Original Article

Correlation Between Serum Matrix Metalloproteinase-9 (MMP-9) and Tissue Inhibitor of Metalloproteinase -1 (TIMP-1) Levels and the Clinical Characteristics of Patients with Pleural Effusion

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Abstract

Background: Clinically, it can be difficult to distinguish between benign and malignant exudative pleural effusion (PE), and in certain cases. MMP-9 contributes to persistent inflammation and is linked to the aggressivity and metastatic potential of tumors. **Objectives:** The aim of the present study was to determine the correlation between matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 and to distinguish between benign and malignant exudative pleural effusions. **Materials and Methods:** This is a case-control study comprising 60 patients with malignant PEs and 60 patients with benign PEs who visited the medical city – Baghdad Hospital. All patients were examined and asked about their medical history, and they measured the levels of serum MMP-9 and TIMP-1 in the serum as markers for differentiation between benign and malignant exudative pleural effusion. It was determined by using the quantitative sandwich (ELISA) technique. **Results:** It was observed that there is a strong positive correlation between MMP-9 and TIMP-1 with P value = 0.007 in Benign PEs and ($P < 0.001$) in Malignant PEs. It was found that patients with malignant pleural effusion have greater serum levels of MMP-9 and TIMP-1 than patients with benign pleural effusion with mean ± SD of MMP-9 ng/mL are 12.79 ± 5.15 in MPEs and 7.95 ± 2.82 in BPEs, whether mean ± SD of TIMP-1 pg/mL are 1150.56 ± 476.79 in MPEs and 665.51 ± 350.63 in BPEs. **Conclusions:** Our results showed that there is a strong positive correlation between MMP-9 and TIMP-1 indicating that as serum MMP-9 levels increase, serum TIMP-1 level also tends to increase significantly. Also, MMP-9 and TIMP-1 might be valuable markers in differentiating benign from malignant pleural effusions.

Keywords: Exudative pleural effusion, lactate dehydrogenase, matrix metalloproteinase-9, tissue inhibitor metalloproteinase-1, transudative pleural effusion

Introduction

Every healthy person has a little amount of pleural fluid that collects between the parietal and visceral pleura, lubricating the area and supporting normal lung motions during respiration. These systems regulate lymphatic outflow, oncotic and hydrostatic pressure, and this delicate fluid balance; any disturbance in one of them may result in pleural fluid accumulation.[1]

It may manifest on its own or because of an inflammatory, malignant, or infectious parenchymal disease. Pleural effusion is one of the major causes of lung mortality and morbidity.[2-4] It can be caused by a variety of conditions, including heart failure (HF), parapneumonic effusion (PPE), tuberculous pleural effusion (TPE), malignant pleural effusion (MPE), and others.[5]

According to Light's definition, there are two categories of pleural effusion based on the makeup of the pleural fluid:

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- Transudate: the outcome of elevated pulmonary or systemic hydrostatic pressure or an increase in plasma osmotic pressure.
- Exudate: this condition develops because of pleural surface inflammation, infectious disease (such as tuberculosis and pneumonia with effusion), or other diseases (including cancer, pancreatitis, pulmonary infarction, or systemic lupus erythematosus).

Pleural fluid is classified as an exudate according to Light's criterion if at least one of the following three conditions is met:

- Pleural fluid LDH > two-thirds the upper limits of the laboratory's normal serum LDH.
- Pleural fluid protein/serum protein ratio > 0.5.
- Pleural fluid LDH/serum LDH ratio > 0.6.

Benign pleural effusions (BPEs) can be brought on by heart failure, parapneumonic infections, Mycobacterium TB infection, and other conditions.[6-8]

Lung cancer, breast cancer, lymphoma, and other types of cancer are the main causes of malignant pleural effusion (MPE), which is the second most common cause of pleural exudate.[9] A shorter life expectancy is linked to the presence of malignant cells in the pleural fluid (PF) and/or pleural tissue, which indicates the presence of disseminated or advanced malignancy. It occurs in 15% of people with malignant cancer and is a common observation in patients with metastatic disease.[10-14] MPE can arise from primary or metastatic pleural cancers when cancerous cells move into the lymphatics and into the intrapleural cavity, obstructing them.[14,15] The onset of MPE significantly disturbs the normal physiologic equilibrium between the release of fluids into the pleural space and subsequent reabsorption.

