Review

Towards a Better Understanding of Mesothelioma: A Comprehensive Review of Diagnosis, Therapy and Biomarkers

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Towards a Better Understanding of Mesothelioma: A Comprehensive Review of Diagnosis, Therapy and Biomarkers

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Abstract: Malignant pleural mesothelioma (MPM) is a rare but highly aggressive cancer, primarily caused by asbestos exposure, with limited diagnostic and therapeutic options. The disease is characterized by late-stage diagnosis and poor prognosis, necessitating advancements in early detection and treatment strategies. Biomarkers have emerged as vital tools in addressing these challenges, providing opportunities for early diagnosis, prognostic evaluation, and therapeutic guidance. This review explores the recent developments in MPM biomarkers, including soluble mesothelin-related peptides (SMRP), fibulin-3, osteopontin, and novel genetic and epigenetic markers. We also examine the potential of liquid biopsy technologies, encompassing circulating tumor cells (CTCs), cell-free DNA (cfDNA), and exosomal markers, in improving diagnostic precision and monitoring treatment response. Despite promising advancements, significant hurdles remain, including variability in biomarker sensitivity and specificity, lack of standardization in clinical settings, and the need for extensive validation studies. Recommendations for future research include integrating multi-omic approaches, leveraging artificial intelligence for biomarker discovery, implementing appropriate screening guidelines and fostering collaboration among research institutions to expedite translational efforts for personalized, biomarker driven treatment strategies. By addressing these gaps, biomarker research can pave the way for personalized medicine in MPM, improving early detection, treatment efficacy, and overall patient outcomes.

Keywords: mesothelioma; biomarkers mesothelioma; malignant mesothelioma biomarkers

1. Introduction

Malignant mesothelioma is an aggressive neoplasm primarily arising from serosal cells of the pleura and peritoneum, with up to 80% of cases being malignant pleural mesothelioma (MPM) [1]. The main cause is prior exposure to asbestos and erionite fibers, with a latency period of 10–40 years before disease presentation [2,4]. Incidence rates vary by region, with the USA reporting 0.9 for males and 0.3 for females per 100,000 people, while Europe reports 1.7 for males and 0.4 for females [3]. Unregulated asbestos use in countries like India, China, Brazil, and Russia continues to pose a global health concern [2,6].

MPM has a poor prognosis due to resistance to current therapies, with only 5% of cases diagnosed at stage 1, where prognosis is better. Thus, new biomarkers for early detection and tailored therapies are crucial [4]. Accurate differentiation from adenocarcinoma is essential, employing immunohistochemical methods alongside microscopic diagnosis. Guidelines recommend a

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combination of at least two positive mesothelial markers (calretinin, cytokeratin 5/6, Wilms' tumor 1, D-240) and two negative adenocarcinoma markers (transcription termination factor 1, carcino-embryonic antigen, Ber-EP4) for diagnosis [5,7,8].

Biomarkers are significant for several reasons: they identify individuals at risk, help differentiate symptoms from other diseases, and facilitate less invasive diagnostic methods. Extensive research has focused on serum and pleural fluid biomarkers for screening, diagnosis, treatment response, and prognosis. Mesothelin is the most studied, showing good specificity but low sensitivity, particularly for non-epithelioid MPM [9]. Pleural fluid analysis is a less invasive, cost-effective technique for detecting malignancy biomarkers, with several molecules, including mesothelin, soluble mesothelin-related peptides (SMRPs), fibulin-3, and osteopontin being investigated [9,10]. Most studies focus on serum biomarkers like mesothelin, osteopontin, integrin-linked kinase (ILK), thioredoxin-1 (TRX), high-mobility group box protein 1 (HMGB1), micro-RNA, and fibulin-3 [11].

This review identifies multiple biomarkers useful for screening, treatment, and prognosis of malignant mesothelioma, emphasizing the need for further research to optimize their clinical application for patient health.

