

## Diagnostic Implications of Putrescine, Spermidine, and Spermine in Pleural Effusions

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### ABSTRACT

**Background:** Pleural effusions are caused by a wide variety of diseases. It is important to elucidate their precise etiologies to differentiate benign from malignant effusions. The polyamines are important molecules governing cell proliferation, survival and apoptosis. Consistent with their elevated levels in cancer, it seemed probable that patients with active cancer might have elevated levels of these compounds in some of their body fluids. **The aim** of the present study was to investigate the diagnostic efficacy of measuring pleural effusion concentration of the polyamines (putrescine, spermidine, and spermine) for discrimination of malignant and benign pleural effusions. **Patients and Methods:** Pleural effusions were collected from 138 consecutive patients in whom the diagnosis was confirmed with cytological and/or histological examinations. Cytological samples were classified as malignant (n=78) and benign (n=60). Polyamines concentrations were measured using the ion exchange chromatography method. **Results:** The results showed that the levels of the three polyamines were significantly higher in malignant pleural effusions when compared to the benign effusions. **Conclusion:** The polyamines putrescine, spermidine, and spermine are of great value in the diagnosis of malignancy and may be used as an adjunct to cytological findings in determining malignant pleural effusions.

**Key words:** Polyamines, Pleural effusion, Malignancy.

### INTRODUCTION

Pleural effusions with unknown etiology are frequent and often create a dilemma in clinical practice; they are common complications of a wide variety of diseases; including malignancies, pneumonia, tuberculosis, pulmonary embolism, cardiac failure and cirrhosis. Differentiating between malignant pleural effusion (MPE) and non-MPE often has important therapeutic implications. It is important to

elucidate their precise etiologies to differentiate benign from malignant effusions<sup>(1,2)</sup>.

Clinically, that differentiation is sometimes difficult using conventional diagnostic methods. The initial diagnostic approach includes thoracentesis and cytologic as well as histologic examinations. However, the sensitivity of these noninvasive techniques is only 40%–70%<sup>(3)</sup>.

To improve the sensitivity of cytological examination for the differential diagnosis of pleural

effusions, numerous procedures, including immunocyto-chemistry, chromosome analysis, tissue culture techniques, deoxyribonucleic acid (DNA) flow or image cytometry, and cell imaging combined with immunocytochemistry have been proposed<sup>(4)</sup>. Despite these sophisticated diagnostic methods, definitive diagnosis of pleural effusions may still be difficult<sup>(4-6)</sup>.

Closed pleural biopsy confers a small additive diagnostic value. Thoracoscopy will establish the diagnosis in approximately 95% of cases, but that interventional procedure may not be available at all facilities<sup>(7)</sup>.

Various adjuvant methods have been proposed, including determining specific tumor markers<sup>(8)</sup>, proteins telomerase<sup>(9)</sup> and chromosome analysis<sup>(10)</sup>. However, there are no currently reliable and effective molecular biomarkers used in diagnosing cancer patients.

Polyamines are aliphatic cations present and synthesized in all human cells; putrescine was first isolated from putrefying meat and was thought of as a decomposition product; spermine was named from its occurrence in semen. These polyamines, however, are now known to have important roles in cell growth and differentiation. Their physiological significance can be studied by analyzing the consequences of depletion of the cellular polyamine content. The results include arrest of cell growth, differentiation, and division<sup>(11-13)</sup>.

At a physiological pH, putrescine, spermidine, and spermine are protonated and possess two, three, and

four positive charges, respectively. Consequently, they are highly soluble in water, and have a high affinity toward negatively charged cellular molecules, mainly cellular DNA. The positive charge distribution in the spermine molecule makes it bind strongly to the negatively charged phosphate groups in double-helical regions of nucleic acids<sup>(14)</sup>.

Polyamines biosynthetic enzymes and the concentrations of the polyamines are elevated in rapidly proliferating tissues and increase abruptly when growth and differentiation are induced. Activation of polyamine biosynthesis usually precedes DNA, RNA, and protein synthesis, and in cell-free systems physiological concentrations of the polyamines stimulate many of the reactions involved in the synthesis of nucleic acids and proteins<sup>(15)</sup>.

