



ROLE OF SERUM CA125 AS A PREDICTOR OF ACTIVITY OF PULMONARY TUBERCULOSIS - A COMPARATIVE ANALYSIS IN SPUTUM SMEAR POSITIVE, SMEAR NEGATIVE PULMONARY TUBERCULOSIS AND NON-TB PULMONARY INFECTIONS

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ABSTRACT

Background - TB has been the leading cause of death and a major public health problem, despite various efforts from government sectors and NGOs to provide high quality TB services. It has been reported that serum Ca125 levels are elevated in patients with pulmonary and extrapulmonary tuberculosis and its concentration decreases gradually once ATT is initiated⁷. This study aims at finding a correlation between serum Ca125 and activity of pulmonary TB. **Aims and Objectives** - To compare serum Ca125 levels in patients with sputum smear positive, smear negative pulmonary tuberculosis and non-tubercular pulmonary infections. To evaluate if serum Ca125 values act as a marker of activity of tuberculous infection. **Methodology** - It was a prospective cohort study with a study duration of 24 months. 150 patients were divided into three groups of 50 each comprising of new sputum smear positive PTB, sputum smear negative, but chest x-ray suggestive PTB and non PTB respiratory patients. Ca125 was done using electro-chemiluminescent assay using venous blood samples of subjects. The serum Ca125 values were done at start of ATT and the patients followed up at 3 and 6 months with serum Ca125 levels. **Results** - There was a significant correlation between grade of sputum positivity and mean value of Ca125 (p value - <0.05) and also the mean values of Ca125 declined during the course of treatment. The sensitivity, specificity, PPV and NPV were 80%, 90%, 94.126% and 69.199% respectively in our study. **Conclusion** - Ca125 can be used as screening test for active tuberculosis, to assess severity of disease and as a monitoring tool to assess response to ATT.

KEYWORDS : Serum Ca125, pulmonary tuberculosis, sputum

BACKGROUND

TB has been the leading cause of death and a major public health problem, despite various efforts from government sectors and NGOs to provide high quality TB services. A number of parameters like cell activation markers, acute phase reactants like CRP levels¹, tumour markers² and various serological tests like Ca125^{3,4} have been evaluated as measures of disease severity in TB, but their usefulness remains uncertain. Over the years, researches have been finding out if tumour marker Ca125 can be used as a tool for diagnosis of TB.

Though traditionally related to ovarian malignancies⁵, its concentration is increased in wide array of benign as well as malignant conditions⁶. It has been reported that serum Ca125 levels are elevated in patients with pulmonary and extrapulmonary tuberculosis, including pleural, peritoneal, pelvic, miliary, abdominal tuberculosis and also that its concentration decreases gradually once ATT is initiated^{7,8}. This study aims at finding a correlation between serum Ca125 and activity of pulmonary TB.

Aims and Objectives

- To compare serum Ca125 levels in patients with sputum smear positive, smear negative pulmonary tuberculosis and non-tubercular pulmonary infections.
- To evaluate if serum Ca125 values act as a marker of activity of tuberculous infection.

Methodology

The study was conducted in the Department of Pulmonary Medicine, Goa Medical College from September 2018 to June 2020. 150 patients [outpatients and inpatients] were included in the study. It was a prospective cohort study with a study duration of 24 months. Serum Ca125 was determined using electro-chemiluminescent assay using venous blood samples of subjects.

Inclusion Criteria

- GROUP 1- patients with at least one sputum smear positive for AFB by fluorescent microscopy and chest radiographic features consistent with active PTB.
- GROUP 2- the patient whose sputum smear was negative for AFB and chest radiographic abnormality consistent with active pulmonary TB.
- GROUP 3- the patient was sputum smear negative for AFB

and radiographic features not suggestive of tuberculosis but had features of chronic obstructive pulmonary disease, asthma, pneumonia etc.

Exclusion Criteria

Patients with progressive malignancy (lung or ovarian cancer), heart failure and liver disease, non-malignant gynaecological conditions (endometriosis, pregnancy), patients not willing to be a part of the study, immunocompromised and terminally ill patients were excluded from the study.

The informed consent was taken from all the patients. The Institutional Ethics Committee approval was obtained prior to the initiation of the study.

The patients were divided into three groups as mentioned in the inclusion criteria and each group comprised of 50 patients.