2. Pathogenesis of Malignant Mesothelioma

MPM pathogenesis is closely linked to asbestos exposure, accounting for 70%-90% of cases, with a latency period of 10–40 years before diagnosis [12,13]. As a carcinogen, asbestos alters the genetic and epigenetic landscape, primarily through increased reactive oxygen species (ROS) that cause DNA damage and affect DNA repair genes [14,16]. Long, thin fibers like crocidolite are particularly oncogenic due to their persistence in the pleura and their ability to evade macrophage engulfment, leading to oxidative stress and chronic inflammation [15–18].

Several mechanisms link asbestos exposure to mesothelioma development: (i) ROS-induced DNA damage, (ii) physical interference with cell division, (iii) absorption of carcinogenic proteins, and (iv) the release of growth factors by mesothelial cells that promote tumor proliferation [5]. High-mobility group box 1 protein is also released during necrotic cell death, contributing to inflammation [7].

ROS production occurs via two main mechanisms: one is iron-mediated in cell-free systems, generating hydroxyl radicals and reactive nitrogen species; the other involves phagocytic cells releasing reactive intermediates [19]. These oxidants activate carcinogenesis-related pathways, leading to DNA strand breaks and mutations, such as increased levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG) in crocidolite-treated rats [18,20,21].

Cytogenetic studies of MPM reveal frequent deletions on chromosomes 1p, 3p, 6q, 9p, 13q, 15q, and 22q, with alterations in tumor suppressor genes like p16/CDKN2A-p14ARF and NF2 [22]. Additionally, simian virus 40 (SV40) has been found in many MPMs, suggesting a co-carcinogenic role with asbestos [22,23].

Asbestos also activates mitogen-activated protein kinase (MAPK) pathways, influencing cell proliferation and apoptosis [24]. MPM exhibits aggressive local spread with low metastatic rates, involving extracellular matrix degradation, cell migration, and proliferation, particularly through matrix metalloproteinases (MMPs) like MMP-2 and MMP-9 [25]. Angiogenesis, stimulated by hypoxia, nutrient deprivation, and ROS, is essential for tumor growth, with studies showing capillary networks surrounding asbestos-containing lesions [26]. ROS accumulation is also implicated in necrotic cell death and is harnessed in cancer treatments like chemotherapy and radiotherapy [27].

3. Diagnosis of Malignant Mesothelioma

The wide array of signs and symptoms of malignant mesothelioma makes it a significant diagnostic problem. Delayed diagnosis is frequently caused by complications with other disorders and a lack of specific symptoms [28]. To apply the right therapeutic approaches and eventually enhance patient outcomes, prompt and correct diagnosis is essential.

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Chest X-rays serve as a useful first screening tool for mesothelioma, identifying abnormalities such as pleural thickening or pleural effusion, though they lack specificity for diagnosis [29,30]. CT scanning represents a key advancement, providing high-resolution images that are crucial for accurate diagnosis, staging, and treatment planning, with findings like pleural thickening and interlobular gaps indicative of malignant mesothelioma [31,32]. MRI, while offering precise anatomical visualization, excels in assessing tumor invasion due to its superior soft tissue contrast and helps differentiate pleural effusions, especially with advancements like Diffusion Weighted Imaging (DWI) [33–36]. PET/CT scanning combines anatomical and metabolic data, using fluorodeoxyglucose (FDG) to identify active tumor sites, making it a valuable tool for diagnosis and staging, as well as monitoring treatment response [37–39]. Studies show that an SUV cutoff value of 2.0–2.2 can differentiate malignant from benign conditions with high specificity and sensitivity [39,40]. Although PET/CT is superior to other modalities for staging and monitoring, it may yield false positives due to inflammation or viral diseases, complicating assessments in patients with asbestos exposure [41–43].

Tissue Diagnosis: Tissue sampling remains the ideal test for confirming malignant mesothelioma as these tests still show limitations in differentiating malignant from benign pleural lesions. Pleural fluid cytology is often what is used as the initial test as it is easier to obtain, however its ability to detect MPM is notoriously low. Research has revealed the challenges associated with cytological examination of pleural fluid in MPM diagnosis [44].

