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# Evaluation of risk factors associated with chronic pulmonary aspergillosis among post tubercular sequelae patients

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**Abstract:**

**Background:** Treatment of Pulmonary Tuberculosis (PTB) emphases on microbiological treatment and radiological progress. Nevertheless, many patients develop Chronic Pulmonary Aspergillosis (CPA) after the completion of anti-tubercular medication which may affect their quality of life. The aim of present study is to evaluate various risk factors accompanying with chronic pulmonary aspergillosis among post tubercular sequelae patients.

**Methods:** The study included 100 post-tubercular sequelae patients who had completed their anti-tubercular treatment (ATT) and had symptoms and radiological abnormalities. Detailed clinical history was taken, and physical examination was done. Chest X-ray was performed to evaluate the presence of disease or cavities. CPA and Non-CPA patients are distinguished by using Partial least square discriminant analysis (PLSDA). Addiction and Comorbidities are the two subgroups of variables/descriptors used.

**Results:** Comorbidities are more predictive of CPA as compared to Addictions feature set and the combination of both Comorbidities and Addiction resulted in better performance evaluation metrics for the PLSDA algorithm.

**Conclusion:** The observed pervasiveness of CPA among post-tubercular sequelae patients in the present study is higher than the previous reported studies. This may be associated with significant morbidity in terms of symptoms and abnormal pulmonary function tests (PFT). Patients with CPA may need further evaluation and treatment with antifungal therapy and/or surgical treatment for improved outcomes..The features: hemoptysis, substance abuse, total duration of illness, cough and expectoration are the five most important variables for the model and are strongly associated with CPA.

**Keywords**: Pulmonary Tuberculosis, Chronic Pulmonary Aspergillosis, Post-Tubercular Sequelae, Cavitation, Anti-Tubercular Treatment.

## Introduction:

Tuberculosis (TB) has been a major cause of suffering and death since times immemorial. In addition to the mortality and morbidity caused by active disease, pulmonary TB (PTB) is associated with a variety of sequelae, which include parenchymal, airway, vascular, mediastinal, pleural and chest wall lesions. Pulmonary TB is associated with various long term lung complications including lung scarring (fibrosis), bronchiectasis, chronic pulmonary aspergillosis (CPA), airway stenosis and chronic obstructive pulmonary disease (COPD) and it may even be a risk factor for lung cancer [1].

*Aspergillus fumigatus* is a ubiquitous dimorphic soil dwelling fungus that can cause a variety of pulmonary diseases, depending on host

immunity.Among the numerous pulmonary diseases, Allergic Pulmonary Aspergillosis (ABPA) and Chronic Pulmonary Aspergillosis (CPA) generally occurs in the immune-competent host whereas invasive pulmonary aspergillosis manifests in the immunocompromised host [2].

The most established relationship of *Aspergillus fumigatus* with PTB is aspergilloma, characterized by saprophytic growth of the fungus in pre-existing tuberculous cavities. Excess matrix metalloproteinase activity by lung epithelial cells has been implicated in the destructive pulmonary pathology of TB, leading to impaired ciliary function and adhesion of the mucus gel layer to the epithelial surface. Consequently, cellular debris, mucus impaction, cavities, and ectatic bronchi can trap *Aspergillus* spores, enabling *Aspergillus* infection [3-5]. Chronic Pulmonary Aspergillosis arises in several forms such as simple aspergilloma, chronic cavitary pulmonary aspergillosis (CCPA) and chronic fibrosing pulmonary aspergillosis (CFPA), aspergillus nodule and subacute invasive aspergillosis (SAIA) [6].

Chronic Pulmonary Aspergillosis (CPA) is an under recognized, but noteworthy health problem throughout the world, resulting in considerable morbidity and mortality. With flexible disease forms, high levels of associated respiratory co-morbidity, limited therapeutic options, and prolonged antifungal treatment strategies, makes CPA a challenging disease for both patients and health care professionals. In India, considerable percentage of TB is treated out of the national TB program. Consequently, CPA assumption is an underestimate of the factual affliction of CPA in India. In this study, efforts have been made to identify the associated risk factors for the development of CPA among post pulmonary TB sequelae patients.

Supervised machine learning algorithms involves the development of predictive models using labeled data which can assist in mining data originating in clinical scenarios which can further facilitate in revealing insightful information. The objective of this study is to find out associations of various clinical and biochemical factors with CPA and to further develop a prediction model using explainable machine learning algorithm.

