

ORIGINAL ARTICLE

Association of CA-125 with Pulmonary Tuberculosis

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Abstract

Background: Ca-125, a biochemical marker may be increased in malignant diseases, like ovarian cancer but also in other medical conditions, such as pulmonary and extrapulmonary tuberculosis. This cross sectional observational study was aimed to find out any association of CA 125 with pulmonary tuberculosis.

Methods: A total of 75 new cases of both smear positive & smear negative pulmonary tuberculosis were enrolled in this study, which was conducted at the Department of Respiratory Medicine in National Institute of Diseases of the Chest and Hospital from June 2018 - June 2019. **Results:** Out of 75 pulmonary tuberculosis patients, half (45.3%) patients belonged to age 21-40 years. The mean age was found 43.5±17.2 years. Almost three fourth (74.7%) patients were male and 19 (25.3%) patients were female. Male female ratio was 2.9:1. Majority 30(40.0%) patients completed primary education level. More than one third (36.0%) patients were service holder. Majority (90.7%) patients were married. More than half (56.0%) of the patients came from rural area. Average monthly income was 25680.0±38050.2 taka. Almost two third (62.7%) patients were smoker. The mean Hb was found 11.2±1.3 gm/dl, mean total count of WBC was 10837.7±4132.8 /mm³, mean ESR was 69.5±27.2 mm in 1st hour, mean MT was 13.9±4.4. Almost two third (64.0%) patients were found patchy opacity followed by 17(22.7%) consolidation, 3(4.0%) cavitory lesion, 2(2.7%) pneumothorax and 2(2.7%) patchy opacity with cavitory lesion. Majority (93.3%) patients were found in abnormal (e³36 U/ml) CA-125. The CA-125 was found 68.3±31.2 U/ml with range from 8.8 to 197.0 U/ml. Only 3(4.0%) patients had diabetes mellitus. Almost three fourth (73.3%) patients was found positive sputum for AFB and 20(26.7%) was negative sputum for AFB. In positive sputum for AFB, 23(41.8%) patients were found two number of zone involved followed by 13(23.6%) were one, 11(20.0%) were three and 8(14.5%) were more than three number of zone involved. Mean CA-125 was found 44.5±13.1 U/ml in negative sputum for AFB and 77.0±31.4 U/ml in positive sputum for AFB. The difference was statistically significant (p <0.05) between two groups. Significant association was found between CA-125 level with number of zone involved and sputum for AFB respectively. Positive significant correlation was found between number of zone involved (r=0.590; p=0.001) and sputum for AFB (r=0.852; p=0.001) with CA-125 level respectively.

Conclusion: In conclusion the present study shows that CA-125 level was significantly higher in positive sputum for AFB patients than negative patients. CA-125 level was significantly associated with number of zone involved. Positive significant correlation was between number of zone involved and sputum for AFB with CA-125 level respectively. Serum CA-125 may be used as a marker for diagnosis of active pulmonary tuberculosis especially when tuberculosis is suspected clinically and radiologically in patients without sputum production or sputum negative for AFB. Serum CA-125 may be used as a marker in assessment of severity of active pulmonary tuberculosis.

Keywords: Cancer antigen 125 (CA-125), Pulmonary tuberculosis

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Introduction

Tuberculosis represents an important health problem worldwide that was declared by World Health Organization (WHO) to be global emergency.¹ The World Health Organization estimates that each year more than 8 million new cases of tuberculosis occur and approximately 3 million persons die from the disease. Ninety-five percent of tuberculosis cases occur in developing countries.² TB currently holds the seventh place in the global ranking of causes of death. Unless intensive efforts are made, it is likely to maintain that position through to 2020.³ Pulmonary TB, the most important type of TB from the public health point of view, can be diagnosed by its symptoms, chest radiography, CRP, TST, MT, ESR, sputum smear microscopy, and by cultivation of *M. tuberculosis*.⁴ However, in some cases of pulmonary TB, acid-fast bacilli stains in sputum samples may be negative or respiratory specimens may not be available, and other methods have to be used to establish the diagnosis of TB. Recent advances in the field of molecular biology have provided new tools for the rapid diagnosis of TB by molecular methods. However, the high cost of most of these techniques, and their requirement for sophisticated equipment or highly skilled personnel have precluded their implementation on a routine basis, especially in low-income countries.⁵ Apart from microbiological molecular diagnostic tests, different biochemical parameters have been proposed as helpful tools for this purpose, including various markers of cellular activity, acute phase reactants and enzymes.⁶⁻¹⁰ The tumor marker Cancer antigen 125 has been proposed as a useful diagnostic tool for tuberculosis.¹¹