There is considerable evidence that altered polyamine metabolism is associated with neoplastic growth. Polyamine content and synthesis are enhanced during tumor promotion and progression and in cancer cells. Polyamines are downstream targets of several oncogenes and inducers of other oncogenes and are thus intimately involved in neoplastic growth<sup>(16-18)</sup>.

There are many studies suggest that elevated levels of polyamines are associated with carcinogenesis<sup>(19-23)</sup>. Collected data indicated that patients with cancer excrete increased amounts of the polyamines, spermidine, and spermine, putrescine, and their metabolites in their urine<sup>(24-26)</sup>, and increased polyamine levels are found in the serum, and CSF of cancer patients<sup>(27, 28)</sup>. Elevated levels may

reflect increased polyamine production by rapidly dividing cells or the release of polyamines from dead tumor cells<sup>(29)</sup>.

Therefore, possibly, polyamines levels can be used to diagnose malignant pleural effusions. However, to our knowledge, practically no researches have been conducted on polyamines levels in pleural effusion fluid specimens. We conducted the present study to outline the diagnostic value of polyamines levels for the diagnosis of malignant pleural effusion and compared the results with that of cytological examination.

### AIM OF THE WORK

The present study aimed to investigate the diagnostic efficacy of measuring pleural effusion levels of the polyamines (putrescine, spermidine and spermine) for discrimination of malignant and benign pleural effusion.

### PATIENTS & METHODS

#### Pleural effusion samples:

Pleural fluid samples were collected from 138 consecutive patients who underwent diagnostic or therapeutic thoracentesis in Cardiothoracic Department- Tanta University Hospital- Tanta - Egypt and Al-Eiman Hospital – Riyadh - Kingdom of Saudi Arabia between June 2009 and August 2010. The patients included 87 males (63%) and 51 females (37%), with a mean age of  $61.3 \pm 18.3$  years (range 35-73 years). Specimens were sent to the clinical laboratory for routine tests, cytologic examination and smear/culture for bacterium and *Mycobacterium*

*tuberculosis* for evaluating pleural effusion etiology. Pleural biopsy was performed on 35 (25.4%) patients to determine the diagnosis.

The effusions were considered malignant if malignant cells were found on cytologic examination. In cases suspicious where cytologic examinations were negative (35 cases), thorascopic pleural biopsies were performed. The median follow-up of all patients was 16 months (range 6–20 months).

The malignant group consisted of 78 patients with malignant pleural effusion. The patients included 46 males (59%) and 32 females (41%), with a mean age of  $56.1 \pm 11.7$  years (range 41 –71 years), 17 (21.8%) cases showed negative cytologic examination and were confirmed with thorascopic pleural biopsy.

The benign group consisted of 60 patients with benign pleural effusion. The patients included 42 males (70%) and 18 females (30%), with a mean age of  $58.1 \pm 19.8$  years (range 35–73 years). Diagnosis was made on the basis of clinical and radiological features, response to therapy and cytological examinations of pleural fluids. In addition, diagnosis was confirmed in 18 patients with thorascopic pleural biopsy.

The study was approved by the hospital ethics committee of the participant hospitals, and all the patients provided written informed consents.

#### Procedure:

Pleural fluid was collected from each patient prior to any therapy. Because these polyamines are somewhat unstable at neutral and basic pH, shortly after collection, all

samples were acidified and centrifuged at 900 x g for 10 minutes at 2°C, and the supernatants were frozen at -80 °C until analyzed. Five ml aliquots of pleural effusion were lyophilized, and the residues were reconstituted with 1 ml of 6 M HCl and hydrolyzed at 110 °C for 14 to 16 hours. The hydrolyzate was lyophilized, reconstituted in 200µl of 4% 5-sulfosalicylic acid, and centrifuged at 8000xg for 10 minutes, after which 50-µl aliquots of the supernatants were analyzed for polyamine content using a Biochrom 20 Amino Acid Analyzer (Amersham Pharmacia Biotech) by post-column derivatization with ninhydrin. The polyamine sample was loaded on to a 100 mm × 4 mm cation-exchange column (Bio 20 Peek, polyamine column, Amersham Pharmacia Biotech) and the polyamines were eluted according to the manufacturer's instructions. After each sample analysis, the column was regenerated with 0.4M NaOH, followed by equilibration with 1.2M sodium citrate buffer (pH 6.45) <sup>(30)</sup>.