**Materials and Methods:**

Dataset: The study population in this prospective observational study consists of 100 adult patients between 18-65 years of age, who have been successfully treated for pulmonary tuberculosis. Informed consent was taken from the patients, and ethical clearance was obtained from the Ethical Review Board of the institution. Patients who visited the outpatient department and those admitted in non-tubercular wards with clinical symptoms of more than 1 month duration, including chronic cough, fever, hemoptysis, shortness of breath, chest pain or weight loss after completion of antitubercular treatment and had abnormal chest X-ray were included in the study. Radiological lesions include cavitary pulmonary lesion with evidence of para-cavitary infiltrates, new cavity formation or expansion of cavity size over time, air crescent sign, pleural thickening, parenchymal destruction, and/or fibrosis. Those patients with active pulmonary tuberculosis, history suggestive of asthma before the development of TB, intake of immunosuppressive medication or with immunosuppressive conditions, HIV seropositive cases, pregnancy, and failure to provide written informed consent were excluded from the study. All cases were subjected to detailed clinical history and physical examination. Details of symptoms such as chronic (>1 month) cough, expectoration, dyspnoea, hemoptysis, fever, and chest pain were recorded. There were 45 and 55 records in CPA and Non-CPA groups respectively. The addiction set of descriptors includes: Smoker, type_of_smoking, Ex_Smoker, No._per_day, Smoke_Index, alcohal_intake and substance_abuse. (Qualitative: Smoker, type_of_smoking, alcohal_intake and substance_abuse; Quantitative: Ex_Smoker, No._per_day and Smoke_Index ).The comorbidities set of descriptors included: Hiv_status, diabetes, tot_dura_illness, cough, expecoration, hemoptysis, breathlessness, chest pain and fever (Qualitative: Hiv_status, diabetes, hemoptysis and chest pain; Quantitative: tot_dura_illness, cough, expecoration, breathlessness and fever).

White Box Approach using Partial least square discriminant analysis:

Partial least square discriminant analysis (PLSDA) [7-10] is used for generating discriminatory model to distinguish CPA and Non-CPA patients. It is a multivariate statistical method which uses multiple response and multiple independent variables to build



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explanatory predictive models. It finds its application more useful in multicolinearity scenarios. PLSDA is similar to Principal component analysis as it involves the linear transformation of the independent variables into new components with the exception that it uses the class information. We used two subgroups of variables (descriptors): Addiction and Comorbidities. These two groups of descriptors are used separately and in combination for the generation of PLSDA models. We implemented PLSDA with maximum of three components.

**Results:**

Initially we used individual feature sets for modelling with PLSDA algorithm. On using the addiction subgroup of descriptors for modelling with PLSDA, we observed that the overall classification accuracy between CPA and Non-CPA is only 58% (table 1).

| Confusion matrix for the estimation sample: | | | | |
|---|---|---|---|---|
| | | | | |
| from \ to | CPA | Non-CPA | Total | % correct |
| CPA | 5 | 40 | 45 | 11.11% |
| Non-CPA | 2 | 53 | 55 | 96.36% |
| Total | 7 | 93 | 100 | 58.00% |

**Table 1 Confusion matrix for PLSDA with Addiction subgroup of feature**

The most important variables/descriptors for PLSDA with addiction subset of descriptors is shown in Fig.1 as Variable Importance Plots (VIP) and the corresponding receiver operating characteristic curve (ROC) is shown Fig.2.