Matrix metalloproteinases (MMPs), or matrix metalloproteinases, are membrane-bound endopeptidases that are found inside cells and need zinc (Zn^{2+}). They promote the degradation of extracellular matrix (ECM) proteins such as collagen, laminin, elastin, and fibronectin and contribute to extracellular matrix remodeling in several physiological and pathological processes.[16]

The human proteome contains the majority of the 26 MMPs that have been identified so far.[17,18] The first MMP to be named was collagenase-1 (MMP-1), which was discovered in 1962.

Based on the substrate specificity, MMPs are divided into six types: membrane-type MMPs, collagenase, gelatinase, matrilysins, stromelysins, and other types of MMPs.[19]

MMPs have been proposed as possible biomarkers for diagnosis and prognosis in a variety of cancer types.[20] In addition to maintaining pro-enzyme activation, transcription is one way that MMPs are regulated. The activity of MMPs is inhibited by tissue inhibitor of metalloproteinase (TIMP).[21] TIMPs fall into one of four categories: TIMP-1, TIMP-2, TIMP-3, and TIMP-4. The imbalance between MMP activation and inhibition is a key factor in the etiology of cancer.[22]

Matrix metalloproteinases-9 (MMP-9), one of the most complex MMPs, is a member of the gelatinase family.[23] It either slows down or accelerates the ECM's decomposition. Gelatin and type IV, V, XI, and XVI collagens degrade during tissue remodeling, which is important for tumor invasion and metastasis.[24] MMP-9 is commonly located in the cerebral cortex, cerebellum, and hippocampus.[23] It was identified in 1974 and goes by the name gelatinase B of the proteolytic family. MMP-9 is released as zymogens or inactive forms by leukocytes, fibroblasts, neutrophils, macrophages, endothelial cells, and leukocytes. During the process of granulocyte development, MMP-9 is normally produced in the bone marrow.[25]

MMP-9 is inhibited by tissue inhibitor of metalloproteinase (TIMP-1), which binds to both the precursor and active forms of MMP-9.

Matrix metalloproteinase inhibitors (MMPIs), which have the potential to treat cancer, function by binding to the zinc (Zn^{2+}) ion at the catalytic site and preventing MMP activity.[17] A few scientists claimed that MMPIs stop the development of cancer cells, while other research revealed that MMPIs inhibit tumor growth by triggering apoptosis and releasing the ligands TNF and TRAIL from their membrane-bound inactive forms.[20]

MMPs are released as zymogens or pro-enzymes. They remain inactive due to their interaction with the zinc (Zn^{2+}) ion of the catalytic domain and the cysteine sulphydryl group of the pro-domain. They become active either after this connection is severed or because of proteinases.[26]

The MMP-9 enzyme and TIMP-1, which suppress it, are the main subjects of our research. Overexpression of MMP-9 and TIMP-1 has been associated with a variety of cancers, including breast, lung, prostate, colon, stomach, and pancreatic cancers.

Materials and Methods

Study design

This is an observational case-control study consisting of 120 adult patients between 20 and 75 years old of both genders, male and female. Samples had been collected from Medical City-Baghdad Hospital.

Inclusion criteria

Group 1: 60 patients with malignant pleural effusion diagnosed by pleural fluid cytology (presence of malignant cells in pleural fluid), blood samples, and pleural fluid were collected.

Group 2 (control group): 60 patients with benign pleural effusion diagnosed by pleural fluid cytology (absence of malignant cells in pleural fluid), blood samples, and pleural fluid were collected.

Exclusion criteria

Patients were excluded from the study if they had a definite diagnosis at presentation, or if they refused to sign a consent for sharing data in the study.

The diagnosis of exudative PE was confirmed by pleural fluid analysis, and the fluid was defined as exudative if it fulfilled at least one of the following criteria: 9 pleural/serum ratio of total protein >0.5, pleural/serum ratio of total lactate dehydrogenase (LDH) > 0.6, or pleural LDH more than two-thirds of the upper limit of normal for serum LDH.