#### Statistical analysis:

Results are shown as mean ± standard deviation. Statistical differences were determined by Student's t test. A p value of <0.05 was considered significant.

## RESULTS

The 138 patients who entered the study, 78 patients (46 men and 32 women, with mean age of 56.1±11.7 years had malignant PE, and 60

patients (42 men and 18 women, with mean age of 58.1±19.8 years) had benign PE. The specific etiologies and types of tumors are presented in Table 1. Among the malignant PE group, there were 61 patients (78.2%) with positive pleural fluid cytology findings and 17 (21.8%) patients with cytology-negative PE, and the malignant nature of their effusion were confirmed with thoracoscopic pleural biopsy.

The traditional pleural markers, including the cell count, pleural fluid levels of total proteins and lactate dehydrogenase (LDH), and the cytologic yields, are presented in Table 2.

Pleural effusion cell count, total proteins and LDH results did not show any statistically significant difference between the two types of effusion.

The mean ± SD for the levels of the various polyamines in the pleural fluid were significantly higher in patients with malignant PEs than in those with benign PEs. The polyamines spermine and spermidine showed higher degrees of statistical significance compared to putrescine. Also, the total polyamines levels showed significantly higher values in malignant pleural effusions. (Table 3)

Correlation studies showed that the correlation coefficient was higher between the different polyamines in malignant pleural effusions compared to benign effusions. Also, the correlation between spermine and the other two polyamines in the benign effusions showed the lowest correlation coefficient. (Table 4)

**Table (1):** The number and percent of patients with different causes of benign and malignant pleural effusions

Type of effusion	No	%
<b>Benign</b>		
Pneumonia	16	26.7
Pulmonary TB	15	25.0
Congestive heart failure	9	15
Liver cirrhosis	9	15
Empyema	8	13.3
Nephrotic syndrome	3	5
Total	60	100
<b>Malignant</b>		
Lung cancer:	(28)	(35.9)
Non small cell (NSCLC)	19	24.4
Small cell (SCLC)	9	11.5
Malignant mesothelioma	17	21.8
Breast cancer	12	15.4
Ovarian cancer	6	7.7
Pancreas cancer	6	7.7
Hepatoma	5	6.4
Malignant lymphoma	4	5.1
Total	78	100

**Table (2):** Cell count, total proteins, and LDH levels (mean  $\pm$  SD), and cytologic yield of the pleural fluid in the two groups.

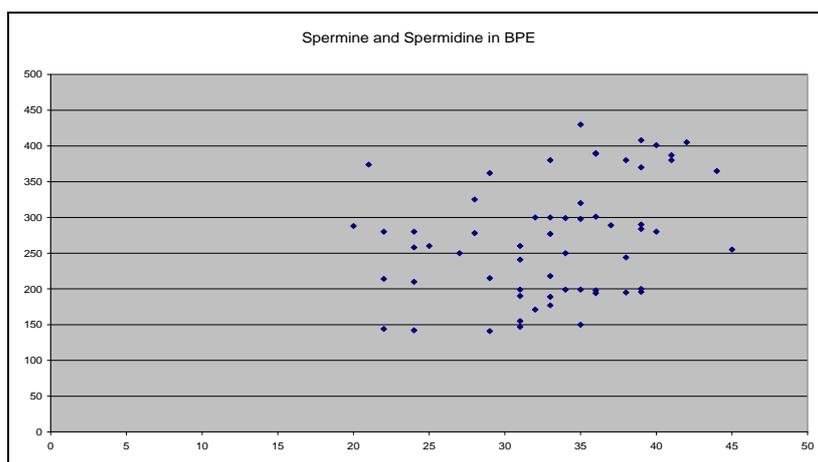
Parameter	Benign PE	Malignant PE	p value
WBC count (/ $\square$ l)	3167 $\pm$ 2112	3542 $\pm$ 1725	p>0.05
Neutrophil (%)	29 $\pm$ 24.2	32.8 $\pm$ 22.8	p>0.05
Lymphocytes (%)	45 $\pm$ 31	42 $\pm$ 20	p>0.05
Total Proteins (g/dl)	7.2 $\pm$ 4.5	6.9 $\pm$ 0.7	p>0.05
LDH (U/l)	604 $\pm$ 514	521 $\pm$ 354	p>0.05
Positive cytology, n (%)	0	61/78 (78.2)	

**Table (3):** Pleural effusion levels of polyamines (pmol/l) in patients with benign and malignant effusions (mean  $\pm$  SD).