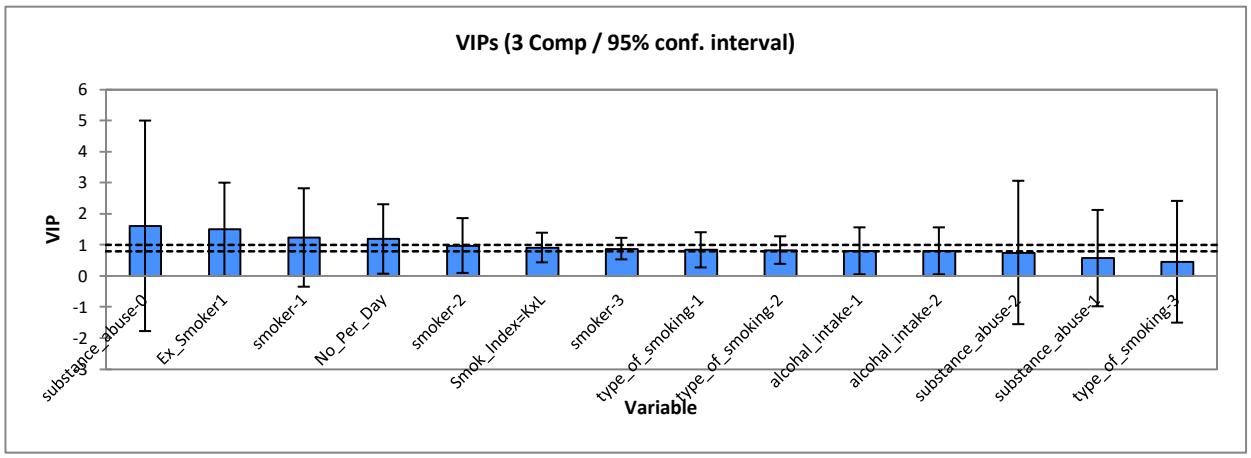


**Fig. 1 Variable Importance Plots for the three components of PLSDA with Adddiction subgroup of descriptors.**



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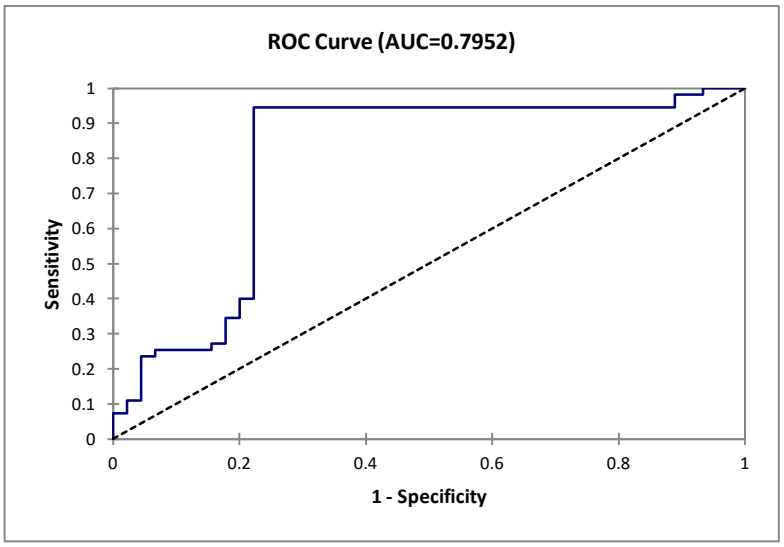


**Fig. 2 ROC for the PLSDA model with Addiction subgroup of features**.

Further we used only Comorbidities descriptors with PLSDA. The confusion matrix is shown in table 2 and the most important variables/descriptors is shown in fig.3.

| Confusion matrix for the estimation sample: | | | | |
|---|---|---|---|---|
| | | | | |
| from \ to | CPA | Non-CPA | Total | % correct |
| CPA | 16 | 29 | 45 | 35.56% |
| Non-CPA | 5 | 50 | 55 | 90.91% |
| Total | 21 | 79 | 100 | 66.00% |

