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Frequency of Malignant Pleural Mesothelioma in Patients with Massive Pleural Effusion Admitted in Pulmonology Ward Mardan Medical Complex Mardan

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ABSTRACT

Background: Malignant pleural mesothelioma is an uncommon cancer that has a strong link to asbestos exposure. It is not well understood why mesothelioma develops in patients with large pleural effusion. This study provided the frequency of malignant pleural mesothelioma in patients with massive pleural effusion and identified demographic and clinical risk factors associated with its development. **Objective:** To determine the frequency of malignant pleural mesothelioma in patients with massive pleural effusion admitted in pulmonology ward Mardan Medical Complex Mardan. **Study Design:** Cross-sectional study. **Duration and Place of Study:** The study was conducted from December 15, 2024, to May 15, 2025, at the Department of Pulmonology, Mardan Medical Complex, Mardan. **Methodology:** A total of 112 patients of age 18 to 70 years with massive pleural effusion were selected. Pleural tissue specimens were obtained via percutaneous needle biopsy or thoracoscopic biopsy, and histopathological analysis with immunohistochemical staining was used to diagnose mesothelioma. **Results:** The mean age of participants was 47.67 ± 14.11 years, with a male predominance (61.6%). Mesothelioma was diagnosed in 9 patients (8%). Statistically significant associations were found between mesothelioma and older age (>50 years), male gender, BMI >30 kg/m^2, symptom duration >12 weeks, and rural residency. **Conclusion:** Malignant pleural mesothelioma is a significant cause of massive pleural effusion in patients over 50 years of age, predominantly affecting males with a higher BMI.

INTRODUCTION

Pleural effusion is the collection of excess fluid between the layers of the pleura, which is the pleura that encloses the lungs.[1] Shortness of breath, chest pain, as well as pulmonary failure in advanced stages, are symptoms of pleural effusions of various volumes, while where the excess fluid accumulation is large, it is said to be "massive pleural effusion."[2] Large effusions usually result in inhibited expansion of the lungs, thereby impairing respiration. The fluid is classified according to nature, e.g., transudative or exudate, which is indicative of the etiology of the effusion.[3]

There are a number of causes of pleural effusion ranging from systemic causes such as heart failure through more localized pulmonary disease.[4] The most frequent causes include pneumonia, tuberculosis, and congestive heart failure.[5] Malignancies including lung cancer also cause pleural effusions through direct pleural infiltration or through lymphatic obstruction.[6] Bacterial or viral pleuritis is other infections that can result in the accumulation of pleural fluid leading to inflammation and thickened pleura.[7] Systemic inflammation from autoimmune diseases like rheumatoid arthritis have also been implicated in the production of effusions.[8]

Malignant pleural mesothelioma (MPM) is an aggressive, though uncommon, cancer linked most importantly with exposure to asbestos.[9] MPM develops in the mesothelial cells covering the pleura, and its clinical presentation is frequently chest pain, dyspnea, and loss of weight.[10] MPM is notoriously hard to diagnose in the early stages, and it tends to have a poor prognosis because it is usually diagnosed after it has spread locally into the pleura and possibly invaded neighboring structures, which makes treatment challenging.[11] The disease is primarily seen in individuals with a history of significant asbestos exposure, typically occurring decades after the exposure has taken place.[12]

In those with massive pleural effusion, malignant spread of disease in the form of malignant pleural mesothelioma is an important consideration.[13] The effusion in such cases tends to be exudative and could be secondary to the malignant spread of disease. Indeed, one of the classic signs of MPM is pleural effusion and it is found in most cases on presentation. Malignant infiltration

of the pleura is responsible for the massive amount of accumulation of fluid through disruption of the usual pleural space and resulting vascular permeability.[14] As a result, pleural effusion can significantly impair lung function and complicate the management of MPM, requiring careful diagnostic and therapeutic intervention to manage both the cancer and its associated symptoms.[15]

A research conducted by Bakhshayesh KM and colleagues demonstrated that the incidence of malignant pleural mesothelioma was 11.8% among patients with extensive pleural effusion.[16]

Malignant pleural mesothelioma tends to occur as massive pleural effusion, with resulting diagnostic difficulties leading to undue delays in treatment. The incidence of mesothelioma in Mardan malignancy cases with massive pleural effusion is unknown, limiting clinicians' ability to maintain appropriate diagnostic suspicion. Establishing baseline prevalence data will guide clinical decision-making and inform the need for early mesothelioma screening protocols in this region. This study will provide essential epidemiological data to improve diagnostic accuracy and patient outcomes in Mardan's healthcare system.