Ca 125 is most consistently elevated in epithelial ovarian cancer, but can be expressed in a number of gynecologic (endometrial, fallopian tube) and non-gynecologic (pancreatic, breast, colon and lung) cancers.¹² High levels of Ca-125 have been reported in patients with pulmonary disease.¹³⁻¹⁷ In pulmonary TB, it was claimed that raised levels of Ca 125 can greatly increase the likelihood of tuberculosis activity. The diagnostic value of Ca-125 to help differentiate pulmonary tuberculosis from other pulmonary infections has been poorly studied.¹³⁻¹⁵ Serum CA-125 may be used as a marker in assessment of severity of active pulmonary tuberculosis.

Materials and methods

Study subjects

With approval of protocol by Institutional Review Board of National Institute of Diseases of the Chest and Hospital (NIDCH), this cross sectional observational study was carried out in the Department of Respiratory Medicine in NIDCH, Mohakhali, Dhaka during the period from January 2018 to December 2018, to find out any association of CA 125 with pulmonary tuberculosis.

For this purpose, a total of 75 new pulmonary tuberculosis (both smear positive and smear negative) patients were attending in the above hospital were included this study. Active malignancy, patient with benign gynaecological lesions (eg: PID, endometriosis), malignant gynaecological tumours, pregnancy, menstruating women, liver cirrhosis, renal failure and heart failure patients were excluded from the study.

Data analysis

All data were analyzed by using computer based SPSS 23 (statistical package for social sciences). Data were presented in frequency, percentage and mean and standard deviation as applicable. Mann Whitney U test and ANOVA test was used for continuous variables as shown cross tabulation. Spearman's rank correlation coefficient was used for number of zone involved and sputum for AFB with CA-125 level. P value of less than 0.05 was considered as significant.

Results:

Table-I

Baseline characteristics of the study subjects (n=75)

Variables	
Male/female (n)	56/19
Age (years)	43.5±17.2
Smoker (%)	62.7
Diabetes mellitus (%)	96
Monthly income (taka)	25680.0±38050.2
Hb (gm/dl)	11.2±3
Total count of WBC (/mm ³)	10837.7±4132.8
ESR (mm in 1 st hour)	69.5±27.2
MT	13.9±4.4
CA-125 (U/ml)	68.3±31.2

Continuous variables reported as mean±SD & categorical variables as absolute or relative frequencies.

Table-II

Distribution of the study patients according to sputum for AFB (n=75)

Sputum for AFB	Number of patients	Percentage
Negative	20	26.7
Positive	55	73.3
+	18	24.0
++	19	25.3
+++	18	24.0

Table 2 shows that 55(73.3%) patients was found positive sputum for AFB and 20(26.7%) was negative sputum for AFB.

Table-III

Distribution of the study patients according to CA-125 (n=75)

CA-125 (U/ml)	Number of patients	Percentage
0-35 U/ml (Normal)	5	6.7
≥36 U/ml (Abnormal)	70	93.3
Mean ±SD		68.3±31.2
Range (min-max)		8.8-197.0

Table 3 shows that majority (93.3%) patients were found in abnormal (≥36 U/ml) CA-125. The CA-125 was found 68.3±31.2U/ml with range from 8.8 to 197.0 U/ml.

Table-IV

Distribution of the study patients according to number of zone involved in chest X-ray (n=55)

Number of zone involved	Number of patients	Percentage
1	13	23.6
2	23	41.8
3	11	20.0
>3	8	14.5

In positive sputum for AFB, 23(41.8%) patients were found two number of zone involved followed by 13(23.6%) were one, 11(20.0%) were three and 8(14.5%) were more than three number of zone involved.