**Table 2 Confusion matrix for PLSDA with Addiction subgroup of features**

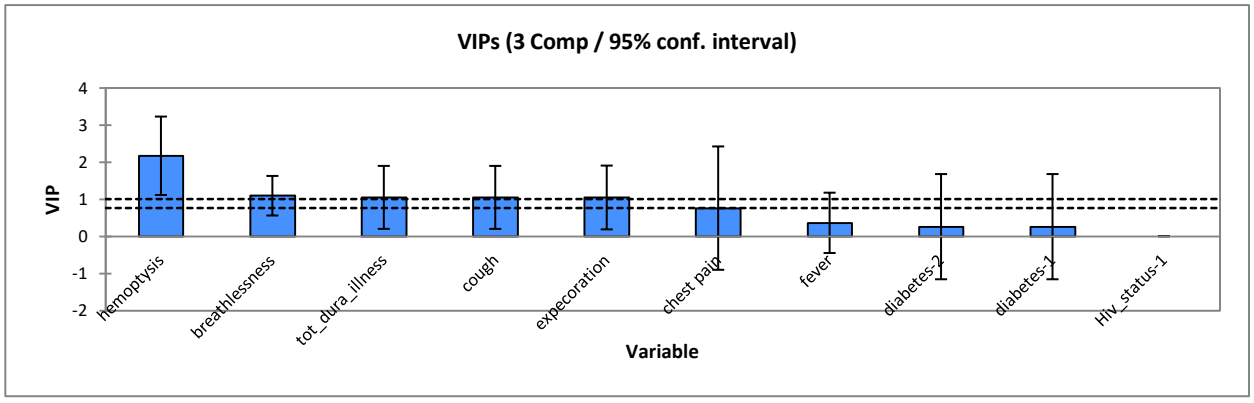


**Fig. 3 Variable Importance Plots for the three components of PLSDA with Comorbidities subgroup of descriptors.**



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ROC for the PLSDA model with comorbidities feature subset is depicted in fig.4. An overall accuracy of 66% (an 8% rise in accuracy as compared to addiction subgroup) is obtained (table 2).

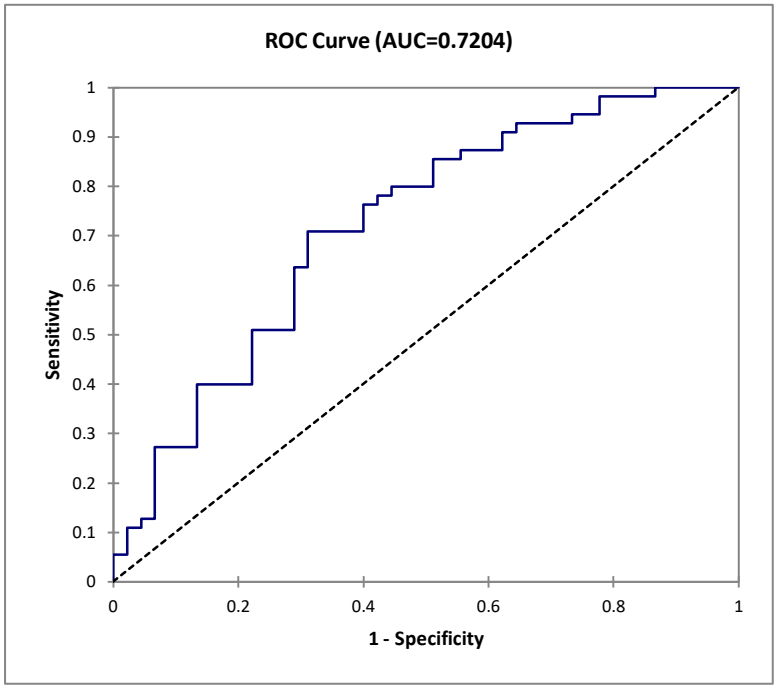


**Fig. 4 ROC for the PLSDA model with Comorbidities subgroup of features.**

In order to construct a more accurate discriminatory model, we combined both the Addiction and Comorbidities subgroups as a combined descriptor set for generating classification/discriminatory models with PLSDA. The correlations plot with both Addiction and Comorbidities as descriptor set is presented in fig. 5, where it can be observed that hemotysis, breathlessness, cough, expectoration, and total duration of illness are found to be positively correlated with the CPA group.