The landmark study that showed this was done by Arnold et al [44], which demonstrated an overall pleural fluid cytology sensitivity of just 46%. It also showed that sensitivities are highly variable according to the tumor's origin, whether mesothelioma, carcinoma, or sarcoma. Moreover, in selected patient groups with a high likelihood of mesothelioma, such as males with prior asbestos exposure and exudative pleural effusions, the sensitivity of pleural fluid cytology was as low as 11% in this subgroup.

These findings with other studies as well [45] pointed out the importance of obtaining tissue biopsies for the definitive diagnosis in suspected cases of MPM.

Pleural biopsies are considered the gold standard for validating the diagnosis of mesothelioma by both the American Society of Clinical Oncology (ASCO) [46] and the European Respiratory Society (ERS) [47]. These biopsies, which are usually carried out via CT-guided techniques or thoracoscopy, provide histological confirmation that is essential for a precise diagnosis.

4. Management of Malignant Mesothelioma

Both the ASCO and the ERS guidelines for the management of malignant mesothelioma provide valuable access to optimal treatment strategies.

4.1. Surgery

The MesoVATS which is a large randomized controlled trial compared partial pleurectomy performed by Video Assisted Thoracoscopic Surgery (VATS) with talc pleurodesis in patients with MPM [48]. Although overall survival at 1 year was equivocal in both groups, nonetheless, the median length of hospital stay was higher and surgical and respiratory problems were noticeably more frequent in patients who had VATS pleurectomy. l. Therefore, Talc pleurodesis is still the recommended choice [46,47].

Radical surgery, whether extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/D), has been studied extensively, including the famous MARS trial [49], that assessed the feasibility of EPP but it lacks power to demonstrate any survival benefit. Observational studies failed to show any survival benefit of surgical resection versus medical therapy alone [50,51]. Due to the variability in outcomes and the limited data, recommendations are that surgery may be appropriate for carefully and precisely selected patients with MPM. It is usually P/D rather than EPP because it is lower due to comparable post-respiratory morbidity and preserved quality of life [52].

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4.2. Medical Therapy

Both ASCO and ERS recommend platinum-based chemotherapy combined with pemetrexed as the preferred first-line treatment for unresectable malignant mesothelioma [46,47]. Whether the addition of bevacizumab to platinum/pemetrexed doublet therapy be implemented or not is still an area of clinical research. Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS), a large phase III trial demonstrated the benefit of adding bevacizumab to cisplatin (cis)/pemetrexed (pem) doublet as first-line treatment [53]. The bevacizumab arm showed a 2-month increase in progression-free survival and only a mild and manageable increase in toxicity, with no detrimental effects on quality of life. The National Comprehensive Cancer Network (NCCN) guidelines recommend medical treatment of unresectable MPM based on histologic subtype. Platinum based chemotherapy combined with pemetrexed is recommended as first line therapy for epithelioid subtype, whereas nivolumab/ipilimumab immunotherapy is preferred in sarcomatoid or biphasic subtype. The Checkmate 743 trial explored this regimen and concluded nivolumab/ipilimumab immunotherapy to be superior to chemotherapy in unresectable MPM irrespective of histologic subtype.

4.3. Radiotherapy

Palliative: Recent research on palliative radiotherapy for MPM has been limited. The available evidence is largely based on retrospective studies and underpowered trials [54,55]. Studies showed that radiotherapy is effective in up to 50% of patients in relieving pain without increasing survival. one recent study, the Radiotherapy Symptoms in Mesothelioma Study (SYSTEMS-1) which recruited only 40 patients managed to show pain relief in almost half of the patient included [56], However, this relief did not significantly extend to other symptoms, as post-treatment survival was short.