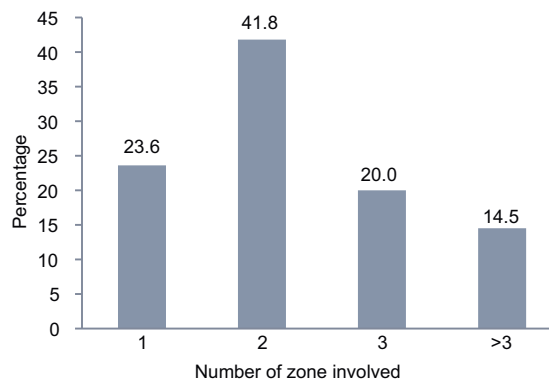


Fig.-1: Bar diagram showing number of zone involved of the study patients.

Table-V

Association between CA-125 with sputum for AFB (n=75)

	Sputum for AFB		P value
	Negative (n=20)	Positive (n=55)	
	Mean±SD	Mean±SD	
CA-125 (U/ml)	44.5±13.1	77.0±31.4	0.001 ^s
Range (min-max)	8.8-56.0	20.0-197.0	
Mean rank	15.58	46.15	

s= significant

P value reached from Mann-Whitney U test

Table 5 shows that mean CA-125 was found 44.5±13.1 U/ml in negative sputum for AFB and 77.0±31.4 U/ml in positive sputum for AFB. The difference was statistically significant ($p < 0.05$) between two groups.

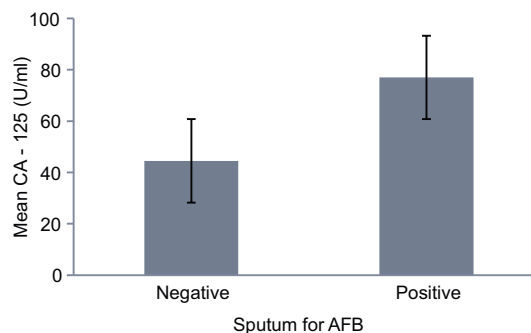


Fig.-2: Bar diagram showing association between CA-125 with sputum for AFB.

Table-VI

Association between CA-125 with number of zone involved in chest X-ray (n=55)

Number of zone involved	n	Mean±SD	Min-max	P value
1	13	52.6±18.7	20.0-78.0	0.001 ^s
2	23	73.3±10.6	55.0-100.0	
3	11	94.4±42.8	46.9-177.0	
>3	8	103.6±39.9	70.0-197.0	

s= significant

P value reached from ANOVA test

Thirteen patients were found one number of zone involved and their mean CA-125 was found 52.6±18.7 U/ml. Twenty three patients were found two number of zone involved and their mean CA-125 was found 73.3±10.6 U/ml. Eleven patients were found three number of zone involved and their mean CA-125 was found 94.4±42.8 U/ml. Eight patients were found more than three number of zone involved and their mean CA-125 was found 103.6±39.9 U/ml. The difference was statistically significant ($p<0.05$) among four groups.

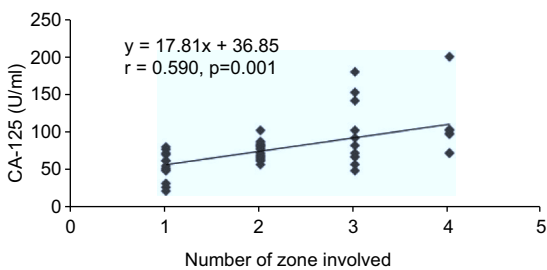


Fig.-3: Scatter diagram showing positive significant correlation ($r=0.590$; $p=0.001$) between number of zone involved and CA-125.