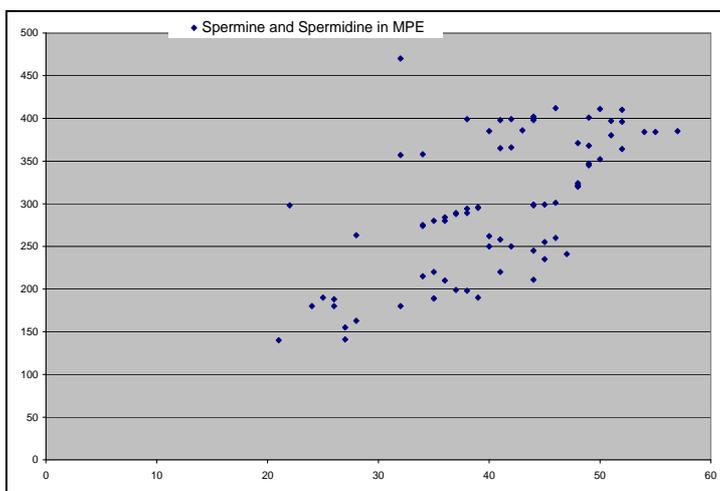
Polyamine level (pmol/l)	Benign	Malignant	p value
Spermine	33.2 $\pm$ 5.54	40.45 $\pm$ 8.3	p<0.01
Spermidine	269.52 $\pm$ 81.21	297.3 $\pm$ 81.6	p<0.05
Putrescine	356.3 $\pm$ 98.3	399.0 $\pm$ 135.7	p<0.05
Total	658.8 $\pm$ 156.8	736.8 $\pm$ 201.9	p<0.05

**Table (4):** Correlation matrix between the three polyamines in both benign (n= 60) and malignant n= 78) effusions.

		Spermine	Spermidine	Putrescine
<b>Spermine</b>	Benign	r = 1.00	r = 0.34	r = 0.23
	Malignant	r = 1.00	r = 0.64	r = 0.49
<b>Spermidine</b>	Benign	r = 0.34	r = 1.00	r = 0.48
	Malignant	r = 0.64	r = 1.00	r = 0.62
<b>Putrescine</b>	Benign	r = 0.23	r = 0.48	r = 1.00
	Malignant	r = 0.48	r = 0.62	r = 1.00



**Figure 1:** correlation between Spermine and Spermidine levels in benign pleural effusion.



**Figure 2:** correlation between Spermine and Spermidine levels in malignant pleural effusion.

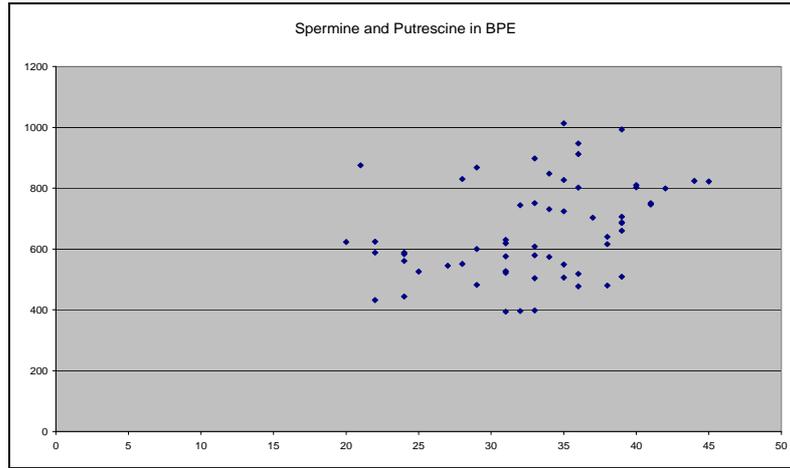


Figure 3: correlation between Spermine and Putrescine levels in benign pleural effusion.

