screening of people formerly exposed to asbestos (71).

In conclusion, the current status of MPM biomarkers is not satisfactory but encouraging due to emerging more sensitive and specific non-invasive biomarkers.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Ceresoli GL, Betta GP, Castagneto B, et al. Malignant pleural mesothelioma. Ann Oncol 2006;17:ii13-6.
2. Cristaudo A, Bonotti A, Simonini S, et al. Soluble markers for diagnosis of malignant pleural mesothelioma. Biomark Med 2011;5:261-73.
3. Treasure T, Lang-Lazdunski L, Waller D, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. Lancet Oncol 2011;12:763-72.
4. Bonotti A, Simonini S, Pantani E, et al. Serum mesothelin, osteopontin and vimentin: useful markers for clinical monitoring of malignant pleural mesothelioma. Int J Biol Markers 2017;32:e126-31.
5. Chang K, Pastan I. Molecular cloning and expression of a cDNA encoding a protein detected by the K1 antibody from an ovarian carcinoma (OVCAR-3) cell line. Int J Cancer 1994;57:90-7.
6. Chang K, Pai LH, Batra JK, et al. Characterization of the antigen (CAK1) recognized by monoclonal antibody K1 present on ovarian cancers and normal mesothelium. Cancer Res 1992;52:181-6.
7. Robinson BW, Creaney J, Lake R, et al. Mesothelin-family proteins and diagnosis of mesothelioma. Lancet 2003;362:1612-6.
8. Robinson BW, Creaney J, Lake R, et al. Soluble mesothelin-related protein--a blood test for mesothelioma. Lung Cancer 2005;49:S109-11.
9. Hassan R, Remaley AT, Sampson ML, et al. Detection and quantitation of serum mesothelin, a tumor marker for patients with mesothelioma and ovarian cancer. Clin Cancer Res 2006;12:447-53.
10. Scherpereel A, Grigoriu B, Conti M, et al. Soluble mesothelin-related peptides in the diagnosis of malignant pleural mesothelioma. Am J Respir Crit Care Med 2006;173:1155-60.
11. Cristaudo A, Foddis R, Vivaldi A, et al. Clinical significance of serum mesothelin in patients with mesothelioma and lung cancer. Clin. Cancer Res 2007;13:5076-81.
12. Grigoriu BD, Scherpereel A. Diagnostic value of soluble mesothelin in malignant mesothelioma. Thorax 2008;63:87-88; author reply 87.
13. Wheatley-Price P, Yang B, Patsios D, et al. Soluble mesothelin-related Peptide and osteopontin as markers of response in malignant mesothelioma. J Clin Oncol 2010;28:3316-22.
14. Hollevoet K, Nackaerts K, Gosselin R, et al. Soluble mesothelin, megakaryocyte potentiating factor, and osteopontin as markers of patient response and outcome in mesothelioma.J Thorac Oncol 2011;6:1930-7.
15. Hollevoet K, Reitsma JB, Creaney J, et al. Serum mesothelin for diagnosing malignant pleural mesothelioma: an individual patient data meta-analysis. J Clin Oncol 2012;30:1541-9.
16. Smolková P, Nakládalová M, Zapletalová J, et al. Validity of mesothelin in occupational medicine practice. Int J Occup Med Environ Health 2016;29:395-404.
17. Franko A, Dolzan V, Kovac V, et al. Soluble mesothelin-related peptides levels in patients with malignant mesothelioma. Dis Markers 2012;32:123-31.
18. van Zandwijk N, Clarke C, Henderson D, et al. Guidelines for the diagnosis and treatment of malignant pleural mesothelioma. J Thorac Dis 2013;5:E254-307.
19. Chen RX, Xia YH, Xue TC, et al. Osteopontin promotes hepatocellular carcinoma invasion by up-regulating MMP-2 and uPA expression. Mol Biol Rep 2011;38:3671-7.
20. Ohashi R, Tajima K, Takahashi F, et al. Osteopontin modulates malignant pleural mesothelioma cell functions in vitro. Anticancer Res 2009;29:2205-14.
21. Coppola D, Szabo M, Boulware D, et al. Correlation of osteopontin protein expression and pathological stage across a wide variety of tumor histologies. Clin Cancer Res 2004;10:184-90.
22. Pass HI, Lott D, Lonardo F, et al. Asbestos exposure, pleural mesothelioma, and serum osteopontin levels. N Engl J Med 2005;353:1564-73.
23. Cristaudo A, Foddis R, Bonotti A, et al. Comparison between plasma and serum osteopontin levels: usefulness in diagnosis of epithelial malignant pleural mesothelioma. Int J Biol Markers 2010;25:164-70.
24. Creaney J, Yeoman D, Musk AW, et al. Plasma versus serum levels of osteopontin and mesothelin in patients with malignant mesothelioma--which is best? Lung Cancer 2011;74:55-60.