All patients had pleural fluid cytology for malignant cells. Thoracoscopic pleural biopsy was performed in all patients because it is the most accurate diagnostic procedure, and a definite diagnosis is needed to calculate the sensitivity and specificity of any new diagnostic test.

Sample collection

Under complete aseptic conditions, 5-mL venous blood samples were collected in sterile plain tubes, allowing the blood to clot by leaving it undisturbed at room temperature 25–28°C, this usually takes 10–20 min. The clot was moved by centrifuging at 3000 rpm for 20 min. Then the serum was separated and divided into small amounts in tubes for:

1. Immediate measurement of serum total proteins and LDH (LDH isoenzymes have no clinical value), to get Light's criteria for determining whether a pleural effusion is exudative or transudative. This was done using appropriate spectroscopy ways (Routine work).
2. The rest of the clear serum was separated and transferred to Eppendorf (microfuge tube) and kept at (−20°C) until assayed for measuring levels of matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) in both groups of pleural effusion (malignant and benign) and were determined using quantitative sandwich enzyme immunoassay technique (ELISA) kits Sunlongbiotech (Routine work).

Ethical Approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The study protocol and subject information were reviewed and approved by a local ethics committee according to the document No. 32/2023 on April 17, 2023.

Results

Age

The mean age in the BPE group (52.97 ± 18.59) is significantly lower compared to the MPE group (55.67 ± 15.56) (p = 0.0016). This suggests that there is a statistically significant difference in age between the two groups [Table 1].

Gender

Regarding the variable "Gender," the distribution among the two groups was as follows: In the MPE group, an equal distribution of 30 individuals (50%) was observed for both females and males. In the BPE group, 27 individuals (45%) were female, while 33 individuals (55%) were male. Age appears to be slightly higher in the Malignant group compared to the BPE group [Table 2].

Smoking

Regarding the Smoking, it was found that in the MPE group, a total of 2 individuals (3.33%) had a previous history of smoking, while none of the individuals in the BPE group reported such a history. Additionally, only individuals within the BPE group (6.67%) were identified as both smokers and alcoholics, with no similar cases found in the MPE group. The distribution of heavy smokers was consistent across both groups, with 2 individuals (3.33%) in both the MPE and BPE groups. Moreover, most individuals in both groups were non-smokers, accounting for 61.67% in the MPE group, and 73.33% in the BPE group. A portion of individuals in each group were classified as smokers, comprising 31.67% in the MPE group, and 16.67% in the BPE group [Table 3].

Oxygen Saturation (SpO2 %)

The mean SpO2 % in the benign group (94.23 ± 2.98) is significantly higher compared to the malignant group (93.53 ± 3.26) (p < 0.001). These findings indicate that there are significant differences in oxygen saturation levels

Table 1: Present the mean and standard deviation Age in different groups, along with the corresponding p-values for group comparisons

Parameters	subjects	N	Mean ± SD	Malignant	Benign	P-value
Age	Benign	60	52.97 ± 18.59	55.67	52.97	0.0016
	Malignant	60	55.67 ± 15.56			

between the groups, with the BPE group having the highest SpO2 % values, then MPE group [Table 4].

Pleural Effusion Duration in days

The mean duration of pleural effusion in the Benign group is 19.19 ± 35.78, whereas in the Malignant group, it is 11.17 ± 13.18. However, the difference in means is not statistically significant (p = 0.109), suggesting that there is no strong evidence to conclude a significant difference in pleural effusion duration between the Benign and Malignant groups. The means and standard deviations are presented in Table 5