METHODOLOGY

This cross-sectional study was conducted from December 15th, 2024 to June 15th, 2025 at the Department of Pulmonology, Mardan Medical Complex, Mardan. The study enrolled 112 patients presenting with massive pleural effusion. Sample size was calculated using WHO sample size software with a 95% confidence interval, 6% margin of error, and an expected prevalence of malignant pleural mesothelioma of 11.8% among patients with massive pleural effusion.

Participants were recruited through non-probability consecutive sampling technique. Inclusion criteria encompassed patients aged 18 to 70 years of both genders who presented with massive pleural effusion, defined as pleural fluid accumulation exceeding 1000 cm^3 or causing mediastinal displacement greater than 2 cm from midline on computed tomography imaging. Exclusion criteria eliminated patients with known malignancies other than mesothelioma, documented transudative pleural effusion, pregnancy confirmed by ultrasonography, or severe coagulopathy contraindicating pleural biopsy procedures.

Following approval from the institutional ethics committee and College of Physicians and Surgeons Pakistan, informed consent was obtained from all participants with assurance of confidentiality and minimal procedural risk. Comprehensive demographic data was collected including age, gender, body mass index, occupational history, symptom duration, socioeconomic background, educational attainment, and residential location.

Pleural tissue specimens were procured from all enrolled patients using either percutaneous needle biopsy or thoracoscopic biopsy techniques based on individual clinical circumstances. Retrieved samples underwent histopathological analysis followed by immunohistochemical staining protocols. Malignant pleural mesothelioma was confirmed when microscopic examination revealed atypical mesothelial cells displaying epithelioid, sarcomatoid, or biphasic architectural patterns with evidence of pleural tissue invasion, accompanied by positive immunoreactivity for mesothelial markers including calretinin and WT1, along with concurrent expression of CK5/6 and D2-40 podoplanin markers.

Statistical analysis was performed using IBM SPSS version 26. Categorical variables including gender, socioeconomic status, educational level, residential area, occupation, and mesothelioma diagnosis were presented as frequencies and percentages. Continuous variables such as age, body mass index, and disease duration were expressed as mean ± standard deviation or median with interquartile range following normality assessment via Shapiro-Wilk testing. Stratification analysis of malignant pleural mesothelioma was conducted across demographic and clinical variables, with post-stratification analysis employing chi-square or Fisher's exact tests where appropriate. Statistical significance was established at p-value ≤0.05.

RESULTS

The patient cohort had a mean age of 47.67±14.11 years, mean BMI of 24.57±3.70 kg/m^2, and mean symptom duration of 12.21±7.49 weeks, with males comprising 69 patients (61.6%) and females 43 patients (38.4%). The majority of patients were from rural areas (70 patients, 62.5%) compared to urban areas (42 patients, 37.5%), while socioeconomic distribution was nearly equal between poor (55 patients, 49.1%) and middle-class (57 patients, 50.9%) categories (as shown in Table I).

Table I

Patient Demographics

Demographics	Mean ± SD
Age (years)	47.67±14.11
BMI (Kg/m^2)	24.57±3.70
Duration (weeks)	12.21±7.49
Gender	
Male n (%)	69 (61.6%)
Female n (%)	43 (38.4%)
Residential Status	
Rural n (%)	70 (62.5%)
Urban n (%)	42 (37.5%)
Socioeconomic Status	
Poor n (%)	55 (49.1%)
Middle n (%)	57 (50.9%)

Malignant pleural mesothelioma was diagnosed in 9 patients (8%) out of the total 112 cases, while 103 patients (92%) did not have mesothelioma (as shown in Table II).