25. Hu ZD, Liu XF, Liu XC, et al. Diagnostic accuracy of osteopontin for malignant pleural mesothelioma: a systematic review and meta-analysis. Clin Chim Acta 2014;433:44-8.
26. Rai AJ, Flores RM, Mathew A, et al. Soluble mesothelin related peptides (SMRP) and osteopontin as protein biomarkers for malignant mesothelioma: analytical validation of ELISA based assays and characterization at mRNA and protein levels. Clin Chem Lab Med

2010;48:271-8.
27. Cristaudo A, Bonotti A, Simonini S, et al. Combined serum mesothelin and plasma osteopontin measurements in malignant pleural mesothelioma. J Thorac Oncol 2011;6:1587-93.
28. Cristaudo A, Foddis R, Buselli R, et al. Medical surveillance of workers previously exposed to asbestos. Med Lav 2006;97:475-81.
29. Chen Z, Gaudino G, Pass HI, et al. Diagnostic and prognostic biomarkers for malignant mesothelioma: an update. Transl Lung Cancer Res 2017;6:259-69.
30. Kaya H, Demir M, Taylan M, et al. Fibulin-3 as a diagnostic biomarker in patients with malignant mesothelioma. Asian Pac J Cancer Prev 2015;16:1403-7.
31. Pass HI, Levin SM, Harbut MR, et al. Fibulin-3 as a blood and effusion biomarker for pleural mesothelioma. N Engl J Med 2012;367:1417-27.
32. Creaney J, Dick IM, Meniawy TM, et al. Comparison of fibulin-3 and mesothelin as markers in malignant mesothelioma. Thorax 2014;69:895-902.
33. Ren R, Yin P, Zhang Y, et al. Diagnostic value of fibulin-3 for malignant pleural mesothelioma: A systematic review and meta-analysis. Oncotarget 2016;7:84851-9.
34. Pei D, Li Y, Liu X, et al. Diagnostic and prognostic utilities of humoral fibulin-3 in malignant pleural mesothelioma: Evidence from a meta-analysis. Oncotarget 2017;8:13030-8.
35. Bononi I, Comar M, Puozzo A, et al. Circulating microRNAs found dysregulated in ex-exposed asbestos workers and pleural mesothelioma patients as potential new biomarkers. Oncotarget 2016;7:82700-11.
36. Gee GV, Koestler DC, Christensen BC, et al. Downregulated microRNAs in the differential diagnosis of malignant pleural mesothelioma. Int J Cancer 2010;127:2859-69.
37. Busacca S, Germano S, De Cecco L, et al. MicroRNA signature of malignant mesothelioma with potential diagnostic and prognostic implications. Am J Respir Cell Mol Biol 2010;42:312-9.
38. Santarelli L, Strafella E, Staffolani S, et al. Association of MiR-126 with soluble mesothelin-related peptides, a marker for malignant mesothelioma. PLoS One 2011;6:e18232.
39. Kirschner MB, Cheng YY, Badrian B, et al. Increased circulating miR-625-3p: a potential biomarker for patients with malignant pleuralmesothelioma. J Thorac Oncol 2012;7:1184-91.
40. Bonotti A, Foddis R, Papa A, et al. Identification and characterization of microRNA involving in malignant pleural mesothelioma. G Ital Med Lav Ergon 2012;34:552-4.
41. Tomasetti M, Staffolani S, Nocchi L, et al. Clinical significance of circulating miR-126 quantification in malignant mesothelioma patients. Clin Biochem 2012;45:575-81.
42. Sturchio E, Amadori A, Businaro J, et al. Possible use of microRNAs as biomarkers for monitoring of workers exposed to asbestos. G Ital Med Lav Ergon 2012;34:571-3.
43. Reid G. MicroRNAs in mesothelioma: from tumour suppressors and biomarkers to therapeutic targets. J Thorac Dis 2015;7:1031-40.
44. Micolucci L, Akhtar MM, Olivieri F, et al. Diagnostic value of microRNAs in asbestos exposure and malignant mesothelioma: systematic review and qualitative meta-analysis. Oncotarget 2016;7:58606-37.
45. De Santi C, Melaiu O, Bonotti A, et al. Deregulation of miRNAs in malignant pleural mesothelioma is associated with prognosis and suggests an alteration of cell metabolism. Sci Rep 2017;7:3140.
46. Cavalleri T, Angelici L, Favero 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:e0176680.
47. Mozzoni P, Ampollini L, Goldoni M, et al. MicroRNA Expression in Malignant Pleural Mesothelioma and Asbestosis: A Pilot Study. Dis Markers 2017;2017:9645940.
48. Weber DG, Gawrych K, Casjens S, et al. Circulating miR-132-3p as a Candidate Diagnostic Biomarker for Malignant Mesothelioma. Dis Markers 2017;2017:9280170.