Pleural effusion causes

In this study, the distribution of BPE associated causes among the total of 60 patients with PEs. The findings as presented in Table 6 indicate that approximately 36.66% of the patients were found to have pleural effusion associated with inflammation, while tuberculosis and pulmonary embolism both had about 11.66 %. Additionally, pleural effusion attributed to heart failure was observed in approximately 28.33% of the patients, and the percentage of patients with pleural effusion due to parapneumonic causes was found to be 6.66%. Moreover, around 10% of the patients were diagnosed with pleural effusion classified as empyema. While approximately 8.33% were diagnosed with CKD, 3.33% post CABG, Hypothyroidism and Pancreatitis both had 1.66%. For 60 patients diagnosed with malignant pleural effusion analysis was done to identify the frequency of the underlying causes. The results revealed the following distribution: Most cases (43.3%) were attributed to Lung Cancer, while Breast Cancer accounted for 28.3% of the cases. Lymphoma was responsible for 5% of the diagnosed cases, and GIT Ca. was found in 8.33% of patients. Additionally, Bone Ca. and Thyroid Ca. both had 6.66%, (Pancreas Ca., Uterine Ca., Ovarian Ca., and Lymphoma) had 5%, and the least frequency was liver Ca. with 3.33%. These findings highlight the prevalence of different causes of MPE in the studied patient population. Lung cancer and breast cancer were the most common etiologies.

Table 2: Present Gender Percentage in the different groups Malignant and Benign

	Variable	Group	
		Malignant	Benign
Gender	F	30 (50.00%)	27 (45.00%)
	M	30 (50.00%)	33 (55.00%)
	Total	60 (100.00%)	60 (100.00%)

Table 3: Present Smoking Percentage in the different groups Malignant and Benign

	Variable	Group	
		Malignant	Benign
Smoking	Previous smoker	2 (3.33%)	NA
	Smoker + Alcoholic	NA	4 (6.67%)
	Heavy smoker	2 (3.33%)	2 (3.33%)
	Non-smoker	37 (61.67%)	44 (73.33%)
	Regular Smoker	19 (31.67%)	10 (16.67%)
	Total	60 (100.00%)	60 (100.00%)

Correlation between MMP-9 and clinical characteristics

BPE group

Table 7 presents the Pearson Correlation Matrix, which illustrates the relationships among various variables in the BPE group. This matrix provides valuable insights into the associations between key factors in the study.

Serum MMP-9 exhibited a significant positive correlation with Serum TIMP-1 ($r = 0.51$, $p < 0.05$), indicating a strong association between these two factors.

Pleural effusion duration displays positive correlations with age ($r = 0.15$, $p < 0.05$), while age also exhibits negative correlations with SpO2 ($r = -0.11$, $p < 0.05$). SpO2, a measure of oxygen saturation.

These findings suggest complex interrelationships among serum biomarkers, patient characteristics (age), pleural effusion duration, and SpO2 in the context of BPE. The significance levels ($p < 0.05$) for several correlations underscore the importance of these associations in understanding the pathophysiology of pleural effusion [Figure 1].

MPE group

Table 8 presents the Pearson Correlation Matrix, which illuminates the relationships among various variables in the MPE group.

Serum MMP-9 exhibited a significant positive correlation with Serum TIMP-1 ($r = 0.68$, $p < 0.05$), highlighting a robust association between these two variables.

Table 4: Present the mean and standard deviation Age and Oxygen Saturation Percentage in different groups, along with the corresponding p-values for group comparisons

Parameters	subjects	N	Mean ± SD	Malignant	Benign	P-value
SpO2 %	Benign	60	94.23 ± 2.98	93.53	94.23	< 0.001
	Malignant	60	93.53 ± 3.26			
	Normal	25	98.08 ± 0.78			

Pleural effusion duration demonstrates a negative correlation with S. MMP-9 ($r = -0.22$, $p < 0.05$) and S. TIMP-1 ($r = -0.25$, $p < 0.05$), suggesting shorter durations in cases with higher levels of these markers. Age has negligible correlations with most variables [Figure 2].

Lastly, SpO2, a measure of oxygen saturation, displays correlations with several markers. It has a weak negative correlation with S. MMP-9 ($r = -0.10$), indicating that lower oxygen saturation may be associated with higher levels of this biomarker..