The variables captured were age, sex, Sputum status, occupation, past history of tuberculosis, addictions and Diabetes mellitus.

Ca125 was done using electro-chemiluminescent assay using venous blood samples of subjects. The serum Ca125 values were done at start of ATT and the patients followed up at 3 and 6 months with serum Ca125 levels.

RESULTS

The study "Role of Serum Ca125 as a Predictor of Activity of Pulmonary Tuberculosis - A Comparative analysis in Sputum Smear Positive, sputum Smear negative Pulmonary Tuberculosis and non-TB Pulmonary Infections" was conducted among the patients visiting the Department of pulmonary Medicine, Goa Medical College, a tertiary care hospital attached to medical college. The duration of the study was 2 years commencing from September 2018 up to August 2020. The patients were from OPD as well those who were admitted for treatment.

150 patients were included in the study of which 100(66.7%) were males and 50(33.3%) were females. 27(18%) patients had Type2DM and 15(10%) patients had past history of tuberculosis. There was a significant correlation between grade of sputum positivity and mean value of Ca125 (p value - <0.05).

In the present study the cut off value of Ca 125 was >55 U/ml

for diagnosis of active PTB. We determined our cut off values using ROC analysis using MedCalc software (Fig. 1). The sensitivity, specificity, PPV and NPV were 80%, 90%, 94.126% and 69.199% respectively in our study. The cut off value of Ca125 was determined by ROC curve analysis

Table 1: Mean Ca125 Values at Baseline 3rd and 6th Month of Treatment.

Group	Ca125 Baseline[U/ml]	Ca125 at 3 months[U/ml]	Ca125 at 6 months[U/ml]
1	196.04	93.12	41.44
2	70.30	43.26	31.66
3	45.54	-	-

The mean values of Ca125 declined during the course of treatment (Table 1). The mean values of Ca125 in group 1 which included patients with smear positive PTB at the start of treatment was 196.04U/ml, which declined to 93.12 U/ml at 3 months and 41.44 U/ml at 6 months.

The values in group 2 which included smear negative but radiologically proven PTB patients was 70.30U/ml at the start of the anti TB treatment. The mean values declined to 43.26U/ml at 3 months and 31.66U/ml at 6 months of anti-TB treatment.

The values in group 3 which was used as control was 45.54U/ml. These patients were followed up but serum Ca125 was not repeated in them (Table 1).

The results were statistically significant and the same were calculated using Greenhouse Geisser statistical test using SPSS software.

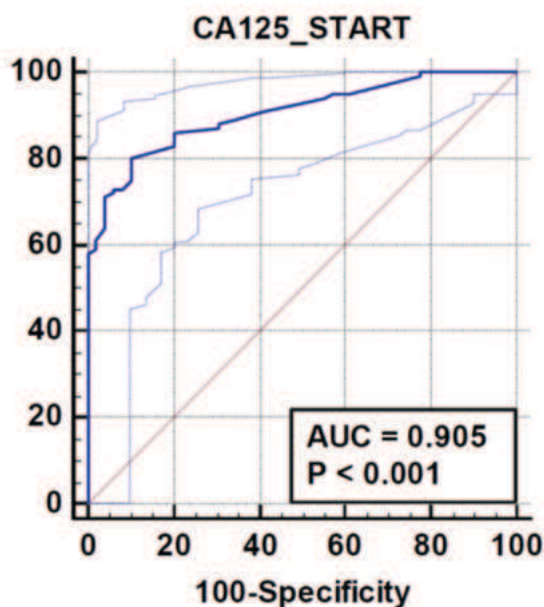


Figure 1: ROC Curve Showing Sensitivity Plotted Against 100-Specificity.

DISCUSSION

Traditionally sputum smear microscopy and conventional culture on LJ slope were used for identification of active cases before the advent of CBNAAT and liquid culture. In sputum smear negative patients with suggestive history, thick and irregularly walled cavity with satellite lesions, upper lobe predominance and infiltrative lesions were considered as radiological evidence of active disease necessitating anti-TB treatment. The challenge was in identifying a case with no visible radiological lesions and minimal symptoms.

importance, and numerous markers have been tried and tested, however the search for the ideal markers still continues. The aim of our study was to determine if Ca125 levels could assist in the diagnosis and most importantly assessing the response of treatment of PTB.