Adjuvant: the paramount trial in this regard was 17/04 SAKK trial (Neoadjuvant Chemotherapy and Extrapleural Pneumonectomy of MPM With or Without Hemithoracic Radiotherapy), 54 patients post-EPP were randomly assigned to either observation or adjuvant radiotherapy [57]. However, the trial closed prematurely due to insufficient participant recruitment. While radiotherapy demonstrated only marginally improved median locoregional relapse-free survival, this difference did not reach statistical significance. Thus it's ERS recommendation that only in the context of clinical trials and/or national/international surgical registries that adjuvant radiation be explored following EPP [47].

5. Extra Pulmonary Involvement in Malignant Pleural Mesothelioma

Understanding the potential for local and distant metastases in mesothelioma is crucial, as metastasis significantly impacts treatment options and patient outcomes. Lymphatic spread is the primary mode of metastasis, with malignant cells entering lymphatic vessels and affecting regional lymph nodes, particularly the mediastinal and hilar nodes [58]. Epithelial and biphasic mesotheliomas show more lymph node metastases compared to sarcomatoid types, while extrapulmonary metastasis rates are similar across histological subtypes [59]. Hematogenous spread, although less common, leads to distant metastases in organs such as the liver, bone, adrenal glands, contralateral lung, and brain [60,61]. Factors influencing hematogenous spread include angiogenesis and interactions with the immune system [62,63]. Autopsy studies by Finn et al. (2012) revealed that 87.7% of patients had tumor extension beyond the ipsilateral pleura, with extrathoracic metastases in over half of the cases; the liver, peritoneum, and bone were the most common sites [64]. Collins et al. (2020) found a 67% metastasis rate with the contralateral lung, peritoneum, and bone being frequent sites [65]. Dagogo-Jack et al. (2023) reported that 44% of patients developed extrathoracic metastases approximately 11.5 months post-diagnosis, primarily affecting the abdomen, peritoneum, and bone, with only 9% having brain involvement [66].

6. Biomarkers in the Diagnosis and Management of Malignant Mesothelioma

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6.1. Mesothelin

Mesothelin is the most commonly researched marker in pleural effusions, characterized by high specificity but low sensitivity, particularly in non-epithelioid pleural mesothelioma. This protein is typically found on mesothelial cells lining the pleura, peritoneum, and pericardium. It seems to be involved in cell adhesion but is likely not a critical component in normal cells [67,68].

The SMRP is the sole FDA-approved biomarker for patients suspected of having mesothelioma. It is specifically indicated for monitoring individuals diagnosed with epithelioid or biphasic mesothelioma. SMRP is a glycoprotein encoded by the MSLN gene, and it has been noted that mesothelin can be released from the cell surface and detected in the bloodstream as well [69,70].

Mesothelin, initially referred to as the CAK1 antigen, was first identified using the murine monoclonal antibody K1 and is now detectable with newer anti-mesothelin antibodies, such as the 5B2 clone. Research on mesothelin in patients with MPM revealed that all patients with the epithelioid subtype expressed mesothelin, while those with the sarcomatous subtype did not. In biphasic MPM cases, only the epithelial component exhibited positive staining for mesothelin. Furthermore, lung adenocarcinomas, irrespective of their histologic differentiation, did not react with the K1 antibody [71].

Subsequent case-control studies from various centers globally have validated that mesothelin levels are significantly elevated in the serum of patients with mesothelioma, demonstrating high specificity for the disease. A meta-analysis of 16 studies involving over a thousand patients with MPM and nearly five thousand controls found that mesothelin had a sensitivity of 32% and a specificity of 95% for diagnosing MPM [72].

In its early stages, mesothelioma is a localized, nonmetastatic cancer, making it potentially curable if detected early. This underscores the importance of finding an appropriate biomarker to facilitate early intervention and treatment strategies. While retrospective studies have been promising, several prospective studies indicate that monitoring serum mesothelin levels in cohorts exposed to asbestos yields false-positive rates exceeding 90%, limiting its effectiveness for early detection of mesothelioma [73].