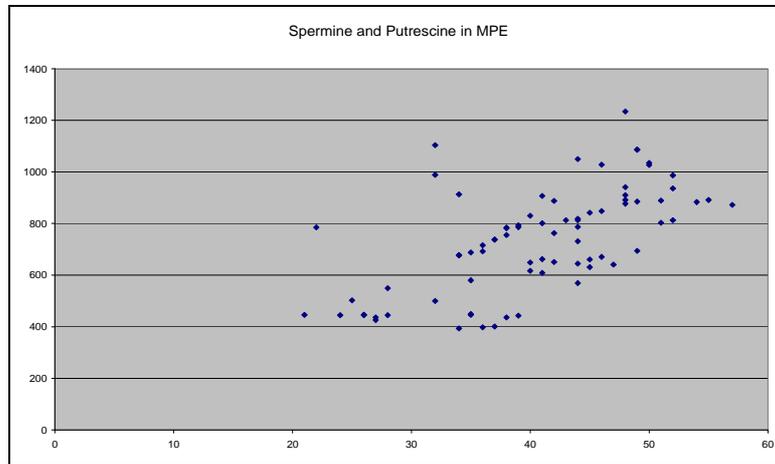


Figure 4: correlation between Spermine and Putrescine levels in malignant pleural effusion.

### DISCUSSION

Accurate diagnosis of pre-assumptive malign effusions using the routine diagnostic methods applied to pleural effusions such as cell count with differential cytology, total Proteins, and lactate dehydrogenase may sometimes be difficult<sup>(31)</sup>. In our

study, measurement of these parameters did not show any statistically significant difference between both malignant and benign pleural effusion groups.

Cytological diagnosis was established in 78.2% of patients with thoracocentesis. The data show that the rate of definitive cytological

diagnosis obtained from single samples differs according to the cause of the malignant pleural effusions, some malignancies, such as Hodgkin's disease, show a lesser rate of diagnostic cytology (23%), while the cytological diagnostic yield ranges 63–73% in lung, metastatic breast and ovarian cancers<sup>(32)</sup>.

Lung cancer, malignant mesothelioma, and breast cancer were the most common types of cancer in the present study, which make the rate for definitive cytological diagnosis is consistent with these findings.

Unless the diagnosis is apparent after the first thoracocentesis, a second thoracocentesis is indicated and should even be accompanied by closed pleural biopsy. The diagnostic yield of pleural biopsy may reach up to 81–90% when combined with cytological examination; however, the diagnostic value of pleural biopsy alone is still not superior to that of cytology<sup>(33)</sup>.

Pleural biopsy was performed on 35 (25.4%) patients to determine the diagnosis. It was positive for malignancy in 17 cases out of the examined 35 cases (48.6%). However, pleural biopsy has a greater risk of complications than simple thoracocentesis and should be reserved for more difficult cases in which the initial thoracocentesis and cytological examination fails to yield a diagnosis.

The determination of tumor markers in pleural effusions has been proposed as an alternative, noninvasive way of establishing a diagnosis of pleural malignancy. However, the use of these measurements in clinical practice remains controversial.

Numerous biomarkers have been investigated to differentiate malignant pleural effusions from benign pleural effusions. Among these, carcinoembryonic antigen appears to be the most sensitive biomarker, with a sensitivity rate ranging 25–57%<sup>(31, 34)</sup>.

More reliable biomarkers, such as the assay of telomerase activity, have been under investigation to detect malignancy in pleural effusions<sup>(35)</sup>.

The natural polyamines putrescine, spermidine, and spermine are found in all cells. They have direct physiological role in cellular functions: cell growth, division, and differentiation.

Because of the importance of cellular growth and differentiation in carcinogenesis and tumor growth, polyamine metabolism has been intensively studied<sup>(14, 36)</sup>. Many data were collected indicated that patients with cancer have elevated blood levels of polyamines, and they excrete increased amounts of the polyamines, spermidine, and spermine, and their precursor, putrescine, in their urine<sup>(24, 25)</sup>.

Also, many studies revealed that definite, statistically valid elevations exist in the CSF polyamine concentrations of patients harboring malignant CNS tumors<sup>(29)</sup>. However, to our knowledge; no studies were conducted about polyamines levels in pleural effusions of different causes.