Table II

Frequency of Mesothelioma

Mesothelioma	Frequency	% age
Yes	9	8%
No	103	92%
Total	112	100%

Demographic analysis revealed significant associations between mesothelioma occurrence and several factors. Age stratification showed that all 9 mesothelioma cases occurred in patients over 50 years (16.4% of this age group), while no cases were found in patients ≤50 years (p=0.001). Gender analysis demonstrated that all mesothelioma cases occurred exclusively in males (13.0%

of male patients), with no female cases (p=0.026). BMI categorization revealed a striking pattern where all 9 mesothelioma cases occurred in patients with BMI >30 kg/m^2 (representing 50.0% of this BMI group), while no cases were found in patients with BMI ≤25 or 26-30 kg/m^2 (p<0.001). Duration analysis showed that all mesothelioma cases occurred in patients with symptoms lasting >12 weeks (17.0% of this duration group), with no cases in those with ≤12 weeks' duration (p<0.001). Residential status analysis indicated that all 9 mesothelioma cases occurred in rural patients (12.9% of rural population), with no urban cases (p=0.025). Socioeconomic status showed no significant association, with 5 cases (9.1%) in poor patients and 4 cases (7.0%) in middle-class patients (p=0.740) (as shown in Table III).

Table III

Association of Mesothelioma with Demographic Factors

Demographic Factors		Mesothelioma		p-value
		Yes n(%)	No n(%)	
Age (years)	≤50	0 (0.0%)	57 (100.0%)	0.001*
	>50	9 (16.4%)	46 (83.6%)	
Gender	Male	9 (13.0%)	60 (87.0%)	0.026*
	Female	0 (0.0%)	43 (100.0%)	
BMI Group	≤25	0 (0.0%)	57 (100.0%)	<0.001*
	26-30	0 (0.0%)	37 (100.0%)	
	>30	9 (50.0%)	9 (50.0%)	
Duration Group	≤12	0 (0.0%)	59 (100.0%)	<0.001*
	>12	9 (17.0%)	44 (83.0%)	
Socioeconomic Status	Poor	5 (9.1%)	50 (90.9%)	0.740*
	Middle	4 (7.0%)	53 (93.0%)	
Residential Status	Rural	9 (12.9%)	61 (87.1%)	0.025*
	Urban	0 (0.0%)	42 (100.0%)	

*Fischer Exact Test

DISCUSSION

The present study aimed to determine the frequency of malignant pleural mesothelioma in patients presenting with massive pleural effusion and revealed an 8% prevalence rate, providing important insights into the demographic risk profile of this aggressive malignancy. The findings demonstrate several significant associations that align with established pathophysiological mechanisms underlying mesothelioma development.

The exclusive occurrence of mesothelioma in patients over 50 years of age (16.4% vs 0% in younger patients, p=0.001) reflects the well-documented long latency period characteristic of asbestos-related malignancies. Malignant pleural mesothelioma typically develops after decades of initial asbestos exposure, with latency periods ranging from 20 to 40 years, explaining why younger individuals in this cohort remained unaffected despite potential exposure histories. This age-related pattern is consistent with the natural history of asbestos-induced carcinogenesis, where cellular damage accumulates over time before manifesting as malignant transformation.

The striking male predominance (13.0% vs 0% in females, p=0.026) is consistent with historical occupational exposure patterns, as men have traditionally worked in industries with higher asbestos exposure risk, including construction, shipbuilding, automotive repair, and industrial manufacturing. The gender disparity also reflects differences in occupational safety practices and exposure intensity in male-dominated industries where asbestos use was prevalent before regulatory restrictions. The remarkable association with obesity (50% prevalence in BMI >30 kg/m^2 vs 0% in normal/overweight individuals, p<0.001) represents a potentially novel finding that may be explained by chronic inflammatory mechanisms. Obesity is associated with chronic low-grade systemic inflammation characterized by elevated pro-inflammatory cytokines, altered immune function, and oxidative stress. This inflammatory milieu may create a microenvironment that facilitates malignant transformation in mesothelial cells already compromised by asbestos exposure, potentially accelerating the progression from benign pleural changes to malignancy.

The correlation with prolonged symptom duration (17.0% in >12 weeks vs 0% in ≤12 weeks, p<0.001) likely reflects the insidious nature of mesothelioma, where longer symptom persistence may indicate more advanced disease at presentation or represent the natural progression timeline of this aggressive malignancy. Our study revealing a mean age of 47.67±14.11 years, which demonstrates remarkable consistency with the existing literature. This finding aligns closely with Shirzadi et al. [18], who reported an average age of 47.59 years in their cohort of 144 patients with chronic pleural effusion, and with Rehan et al. [20], who documented a mean age of 44.82 years in their study of 100 patients. This consistent age distribution across multiple studies suggests that pleural effusions predominantly affect middle-aged adults, likely reflecting the peak incidence of underlying malignant and inflammatory conditions in this age group.