6.2. Fibulin-3

Fibulin-3 is a glycoprotein encoded by the gene for epidermal growth factor-containing fibulin-like extracellular matrix protein 1. It is involved in processes such as cell proliferation and migration. Measuring fibulin-3 levels in serum may help in diagnosing mesothelioma, but these levels do not correlate with patient prognosis [74].

Another study has reinforced the significance of serum and pleural fibulin-3 in diagnosing pleural mesothelioma and distinguishing between malignant and benign pleural conditions. It demonstrated a correlation between serum and pleural fibulin-3 levels. Using a cut-off point of 18 ng/ml for serum fibulin-3, the study achieved an area under the curve (AUC) of 0.931, indicating effective differentiation between malignant mesothelioma and benign pleural effusion [75].

A recent meta-analysis of 468 cases of MPM found a diagnostic sensitivity of 62% and a specificity of 82% for fibulin-3. As a result, while promising, fibulin-3 is not yet fully validated as a reliable diagnostic biomarker and requires additional prospective studies for confirmation [76].

6.3. Hyaluronic Acid

Hyaluronic acid (HA), is a large polysaccharide that contributes to the progression of several types of cancer [77]. HA plays several important roles in malignancy. It serves as a template for assembling various pericellular macromolecules, directly interacts with cell surface receptors to transmit intracellular signals, and promotes anchorage-independent growth and invasiveness of cancer cells [78]

In a study analyzing HA concentrations in pleural fluid, the findings supported the use of HA as an auxiliary diagnostic marker for MPM. Previous research confirmed that HA levels were

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significantly elevated in patients with MPM compared to those with other conditions. Furthermore, a diagnosis of MPM should be strongly considered in patients with pleural fluid HA concentrations exceeding 100,000 ng/ml. In this study, the AUC for HA in differentiating MPM was 0.832 (95% CI, 0.765–0.898) [79].

6.4. microRNA

MicroRNAs are short, noncoding, single-stranded RNA molecules that regulate gene expression at the post-transcriptional level. They play a critical role in various biological processes, including cell division, proliferation, differentiation, apoptosis, and angiogenesis. Changes in microRNA expression have been observed in several types of cancer, indicating that they may function as either oncogenes or tumor suppressors.

MicroRNAs hold promise as diagnostic markers and potential targets in contemporary anticancer therapies. The differentiation and expression profiles of microRNAs can help assess the extent of tumor development, providing insights into therapeutic options. This information can enable the selection of the most suitable treatment for individual cases [80]. Reduced expression or absence of tumor suppressor microRNAs leads to increased levels of genes that promote tumor progression, such as anti-apoptotic proteins and transcription factors. Additionally, specific extracellular vesicle (EV)-associated plasma microRNAs have been identified that can differentiate patients with malignant pleural mesothelioma from cancer-free individuals who have been exposed to asbestos [81,82].

Recently, it has been suggested that exhaled breath condensate (EBC)-microRNAs, the so-called volatile biopsy, could represent novel, non-invasive reliable biomarkers for lung cancer. Further research has suggested that EBC microRNAs, known as "volatile biopsies," could be novel, non-invasive biomarkers for lung cancer. A study aimed to identify microRNA signatures suitable for lung cancer screening using minimally invasive techniques like EBC and plasma collection. The EV-associated miRNome was analyzed in both EBC and plasma from patients with non-small cell lung cancer (NSCLC) and healthy controls. The microRNA signatures were then compared to those associated with malignant pleural mesothelioma to assess the potential of circulating microRNAs for differentiating between these conditions [83].

6.5. Osteopontin

Osteopontin (OPN) is an integrin-binding protein that plays a role in cell-matrix interactions. It may have prognostic significance, as several studies have indicated that elevated OPN levels are associated with poorer outcomes in patients with MPM [84].