49. Chen Z, Gaudino G, Pass HI, et al. Diagnostic and prognostic biomarkers for malignant mesothelioma: an update. Transl Lung Cancer Res 2017;6:259-69.
50. Onda M, Nagata S, Ho M, et al. Megakaryocyte potentiation factor cleaved from mesothelin precursor is a useful tumor marker in the serum of patients with mesothelioma. Clin Cancer Res 2006;12:4225-31.
51. Comar M, Zanotta N, Bonotti A, et al. Increased levels of C-C chemokine RANTES in asbestos exposed workers and in malignant mesothelioma patients from an hyperendemic area. PLoS One 2014;9:e104848.
52. Comar M, Zanotta N, Zanconati F, et al. Chemokines involved in the early inflammatory response and in pro-tumoral activity in asbestos-exposed workers from an Italian coastal area with territorial clusters of pleural malignant mesothelioma. Lung Cancer 2016;94:61-7.

53. Fujimoto N, Ohnuma K, Aoe K, et al. Clinical significance of soluble CD26 in malignant pleural mesothelioma. PLoS One 2014;9:e115647.
54. Nakano T, Chahinian AP, Shinjo M, et al. Interleukin 6 and its relationship to clinical parameters in patients with malignant pleuralmesothelioma. Br J Cancer 1998;77:907-12.
55. Bielefeldt-Ohmann H, Marzo AL, Himbeck RP, et al. Interleukin-6 involvement in mesothelioma pathobiology: inhibition by interferon alpha immunotherapy. Cancer Immunol Immunother 1995;40:241-50.
56. Bonotti A, Foddis R, Landi R, et al. A Novel Panel of Serum Biomarkers for MPM Diagnosis. Dis Markers 2017;2017:3510984.
57. Fitzpatrick DR, Peroni DJ, Bielefeldt-Ohmann H. The role of growth factors and cytokines in the tumorigenesis and immunobiology of malignantmesothelioma. Am J Respir Cell Mol Biol 1995;12:455-60.
58. Maeda R, Tabata C, Tabata R, et al. Is serum thioredoxin-1 a useful clinical marker for malignant pleural mesothelioma? Antioxid Redox Signal 2011;15:685-9.
59. Ghanim B, Hoda MA, Klikovits T, et al. Circulating fibrinogen is a prognostic and predictive biomarker in malignant pleuralmesothelioma. Br J Cancer 2014;110:984-90.
60. Amati M, Tomasetti M, Scartozzi M, et al. Biomarkers for prevention and early diagnosis of malignant pleural mesothelioma. G Ital Med Lav Ergon 2007;29:335-8.
61. Santarelli L, Strafella E, Staffolani S, et al. Association of MiR-126 with soluble mesothelin-related peptides, a marker for malignant mesothelioma. PLoS One 2011;6:e18232.
62. Gube M, Taeger D, Weber DG, et al. Performance of biomarkers SMRP, CA125, and CYFRA 21-1 as potential tumor markers for malignant mesothelioma and lung cancer in a cohort of workers formerly exposed to asbestos. Arch Toxicol 2011;85:185-92.
63. Weber DG, Casjens S, Johnen G, et al. Combination of MiR-103a-3p and mesothelin improves the biomarker performance of malignant mesothelioma diagnosis. PLoS One 2014;9:e114483.
64. Santarelli L, Staffolani S, Strafella E, et al. Combined circulating epigenetic markers to improve mesothelin performance in the diagnosis of malignant mesothelioma. Lung Cancer 2015;90:457-64.
65. Kovac V, Dodic-Fikfak M, Arneric N, et al. Fibulin-3 as a biomarker of response to treatment in malignant mesothelioma. Radiol Oncol 2015;49:279-85.
66. Creaney J, Dick IM, Robinson BW. Discovery of new biomarkers for malignant mesothelioma. Curr Pulmonol Rep 2015;4:15-21.
67. Wolff H, Vehmas T, Oksa P, et al. Asbestos, asbestosis, and cancer, the Helsinki criteria for diagnosis and attribution 2014: recommendations. Scand J Work Environ Health 2015;41:5-15.
68. Cerciello F, Choi M, Nicastri A, et al. Identification of a seven glycopeptide signature for malignant pleural mesothelioma in human serum by selected reaction monitoring. Clin Proteomics 2013;10:16.
69. Ostroff RM, Mehan MR, Stewart A, et al. Early detection of malignant pleural mesothelioma in asbestos-exposed individuals with a noninvasive proteomics-based surveillance tool. PLoS One 2012;7:e46091.
70. Giusti L, Da Valle Y, Bonotti A, et al. Comparative proteomic analysis of malignant pleural mesothelioma evidences an altered expression of nuclear lamin and filament-related proteins. Proteomics Clin Appl 2014;8:258-68.
71. Arnold DT, De Fonseka D, Hamilton FW, et al. Prognostication and monitoring of mesothelioma using biomarkers: a systematic review. Br J Cancer 2017;116:731-41.

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