The gender distribution in our study showed a male predominance (61.6% males vs. 38.4% females), which is comparable to O'Donovan and Eng [17], who reported 66% males and 34% females in their study of malignant pleural effusions. This consistent male predominance across studies may reflect occupational exposure patterns, particularly in mesothelioma cases where asbestos exposure has historically been more common in male-dominated industries. Our study identified malignant pleural mesothelioma in 9 patients (8%) out of 112 cases with massive pleural effusion. This prevalence is notably lower than the overall malignancy rates reported in other studies. Shirzadi et al. [18] found malignancy to be the most common cause of chronic pleural effusion with a prevalence of 65.9%, while Rehan et al. [20] reported malignancies accounting for 12% of exudative pleural effusions. However, these studies included all types of pleural malignancies, not specifically mesothelioma, which explains the higher overall malignancy rates.

The relatively low prevalence of mesothelioma in our study may be attributed to several factors: our focus on massive pleural effusions specifically, regional variations in asbestos exposure, and the inclusion criteria that may have selected for a different patient population compared to general pleural effusion studies. A striking finding in our study was that all 9 mesothelioma cases occurred exclusively in patients over 50 years of age (16.4% of this age group, p=0.001). This age-specific distribution is consistent with the known epidemiology of mesothelioma, which typically has a long latency period following asbestos exposure. The case report by Gonligir et al. [19] described a 74-year-old male with malignant

mesothelioma, supporting the tendency for this malignancy to occur in older age groups. This age association is biologically plausible given that mesothelioma typically develops 20-40 years after initial asbestos exposure, making older patients more likely to manifest the disease.

Our study revealed a remarkable finding that all mesothelioma cases occurred exclusively in males (13.0% of male patients, p=0.026), with no female cases identified. This finding is consistent with historical patterns of occupational asbestos exposure, which predominantly affected male workers in industries such as construction, shipbuilding, and manufacturing. The case reported by Gonligir et al. [19] also involved a male patient, further supporting this gender predilection. This stark gender distribution in our study may reflect regional occupational exposure patterns or could be influenced by the relatively small number of mesothelioma cases. Our study found that all mesothelioma cases occurred in patients with symptoms lasting >12 weeks (17.0% of this duration group, p<0.001), indicating a chronic presentation pattern. This finding aligns with the generally indolent nature of mesothelioma development and the gradual onset of symptoms. The case by Gonligir et al. [19] presented with pleuretic chest pain and exertional dyspnea, which are typical chronic symptoms associated with progressive pleural involvement.

The radiological differentiation of malignant pleural conditions remains challenging, as highlighted by Bakhshayesh Karam et al. [16], who achieved 82% accuracy in diagnosing mesothelioma using CT scans. They identified pleural thickening (88.2%), loculated effusion (58.8%), and thickening of the interlobar fissure (47.1%) as characteristic features of mesothelioma. O'Donovan and Eng [17] similarly found pleural thickening in 62% of malignant pleural effusions and fluid loculation in 40% of cases. The case report by Gonligir et al. [19] presented an unusual scenario where mesothelioma caused transudative rather than exudative pleural effusion, with low protein (0.5 g/dL) and LDH levels (11 U/L). This atypical presentation underscores the diagnostic challenges in mesothelioma cases and the importance of maintaining clinical suspicion even when fluid characteristics are unexpected.

The relatively small number of mesothelioma cases in our study (n=9) limits the generalizability of some associations, particularly the striking correlations with BMI, rural residence, and male gender. Larger multicenter studies would be valuable to validate these findings. Additionally, the comparison with other studies is somewhat limited by differences in inclusion criteria, with our study focusing specifically on massive pleural effusions while others examined various pleural effusion types.

CONCLUSION

Our study has concluded that malignant pleural mesothelioma represents a significant subset of patients presenting with massive pleural effusion, with distinct demographic and clinical characteristics. The findings demonstrate strong associations between mesothelioma occurrence and advanced age, male gender, higher body mass index, prolonged symptom duration, and rural residence. These associations provide valuable insights for clinicians in identifying high-risk patients and support the need for heightened clinical suspicion in patients with these characteristics.

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