In a study, plasma and serum OPN levels were found to be significantly higher in patients with epithelial MPM compared to healthy controls and those with benign respiratory diseases. The receiver operating characteristic (ROC) curve analysis for plasma OPN yielded an AUC of 0.780, with an optimal cutoff value of 878.65 ng/mL. This resulted in a sensitivity of 68.8% and a specificity of 84.5% [85]

6.6. Calretinin

Calretinin is a calcium-binding protein initially discovered in neurons but is also expressed on mesothelial cell surfaces. It is commonly used in immunohistochemical evaluations of cyto-histological specimens suspected of MPM, including both epithelioid and sarcomatoid types. Calretinin is considered one of the most valuable immunohistochemical markers for supporting a diagnosis of MPM [86,87].

With a sensitivity of 71% at a predefined specificity of 95%, comparisons between controls and MPM patients yielded AUC values ranging from 0.77 to 0.95 [88–90]. Additionally, blood calretinin levels were effective in pre-diagnosing mesothelioma in an asbestos-exposed population, achieving

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an AUC of 0.77 one to 15 months before a definitive diagnosis. This AUC improved to 0.85 when combined with serum mesothelin levels [91].

6.7. ctDNA

cfDNA arises from both healthy and cancerous tissues undergoing apoptosis or necrosis and has shown considerable promise in oncology. In contrast, circulating tumor DNA (ctDNA) originates solely from tumor cells, contains somatic mutations, and constitutes only a small fraction of the total cfDNA [92].

In a study of 10 patients with MPM who underwent whole-exome sequencing, tumor-specific variants were validated using digital droplet PCR. Patient-specific variants were detected in the circulating DNA of only three treatment-naïve MPM patients, appearing in one or both of the PCR runs [93].

While ctDNA shows promise as a biomarker for assessing treatment response, further validation and the development of cost-effective technologies are needed before it can be routinely implemented in clinical practice.

Name of Biomarker	Ongoing Research	Subtype Specificity
Mesothelin	**Checkmate-743:** Phase III trial of ipilimumab and nivolumab shows survival benefit in non-epithelioid MPM. **SS1P Trials:** Phase I/II trials for mesothelin-targeted immunotherapy. **LMB-100:** An anti-mesothelin immunotoxin tested in refractory MPM.	High levels seen in **epithelioid** subtype; not expressed in sarcomatous subtype. Biphasic subtype shows mesothelin only in the epithelial component..
Fibulin-3	Ongoing prospective trials validating its diagnostic use for differentiating malignant pleural mesothelioma from benign conditions.	Elevated levels in **epithelioid** mesothelioma.
Hyaluronic Acid	Trials explore its use in a biomarker panel for enhanced diagnostic precision, particularly in asbestos-exposed populations.	Seen across subtypes but elevated levels are associated with **epithelioid** MPM.
MicroRNA	Studies evaluating miRNA panels in blood and exhaled breath condensate for early diagnosis and subtype-specific patterns: **Pérez-Sánchez et al [94]**: suggests that EBC-derived miRNA signatures could serve as effective non-invasive biomarkers for lung cancer detection. **Rai Et al [95]:** Many clinical results have demonstrated that miRNAs function as potential biomarkers for diagnosis, prognosis and therapy of lung cancer	Differential expression observed in **all subtypes**, with ongoing research into subtype-specific patterns.
Osteopontin	**Keynote-483:** Phase II/III trials combining pembrolizumab with chemotherapy to evaluate survival outcomes.	Elevated levels correlate with poorer outcomes in **epithelioid** mesothelioma.

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Calretinin	Retrospective and prospective studies using immunohistochemistry in high-risk asbestos-exposed populations. Retrospective: **Shelby Et al [96]-** Studies show that calretinin can identify mesothelioma with up to 90% accuracy in epithelioid cases. However, it's only 55% accurate in sarcomatoid mesothelioma cases, so additional markers are needed for a confirmed diagnosis. **Zupanc Et al [97]-** confirmed that serum calretinin was elevated in patients with MM and, thus, could serve as a potential minimally invasive diagnostic MM biomarker. Prospective: **Johnen et al [98]**- The median concentration for calretinin was 0.359 ng/ml in MM cases and 0.187 ng/ml in controls. The difference between MM cases and controls was statistically significant ($p < 0.0001$). For mesothelin the median concentration was 1.349 nM in MM cases and 0.963 nM in controls ($p = 0.0043$)	Detected in both **epithelioid** and **sarcomatoid** subtypes.
ctDNA	Small-scale trials using digital PCR to validate ctDNA mutations in mesothelioma for diagnostic and prognostic utility. **Hylebos Et al [99]**- presence of ctDNA within circulating DNA of treatment naïve MPM patients	Found **across subtypes;** specific mutations identified in MPM.