Discussion

The two main causes of pleural effusion are heart failure and malignancy. Due to the multifaceted nature of Pleural Effusion formation and the complexity of the differential diagnosis, difficulties can arise. The visceral pleura's interstitial stroma and basement membrane serve as the first line of defense against tumor dissemination. The extracellular matrix is degraded by many proteolytic enzymes. MMP-9 plays a significant function Because it breaks down type IV collagen and contributes to the breakdown of the basement membrane that surrounds blood vessels and lies underneath the mesothelial layer, and it's secreted in the lungs by neutrophils, alveolar macrophages, bronchial epithelial cells, and eosinophils. Tissue inhibitor of metalloproteinase (TIMP-1) is an MMP-9 inhibitor that binds to both the precursor and active forms of MMP-9. The deregulation and imbalance of protease and protease inhibitor activity have consequences for pleural effusion etiology. Where the fluid builds up in the pleural space due to increased capillary permeability in the visceral pleura.[26] MPE is a sign of disease with advanced stage, often carrying poor prognosis, with a survival rate ranging from 1 to 12 months according to the underlying malignancy and other risk factors.[27]

In our study we discovered a highly significant difference in the levels of TIMP-1 and MMP-9 between benign and malignant PE. Other studies support this.[28] The Mean Serum levels of MMP-9 and TIMP-1 were significantly higher in the malignant group than in the benign group. The significant p-values for both MMP-9 and TIMP-1 indicate that these markers can effectively differentiate between malignant and benign pleural effusion. The higher levels of MMP-9 and TIMP-1 in the Malignant group compared to the Benign groups suggest their potential utility as diagnostic markers for distinguishing malignant pleural effusion from non-malignant cases [Table 9].[28]

High levels of MMP-9 and TIMP-1 in serum can be utilized in clinical settings to identify patients who should undergo an invasive pleural tissue biopsy, which is necessary for the identification of malignancy. There was a significant positive correlation in Serum MMP-9 and TIMP-1, indicating that as serum MMP-9 levels increase, Serum TIMP-1 level also tends to increase significantly, Thus, the imbalance between MMP-9 and TIMP-1 levels could provide a favorable biological environment for cancer cell growth and metastasis.[29] MMP-9 facilitates the degradation of the basement membrane of the mesothelial layer and pleural blood vessels by proteolysis of type IV collagen. This contributes to accumulation of fluid within the pleural space and aid migration of leukocytes from the circulation. During tumor development, basement membrane destruction is usually an essential step which supports tumor invasion and metastases.[30]

Because various cell types (epithelioid cells in the granulomas of pleural tissues and lymphocytes are the major cellular source of MMP-9 in patients with malignant effusions), as well as neoplastic cells, can produce MMP-9

Table 5: Present the mean and standard deviation of pleural effusion duration in different groups, along with the corresponding p-values for group comparisons

Parameters	subjects	N	Mean ± SD	P-value
Pleural effusion Duration	Benign	60	19.19 ± 35.78	0.109
	Malignant	60	11.17 ± 13.18	

Table 6: The frequency and percentage of some causes of pleural effusion in malignant and benign groups

Benign Pleural Effusion			Malignant Pleural Effusion		
Cause of pleural effusion	Frequency per category	%	Cause of pleural effusion	Frequency per category	%
Inflammation	22	36.66667	Lung Ca.	26	43.33333
Heart Failure	17	28.33333	Breast Ca.	17	28.33333
TB	7	11.66667	GIT Ca.	5	8.333333
Pulmonary Embolism	7	11.66667	Bone Ca.	4	6.666667
Empyema	6	10	Thyroid Ca.	4	6.666667
CKD	5	8.333333	Pancreas Ca.	3	5
Parapneumonic	4	6.666667	Uterine Ca.	3	5
CABG	2	3.333333	Ovarian Ca.	3	5
Hypothyroidism	1	1.666667	Lymphoma	3	5
Pancreatitis	1	1.666667	Liver Ca.	2	3.333333

and TIMP-1 in the pleural space, these findings explained the identical MMP-9 and TIMP-1 levels reported in Pleural Effusion with positive and negative cytology. That's agreed with.[31] Thus, the high levels of markers identified in our study may be connected to the extent of pleural involvement, whereas lower levels of MMP-9 and TIMP-1 would be predicted when the pleura is only recently damaged by tumor or infection.

Conclusion

The examination of MMP-9 and TIMP-1 may be a quick, affordable, useful, and accurate technique for discriminating between pleural effusions with benign origin and those with malignant origin in the differential diagnosis of pleural effusion. As a result, its application in clinical practice may aid in the identification of individuals who require more invasive procedures like thoracoscopic biopsy.