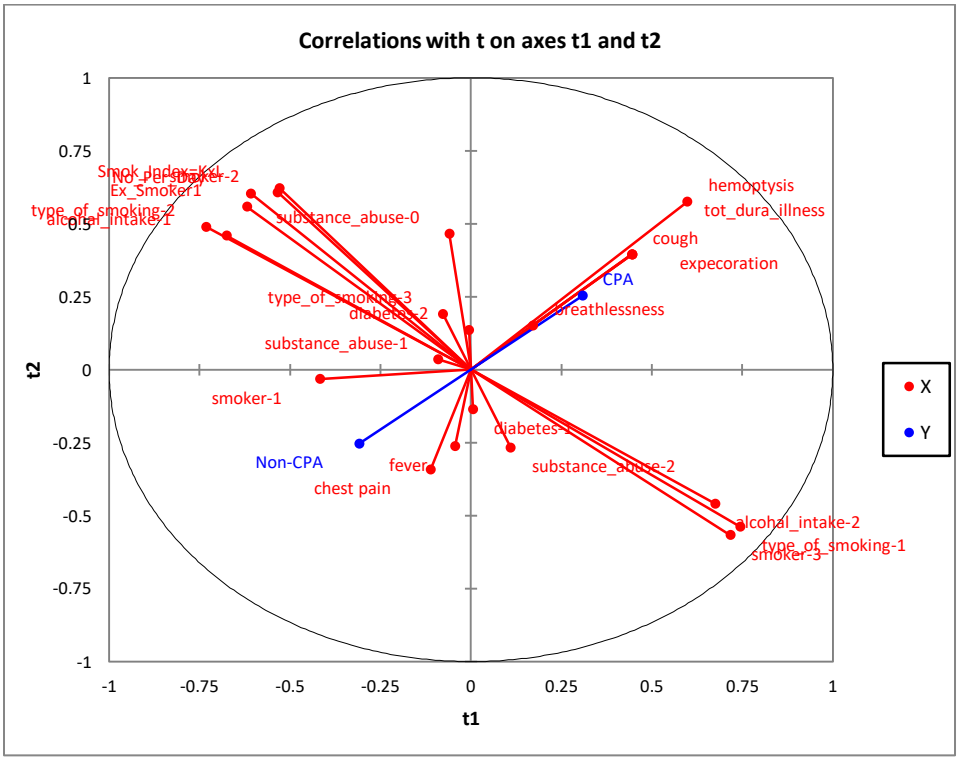


**Fig.5 Correlation plot for the components, dependent and independent variables.**



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We also observed an 1% increase in overall classification accuracy (67%) (table 3) as compared to the Comorbidities subgroup of descriptors.

| Confusion matrix for the estimation sample: | | | | |
|---|---|---|---|---|
| | | | | |
| from \ to | CPA | Non-CPA | Total | % correct |
| CPA | 22 | 23 | 45 | 48.89% |
| Non-CPA | 10 | 45 | 55 | 81.82% |
| Total | 32 | 68 | 100 | 67.00% |
| Total | 32 | 68 | 100 | 67.00% |

**Table 3 Confusion matrix for PLSDA with Addiction and Comorbidities subgroup of features**

The VIP and ROC plots for the combined descriptor set (Addiction and Comorbidities) are presented in fig. 6 and 7.

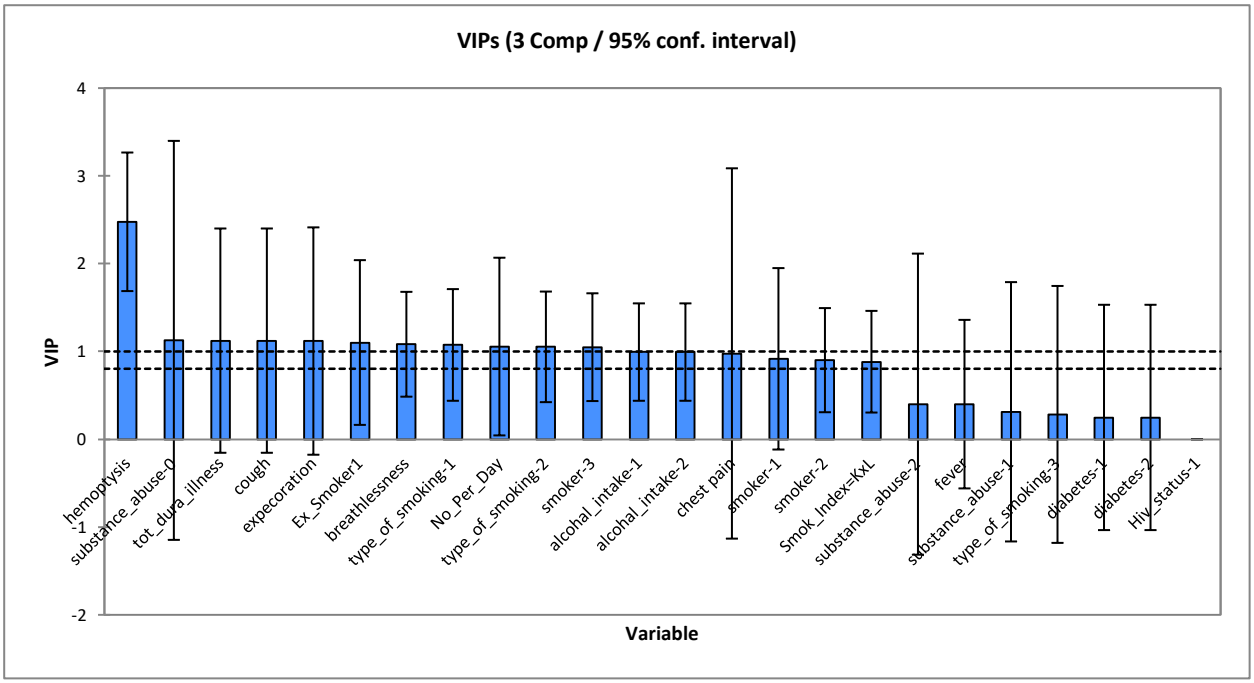


**Fig. 6 Variable Importance Plots for the three components of PLSDA with Addiction and Comorbidities subgroup of descriptors.**