Table-VII

Association between CA-125 with level of sputum for AFB (n=55)

Sputum for AFB	n	Mean±SD	Min-max	P value
Negative	20	44.5±13.1	8.8-56.0	0.001 ^s
+	18	55.6±18.8	20.-100.0	
++	19	69.8±7.9	46.9-80.0	
+++	18	106.0±35.7	70.0-197.0	

s= significant

P value reached from ANOVA test

Twenty patients were found negative sputum for AFB and their mean CA-125 was found 44.5±13.1 U/ml. Eighteen patients were found one plus for

AFB and their mean CA-125 was found 55.6±18.8 U/ml. Nineteen patients were found two plus for AFB and their mean CA-125 was found 69.8±7.9 U/ml. Eighteen patients were found three plus for AFB and their mean CA-125 was found 106.0±35.7 U/ml. The difference was statistically significant ($p<0.05$) among four groups.

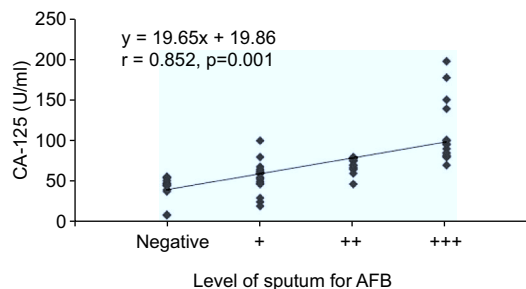


Fig.-4: Scatter diagram showing positive significant correlation ($r=0.852$; $p=0.001$) between sputum for AFB and CA-125.

Discussion

Pulmonary TB, the most important type of TB from the public health point of view, can be diagnosed by its symptoms, chest radiography, sputum smear microscopy, and cultivation of *M. tuberculosis*.⁴ However, in some cases of pulmonary TB, Acid Fast Bacilli stains in sputum samples may be negative or respiratory specimens may not be available, and other methods have to be used to establish the diagnosis of TB.⁵ The tumor marker Cancer antigen 125 has been proposed as a useful diagnostic tool for tuberculosis.¹¹ High levels of Ca-125 have been reported in patients with pulmonary and extra-pulmonary tuberculosis, including pleural, peritoneal, pelvic, miliary, and intraabdominal disease.¹⁶⁻¹⁷

This cross sectional, observational study was carried out with an aim to observe any positive association of serum CA 125 level with pulmonary tuberculosis.

A total of 75 pulmonary tuberculosis patients were attending in the Department of Respiratory Medicine in National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka during the period from June 2018 - July 2019 were included in this study. PTB cases (both smear positive and smear negative) were enrolled in this

study. Active malignancy, patient with benign gynaecological lesions (eg: PID, endometriosis), malignant gynaecological tumours, pregnancy, menstruating women, liver cirrhosis, renal failure and heart failure patients were excluded from the study. The present study findings were discussed and compared with previously published relevant studies.

In this present study it was observed that almost half (45.3%) patients belonged to age 21-40 years. The mean age was found 43.5 ± 17.2 years with range from 18 to 83 years. El Hoshy et al.¹⁸ found their study the age of the studied patients ranged from 26 to 60 years with a mean of 44.87 ± 13.557 years. In a study conducted by Said et al.¹⁹ where they showed mean age was 36.5 years with range of 15–70. Mohammad et al.²⁰ reported that mean age was 34.2 ± 15.15 years with range of 19–75. Another study conducted by Sahin and Yildiz where they consisted mean age was 35.62 ± 9.48 years.²¹

In this study it was observed that almost three fourth (74.7%) patients were male and 19(25.3%) patients were female. Male female ratio was 2.9:1. Similarly, Sahin and Yildiz suggested males were 26(61.9%) and females were 16(38.1%).²¹ Said et al.¹⁹ demonstrated their study males were 14(51.9%) and females were 13(48.1%). Another study conducted by El Hoshy et al.¹⁸ where they documented 12 patients (60%) were males whereas 8 patients (40%) were females.

In this current study it was observed that 30(40.0%) patients completed primary education, 18(24.0%) completed SSC, 16(21.3%) completed HSC, 6(8.0%) completed secondary and 5(6.7%) completed graduate. Zuberi et al.²² found 38.55% below Matric, 61.45% Matric and above level.