Polyamines were separated in many studies by the use of high-voltage electrophoresis on paper. That method was time consuming and not very sensitive or precise when applied to physiological fluids. In the present study, an automated amino acid

analyzer was used to measure the polyamines. Reproducibility was excellent, sensitivity was adequate, and little sample handling was required.

The current study revealed that definite, statistically valid elevations exist in the pleural effusion fluid polyamines concentrations of patients harboring malignant tumors, compared with those concentrations observed in the pleural effusions of patients without neoplasia.

This finding is in agreement with **Bachrach (2004)** who stated that polyamines accumulate in cancerous tissues and their concentration is elevated in body fluids of cancer patients<sup>(30)</sup>, and could be explained by the findings of **Russel (1977)**; who reported that changes in polyamines in physiological fluids reflect cell kinetics<sup>(37)</sup>.

Correlation studies showed that there was positive correlation between the levels of the three polyamines in the malignant pleural effusion. However; in benign pleural effusion spermine showed the lowest correlation coefficient with the other two polyamines. This could be explained by the fact that spermidine, and putrescine are formed by all cell types, either eukaryotes or prokaryotes. So, in cases of benign pleural effusions related to bacterial infection (pneumonia, pulmonary TB, and empyema) which constitute about 65% of our cases, the levels of these two polyamines reflect their formation by both human cells and the infecting micro-organism. On the other hand, the polyamine spermine is formed only by eukaryotes, so it is not formed by bacterial cells, and its level reflect

only the human source, this may also explain the more significant elevation of spermine levels in malignant effusions ( $p < 0.001$ ) than the other two polyamines ( $p < 0.05$ ) when we compared their levels in benign and malignant pleural effusion<sup>(38)</sup>.

Based on the results of the present study; although cytologic examination of pleural effusion remains the 'gold standard' for diagnosing malignant pleural effusion, polyamines levels can be used as an adjuvant diagnostic tool. In cases where cancer is suspected, yet patients have negative cytologic examination, pleural effusion that is high in its polyamines content warrants further diagnostic investigation. If the pleural effusion is low in its polyamines content, the possibility of cancer in these patients is quite low.

However; further studies should be carried out to determine the reference values of different polyamines levels for differentiation of malignant from benign pleural effusions.

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## استخدام البتروسين، السبيرميدين، و السبيرمين للمساعدة في تشخيص سبب الإرتشاح البلوري

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**المقدمة:** الإرتشاح البلوري هو عرض لكثير من الأمراض. و من الضروري معرفة مصدره و سببه للتمييز بين الإرتشاح الحميد و الإرتشاح الخبيث. المركبات عديدة الأمين مركبات مهمة تتحكم في عملية الإنقسام و التكاثر الخلوي و موت و بقاء الخلايا المختلفة. و قد لوحظ ارتفاع مستواها في عدد من سوائل الجسم في الأمراض السرطانية المختلفة.

**هدف البحث:** أجري هذا البحث لدراسة القدرة التشخيصية لمستوى المركبات المتعددة الأمين (البتروسين، السبيرميدين، و السبيرمين) في السائل البلوري للتمييز بين الإرتشاحين الحميد و الخبيث.

**طريقة البحث:** تمت الدراسة على ١٣٨ مريض مصاب بالإرتشاح البلوري، و تم تأكيد التشخيص بالفحص الخلوي لسائل الإرتشاح، و الذي أظهر ان هناك ٧٨ مصابا بإرتشاح نتيجة لمرض حميد، و ٦٠ مصابا بإرتشاح نتيجة لورم خبيث. تم قياس المركبات عديدة الأمين في السائل البلوري لكل المرضى باستخدام طريقة التبادل الأيوني الكروماتوجرافي.

**النتائج و الإستنتاج:** أوضحت النتائج أن مستوي المركبات عديدة الأمين كان أعلى في حالات الإرتشاح الناتج عن ورم خبيث، و كان هذا الارتفاع في مستواها له دلالة إحصائية عند مقارنته بمستواها في حالات الإرتشاح الناتج عن مرض حميد. نستنتج من هذا أن مستوي المركبات عديدة الأمين له أهمية كبيرة في المساعدة في تحديد سبب الأرتشاح، ويمكن استخدامه كمساعد في التمييز بين الإرتشاح الحميد و الإرتشاح الخبيث.