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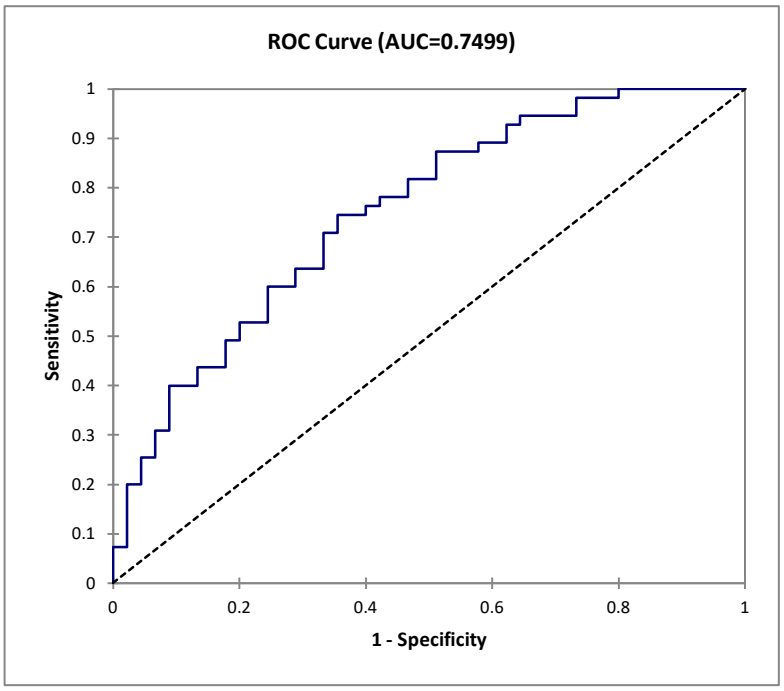


**Fig. 7 ROC for the PLSDA model with Addiction and Comorbidities subgroup of features.**

Observing the VIP charts (fig 6), it can be concluded that hemoptysis, substance abuse, total duration of illness, cough and expectoration are the five most important variables for the model.

**Discussion and Conclusion:**

The medicinal presentation of Aspergillus lung disease is determined by the collaboration between fungus and host.

CPA has only recently been recognised as a significant global health burden and its incidence appreciated [11]. It is associated with significant morbidity and mortality and the optimal management strategy is not well-defined. Because of the occurrence of reversion, treatment is often long-term or lifelong and consequently may be limited by intolerable side effects or the progress of resistance.

CPA nearly always affects patients and results in the formation of an air-filled cavity or bulla. Other associations include atypical mycobacterial infection, COPD, bronchiectasis, sarcoidosis, previously treated lung cancer, ABPA and pneumothorax. Most patients contain more than one underlying condition [12].

Patients with CPA are usually middle-aged, mostly male, and with constitutional symptoms (weight loss, malaise, sweats, anorexia), chronic productive cough, breathlessness, chest discomfort and occasionally haemoptysis. The latter signifies occurrence of an aspergilloma.. Administration of patients with CPA is often complex by the presence of comorbidities such as advanced COPD that leads to reduced lung reserve.

Current work encompasses the use of machine learning algorithms for developing a discriminatory system for CPA from Non-CPA. Comorbidities are more predictive of CPA as compared to Addictions feature set and the combination of both Comorbidities and Addiction resulted in better performance evaluation metrics for the PLSDA algorithm. The features: hemoptysis, substance abuse, total duration of illness, cough and expectoration are the five most important variables for the model and are strongly associated with CPA. The current work establishes the association of comorbidities and addiction descriptors with CPA achieving an acceptable overall accuracy.

Future work involves the use of higher order feature vectors which can be obtained using deep learning autoencoders and use of class specific feature selection that may facilitate in further enhancing the performance evaluation metrics of the PLSDA classifiers. The features: hemoptysis, substance abuse, total duration of illness, cough and



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expectoration are the five most important variables for the model which are found to be are strongly associated with CPA.

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