In this series it was observed that more than one third (36.0%) patients were service holder followed by 15(20.0%) were businessman, 15(20.0%) were farmer, 11(14.7%) were housewives, 5(6.7%) were student, 1(1.3%) was worker abroad and 1(1.3%) was rickshaw puller. Majority (90.7%) patients were married, 6(8.0%) were unmarried and 1(1.3%) was divorce. More than half 42(56.0%) of the patients come from rural area and 33(44.0%) from urban area. Average monthly income was found 25680.0 ± 38050.2 taka with range from 10000 to

300000 taka. Smoker was found 47(62.7%) and non smoker was 28(37.3%).

In this present study it was observed that mean Hb was found 11.2 ± 1.3 gm/dl with range from 8.0 to 14.0 gm/dl. The mean total count of WBC was found 10837.7 ± 4132.8 /mm³ with range from 3380.0 to 29700.0 /mm³. Mean MT was found 13.9 ± 4.4 with range from 5.0 to 22.0.

In this current study it was observed that mean ESR was found 69.5 ± 27.2 mm in 1st hour with range from 20.0 to 142.0 mm in 1st hour. Mohammad et al.²⁰ found their study mean ESR was 51.13 ± 19.99 mm in 1st hour with range from 22 to 100.

In this study it was observed that almost two third (64.0%) patients were found patchy opacity followed by 17(22.7%) consolidation, 3(4.0%) cavitory lesion, 2(2.7%) pneumothorax and 2(2.7%) patchy opacity with cavitory lesion. Mohammad et al.²⁰ observed their study serum CA 125 levels in group I was significantly higher in far advanced and moderate advanced disease than minimal lesion one. These results were in agreement with those reported by Kanagarajan et al.²³ who studied CA-125 as a reliable serum marker for diagnosis of tuberculosis, and found that levels of CA-125 were the highest in cavitory pulmonary TB and in military TB, so they concluded that we can take CA 125 as one of the parameters in the assessment of severity of TB. Also these results were in agreement with those reported by Kim et al.²⁴ who found that CA-125 levels appeared to be the highest in patients with cavitory rather than nodular type and this may reflect the level or extent of the infection. Said et al.¹⁹ also consisted their study 20 patients (74%) of active pulmonary tuberculosis had a moderate advanced lesion on chest X-ray and 7 patients (26%) had a far advanced lesion. No patients had a minimal lesion on chest X-ray.

In this series it was observed that majority (93.3%) patients were found in abnormal (e^{36} U/ml) CA-125. The CA-125 was found 68.3 ± 31.2 U/ml with range from 8.8 to 197.0 U/ml. Similar study documented by Mohammad et al.²⁰ where reported that mean Ca 125 levels was 65.58 ± 69.77 U/ml with range from 4.5 to 285.5. El Hoshy et al.¹⁸ demonstrated their study mean \pm SD level of CA125 in pleural fluid was 41.732 ± 20.744 U/ml. In Yilmaz et al.²⁵ study, the mean Ca-125 level in patients

with active pulmonary tuberculosis was (109.7 ±86.9 U/ml), while it was (118.46± 248.41 U/ml) in Ozsahin et al.²⁶ study which are to some extent close to the value in the present study (93.5± 138.9 U/ml). On the other hand, Kim et al.²⁴ study showed a lower mean value of Ca 125 in patients with active pulmonary TB (54.5± 22.4) than in our study. This may be due to the difference in ways of the diagnosis of tuberculous patients. They depend on sputum culture while in this research; we depended on sputum smear-probably with a higher bacillary load than culture. Another study conducted by Fortun et al.¹¹ where suggested that mean Ca 125 value was 59.5 (± 88.5) IU/ml and the median was 31 (range: 13 to 63)