7. Future Directions

Future research in MPM should prioritize identifying and validating novel biomarkers for early detection, prognosis, and biomarker-driven therapeutic approaches. Advances in molecular and genomic technologies, including next-generation sequencing and proteomics, provide opportunities to discover biomarkers with greater sensitivity and specificity. Collaborative, multi-center clinical trials are essential to evaluate these biomarkers' effectiveness across diverse populations, especially in regions with ongoing asbestos exposure.

Despite the challenges faced by past screening trials using biomarkers and breath tests in asbestos-exposed populations, the potential for effective screening remains significant and warrants further exploration. Integrating multi-omic approaches, leveraging artificial intelligence for biomarker discovery, and developing targeted screening guidelines could enhance detection and treatment strategies.

Furthermore, combining biomarker research with cutting-edge therapeutic approaches, such as immune checkpoint inhibitors and gene-editing strategies, may improve patient outcomes. To ensure translational impact, future efforts should focus on developing personalized protocols for biomarker evaluation, fostering global collaboration among research institutions, and expediting the translation

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of research into clinical practice. Addressing the ongoing risks of asbestos exposure by phasing out its use and raising public health awareness must also remain a key priority.

8. Conclusion

MPM remains a challenging cancer characterized by poor prognosis and complex diagnostic requirements. Asbestos exposure is the primary etiological factor, leading to a long latency period before disease onset. Current diagnostic methods, including imaging and tissue sampling, highlight the need for more accurate and less invasive techniques. Biomarkers like mesothelin, fibulin-3, and osteopontin show promise in improving early detection and guiding treatment, though their effectiveness varies. Continued research is essential to refine these biomarkers and enhance therapeutic strategies, ultimately aiming to improve patient outcomes in this aggressive malignancy.

9. Patents

There are no patents resulting from the work reported in this manuscript.

Supplementary Materials: None

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Abbreviations

The following abbreviations are used in this manuscript:

MPM	Malignant Pleural Mesothelioma
SMRPs	Soluble Mesothelin Related Peptides
CTCs	Circulating Tumor Cells
cfDNA	cell-free DNA
ILK	Integrin Linked Kinase
TRX	Thioredoxin 1
HMGB1	High Mobility Group Box Protein 1
ROS	Reactive Oxygen Species
8-OHdG	8-hydroxy-2′-deoxyguanosine
SV40	Simian Virus 40
MAPK	Mitogen Activated Protein Kinase
MMPs	Matrix Metalloproteinases
DWI	Diffusion Weighted Imaging
FDG	Fluorodeoxyglucose
ASCO	American Society of Clinical Oncology
ERS	European Respiratory Society
VATS	Video Assisted Thoracoscopic Surgery
EPP	ExtraPleural Pneumonectomy

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P/D	Pleurectomy/Decortication
MAPS	Mesothelioma Avastin Cisplatin Pemetrexed Study
cis	Cisplatin
pem	Pemetrexed
NCCN	National Comprehensive Cancer Network
SYSTEMS	Radiotherapy Symptoms in Mesothelioma Study
MPM	Malignant pleural mesothelioma
AUC	Area Under the Curve
HA	Hyaluronic Acid
EV	Extracellular Vesicle
EBC	Exhaled Breath Condensate
NSCLC	Non Small Cell Lung Cancer
OPN	Osteopontin
ROC	Receiver Operating Characteristic
ctDNA	Circulating Tumor DNA

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