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Nil.

Table 7: Pearson Correlation Matrix Among S. MMP-9, S. TIMP-1, PEs Duration, Age, and SpO2 in BPE group

Variable	1	2	3	4
1. S. MMP-9	1			
2. S. TIMP-1	.51*	-		
3. PEs Duration	.13	.00	-	
4. Age	.03	-.01	-.08	-
5. SpO_2	.14	.11	-.15	-.11

Note.

*p < 0.05. Each row and column correspond to specific variables, and the values within the table represent correlation coefficients (r)

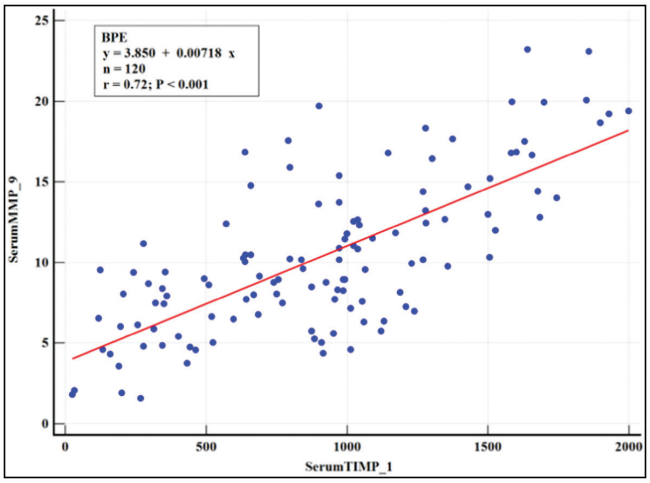

Figure 1: Scatter plot with regression line showing the correlation between serum MMP-9 and serum TIMP-1 in the Benign group

Table 8: Pearson Correlation Matrix Among S. MMP-9, S. TIMP-1, PEs Duration, Age, and SpO2 in MPE group

Variable	1	2	3	4
1. S. MMP-9	-			
2. S. TIMP-1	.68*	-		
3. PEs Duration	-.22	-.25	-	
4. Age	-.02	-.08	-.00	-
5. SpO_2	-.10	.07	.21	.11

Note.

*p < 0.05. Each row and column correspond to specific variables, and the values within the table represent correlation coefficients (r)

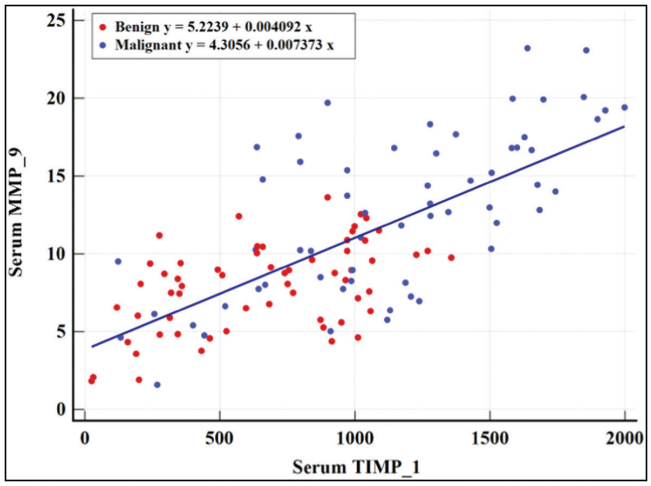

Figure 2: Scatter plot with regression line showing the correlation between serum MMP-9 and serum TIMP-1 in benign and malignant groups

Table 9: The mean and standard deviation values for serum Matrix Metalloproteinase-9 (MMP-9) and Tissue Inhibitor of Metalloproteinase-1 (TIMP-1) levels in Benign and Malignant groups

Parameters	subjects	N	Mean ± SD	Malignant	Benign	P-value
MMP-9 ng/ml	Benign	60	7.95 ± 2.82	12.79	7.95	< 0.001
	Malignant	60	12.79 ± 5.15			
TIMP-1 pg/ml	Benign	60	665.51 ± 350.63	1150.56	665.51	< 0.001
	Malignant	60	1150.56 ± 476.79			

Conflicts of interest

There are no conflicts of interest.

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