In this study it was observed that 55(73.3%) patients was found positive sputum for AFB and 20(26.7%) was negative sputum for AFB. Sputum for AFB +, ++ and +++ was found 24.0%, 25.3% and 24.0% respectively. Mohammad et al.²⁰ observed their study 28 cases (70%) of group I were sputum positive while 12 cases (30%) were sputum negative for AFB. sputum for AFB +, ++ and +++ was 25.0%, 30.0% and 15.0% respectively. Kim et al.²⁴ studied the clinical significance of CA-125 in pulmonary tuberculosis, his study included 100 patients with active pulmonary tuberculosis that were divided into 47 (47%) patients with positive sputum and 53 (53%) patients with negative sputum. Another study documented by Tasc1 et al.²⁵⁻²⁷ where they showed sputum smear results of the 54 patients with pulmonary TB were as follows: four positive acid-fast bacilli in five patients (9.2%), three positive in 16 patients (33.7%), two positive in seven patients (7.7%), and one positive in seven patients (7.7%).

In positive sputum for AFB, 23(41.8%) patients were found two number of zone involved followed by 13(23.6%) were one, 11(20.0%) were three and 8(14.5%) were more than three number of zone involved.

In this present study it was observed that mean CA-125 was found 44.5±13.1 U/ml in negative sputum for AFB and 77.0±31.4 U/ml in positive sputum for AFB. The difference was statistically significant ($p<0.05$) between two groups. Mohammad et al.²⁰ found their study there was a statistically significant difference in serum CA 125

levels in group I regarding the results of sputum analysis for AFB. Kim et al.²⁴ found that CA-125 was higher in patients with positive sputum for AFB than those with sputum negative pulmonary tuberculosis. In the study, there was a statistically significant difference between sputum negative pulmonary tuberculosis in group I and group II regarding CA 125.

In this current study it was observed that 13 patients were found one number of zone involved and their mean CA-125 was found 52.6±18.7 U/ml. Twenty three patients were found two number of zone involved and their mean CA-125 was found 73.3±10.6 U/ml. Eleven patients were found three number of zone involved and their mean CA-125 was found 94.4±42.8 U/ml. Eight patients were found more than three number of zone involved and their mean CA-125 was found 103.6±39.9 U/ml. The difference was statistically significant ($p<0.05$) among four groups. Positive correlation ($r=0.590$; $p=0.001$) between number of zone involved and CA-125.

In this series it was observed that 20 patients were found negative sputum for AFB and their mean CA-125 was found 44.5±13.1 U/ml. Eighteen patients were found one plus for AFB and their mean CA-125 was found 55.6±18.8 U/ml. Nineteen patients were found two plus for AFB and their mean CA-125 was found 69.8±7.9 U/ml. Eighteen patients were found three plus for AFB and their mean CA-125 was found 106.0±35.7 U/ml. The difference was statistically significant ($p<0.05$) among four groups. Tasc1 et al.²⁷ Therefore, the present authors claim that CA 125 can be used in the monitoring of treatment response in pulmonary TB patients. Fortun et al.¹¹ reported that CA 125 values increase in patients with pulmonary TB and decrease to normal values during treatment. According to reported articles, the CA 125 level evaluated in patients with a negative sputum acid-fast bacillus stain. Huang et al.²⁸ suggested that CA 125 serum levels – in combination with clinical responses, chest radiography, and sputum examinations – can offer improved monitoring of therapeutic responses in anti-TB treatment.

In this study it was observed that positive correlation ($r=0.852$; $p=0.001$) was found between

sputum for AFB and CA-125. Similarly, Tasc1 et al.²⁷ consisted their study higher serum CA 125 levels were obtained from the patients with a higher degree of sputum smear positivity ($r = 0.341$, $P = 0.012$).

Conclusion

In conclusion the present study shows that CA-125 level was significantly higher in smear positive patients as well as negative one. CA-125 level was significantly associated with number of zone involved. Positive significant correlation was found between number of zone involved in chest X-ray and sputum for AFB with CA-125 level respectively. Like pleural fluid ADA, Ca-125 may augment diagnosis of pulmonary tuberculosis, specially the smear negative cases where other radiological and clinical evidence suggests the diagnosis. Serum CA-125 may be used in assessment of severity of active pulmonary tuberculosis.

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Author Contribution:

Conflict Of Interest: The authors of this paper have declared that there is no conflict of interest to any of the authors.

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