Ca125 is a simple laboratory investigation and values can be interpreted easily, it doesn't need expertise as in evaluation of sputum smears and chest x-ray, which has intra and inter observer variation. The decision of what is the optimum time of treatment completion could differ in individual patient and can be detrimental too if terminated early, which would ideally require prolongation of ATT.

It also alleviates need of sputum studies which would convert in 4-6 weeks of treatment and further monitoring of treatment is challenging.

Eun Sun Kim et al⁹ analysed 100 sputum smear positive patients, serum Ca125 was done before initiating anti-TB treatment and followed up 6 months and 12months after starting the treatment. The mean serum CA-125 was 38.9 ± 41.4 U/ml (reference value, <35 U/ml). Thirty-eight patients showed elevated CA-125. The CA-125 level decreased with anti-TB treatment ($p = 0.001$). Serum CA-125 was related to the activity and severity of pulmonary TB.

A F Said et al¹⁰ observed that there was a significant increase of Ca-125 among patients with active pulmonary TB than the other groups which consisted of patients with non-TB infections and control group comprising of healthy volunteers, which decrease significantly after anti-tuberculous drugs. The sensitivity and specificity of Ca-125 were found to be 81.4% and 95%, respectively, at a 34.6 U/ml cut-off point.

150 patients were included in the present study of which 100(66.7%) were males and 50(33.3%) females, 27 patients had history of Type2DM and 15 had past history of PTB. The cut off value of serum Ca125 in the present study was >55U/ml determined by using ROC analysis using MedCalc software¹¹ (Fig. 1). The sensitivity, specificity, PPV and NPV was 80%, 90%, 94.126% and 69.199% respectively.

We divided our patients into 3 groups, group 1 having sputum AFB positive cases, group 2 had cases with sputum AFB negative but chest radiograph was suggestive of active PTB and group 3 were controls with pulmonary diseases other than PTB ex. Bronchial asthma, COPD, bacterial pneumonia etc.

In our study, the cut off value was 55U/ml and mean in group 1, group 2 and group3 were 196.04 U/ml, 70.30 U/ml, 45.54 U/ml. We did not find any significance with respect to gender of the patient, we did not take into account the radiological features of the patient, however we found a positive correlation with grading of sputum and that serum values of Ca125 decline gradually with ATT. Our study had sensitivity of 80% and specificity of 90% with cut off of 55U/ml,

Osama Ibrahim Mohammad et al¹² published a study where again the subjects were classified into 3 groups: with group I inclusive of cases with active tuberculosis (newly diagnosed), group II had pneumonia patients, group III had healthy controls. In patients with far advanced and moderately advanced disease, Ca125 values were much higher and significant than in patients with disease having minimal involvement, also as per the sputum analysis in first group there was significant association with higher grades of sputum positivity. The cut off value of 21.05 U/ml had sensitivity of 82.5%, specificity 72.5%, PPV being 77.3%, Negative predictive value of 83.3% with 80% accuracy for diagnosis of active pulmonary tuberculosis.

A serological test for monitoring tubercular activity is of utmost

Limitations of the Study

Our study had a few limitations like the groups were not matched for age, sex, addictions and co morbidities. Cases of latent TB and extrapulmonary TB were not included in the study. All females were not subjected to a gynaecological examination as our centre is around 9kms away from tertiary centre and would not be feasible for asymptomatic patients. Studies have shown that menses and even transient mechanical stress over the mesothelial cells may cause Ca125 values to rise. In our study we did not try to find the relation between values of Ca125 with different phases of menstrual cycle.

CONCLUSION

In the present study, mean Ca125 was higher in group1 which were smear positive PTB. As Ca125 values were significantly higher in group 1 depending on grading of sputum, scant having lower mean values and 3+ having highest values; in group 2 we got a lower mean value but was above the cut off value, so Ca125 could also serve as a guide to predict how infectious a patient would be.

We found a decline of Ca125 values as the patient received treatment, so it could also be used as a useful tool for monitoring treatment.

We did not find any significant difference of Ca125 values, with respect to age, sex, diabetic status of the patient and past history of TB.

- Ca125 can be used as screening test for active tuberculosis.
- To assess severity of disease.
- It can be also used as a monitoring tool to assess response to ATT.

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