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Alcohol use disorders amongst tubercular patients and its association with treatment adherence and outcome: a study at Northern Indian Medical Institution

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ABSTRACT

BACKGROUND: Tuberculosis (TB), a worldwide disease remains the most important problem in India, with 2.69 million new cases per year, comprising over 27% of the global total for incident cases. Alcohol use disorders (AUD) and TB have both been labeled "diseases of poverty", and both can be consequences as well as causes of social marginalization, increased depression and stigma related to this disease. Early detection of alcohol abuse and dependence amongst them provides a critical opportunity for early intervention efforts to reduce adverse impacts of consumption, malnutrition and socio-economic disruption thereby enhancing the success rate of treatment in such patients and impeding its spread in the community.

AIMS AND OBJECTIVES: To identify the association of Alcohol use disorders with treatment adherence and its outcome amongst tubercular patients.

MATERIALS AND METHODS : In this prospective observational study using questionnaire method, newly detected microbiologically confirmed Pulmonary Koch's patients of 15-65 years age group, from October 1, 2017 to December 31,2018(200 cases) presenting to Department of Pulmonary Medicine were considered. Treatment adherence assessed by number of missed doses and followed uptill end of the treatment regimen.

CONCLUSION: AUD leads not only to delay in diagnosis of the disease , but to the late initiation of its treatment, more drug toxicity with poor treatment adherence and outcome leading to increased morbidity and mortality amongst tubercular patients; in addition to the enhanced poverty and malnutrition..

Keywords: Tuberculosis, Alcohol use disorders, Adherence, Outcome, AUDIT, Treatment

INTRODUCTION

TB is a disease responsible for widespread morbidity and mortality around the world. It is one of the top 10 causes of death and remains the leading cause with single most infectious agent known as *Mycobacterium tuberculosis*. It resulted an estimated 1.3 million deaths (range, 1.2–1.4 million) among HIV sero-negative people mainly in countries of Mozambique, the Philippines and South Africa.[1]

Alcohol abuse can lead to ignorance of symptoms of tuberculosis thus with late reporting to doctor, delayed diagnosis and late initiation of disease treatment, thereof. There is documented evidence that patterns of heavy alcohol abuse lead to high smear positivity in patients and the delay in diagnosis and treatment can lead to poor treatment outcomes especially defaulting from treatment. This further leads to increase in TB burden and hence increase the economic costs required in diagnosing and treating the disease.[1,2,3] It has also been noted that time for

sputum conversion had also increased in patients with severe alcohol abuse.[4,5]

Alcohol abuse has been closely associated with poverty, leading to malnutrition. This malnutrition inturn leads to decreased innate and acquired immune response which results in spread of disease influence the complications and poor treatment outcomes. Good nutritional intake results in effective recovery amongst TB patients as has been supported by different studies. [6,7]

Alcohol abuse in addition leads to other substance misuse and contacts with social environments including bars, shelters and prisons, further facilitate the highly infectious tuberculous disease.[8,9] Other substance misuse, especially smoking can further impede immune defences of the body including cardinal macrophage action, thus increasing the severity of the disease. Substance misuse furthermore also can lead to state of homelessness and poor adherence to treatment significantly affecting the outcome.[10,11]

Alcohol's effects on innate immunity are the first pathways on the contributory role for worsened outcomes during treatment. Alcohol has been shown to inhibit phagocytic and bactericidal activity of macrophages [12] It decreases the number and function of dendritic cells [13], also causes a significant increase in cell-associated TNF in macrophages following LPS stimulation decreases proinflammatory cytokine production and the interferon gamma pathway and also increases anti-inflammatory cytokine (IL-10) expression by human monocytes, which has been postulated to be one of the main underlying immunosuppressive effects of alcohol. [14,15]

Heavy alcohol intake or alcohol use disorder has been established to be a risk factor for active TB, contribution of the TB-related morbidity and mortality[16]Effects of alcohol on acquired immunity have also been described especially in Excessive alcohol consumption .The most extensively characterized acquired immune defect caused by alcohol is suppression of Polymorphonuclear leukocyte(PMN) function. Pulmonary recruitment of PMNs in response to bacterial challenge is inhibited by alcohol intoxication in a dose-dependent manner. The dose dependent inhibitory effect on immunity promotes the damaging effects of tuberculosis in chronic alcoholics and heavy drinkers. In addition to reducing T-cell numbers, chronic alcohol exposure disrupts the balance between different T-cell types (i.e., T-cell homeostasis), leading to a shift toward a memory phenotype. decreased frequency of naïve (i.e., CD45RA+) CD4 and CD8 T cells, as well as an increased frequency of memory T cells[17] Excessive alcohol consumption causes undesirable effects on both cell mediated and humoral immunity. The ability to develop delayed hypersensitivity skin test reactions to various antigens is usually poor in alcohol-abusing patients. Immunomodulation may be useful as an adjuvant therapy for the treatment of pulmonary infections in individuals who excessively consume alcohol. Chronic alcohol abusers, especially those with liver disease, frequently develop lymphopenia. [18,19] Alcohol also suppresses lymphocyte blast transformation in response to mitogen stimulation. Lymphocyte proliferative responses to specific antibodies against T-cell receptors are blunted by alcohol. [[20,21]

Chronic heavy drinking is associated with inhibition of phagocytosis and decreased production of growth factors amongst innate immune cells in a time dependent manner suggesting that chronic alcohol use has a greater detrimental effect on the immune response. [22] Alcohol influences on the pharmacokinetics (PK) and pharmacodynamics (PD) of TB drugs, decreases the absorption of drugs in the body further decreasing the bioavailability of anti-tuberculosis medications hence influencing treatment outcomes [23], rather may lead to development of drug resistant tuberculosis (DRTB).

METHODOLOGY:

This prospective and observational study using interview method of AUDIT score was conducted on newly diagnosed, microbiologically confirmed Pulmonary Koch's patients of 15- 65 years age group presenting to Department of Pulmonary Medicine, Government Medical College, Patiala, India over a time period of 15 months from October 1, 2017 to December 31, 2018(200 cases).

Alcohol Use Disorders Identification Test(AUDIT) tool was designed specifically keeping in mind people who would benefit from reducing or ceasing drinking. This was because alcohol was responsible for a number of disorders, injuries, social and legal problems in addition to communicable diseases

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including tuberculosis. The risks were dependent on severity of alcohol abuse and the population screened were grouped into 'hazardous', 'harmful' and 'dependence' groups .AUDIT screening can be administered as questionnaire form method or interview method. Interview method being preferred as it can be administered to illiterate people. The overall advantages of AUDIT being that there is a cross-nation standardization, is brief and rapid, intended for primary health care workers with focus on recent alcohol use.[24]

Microbiologically confirmed pulmonary tuberculosis cases as included in this study were defined as those cases that are detected positive by sputum Ziehl-Neelsen staining for acid fast bacilli or by Fluorescent microscopy.

Screening and grading of alcohol use disorders was done based on AUDIT scoring system, with minimum AUDIT Score being 8.

Treatment adherence assessed by number of missed doses. If the patient has missed one week treatment in a month in any phase is considered to be treatment non adherent (either sporadic or consecutive doses totaling a week).

Patients were followed up by direct interview after initiating the prescribed treatment regimen till the end of treatment (minimum 6 months, more if intensive phase is extended) under Revised National Tuberculosis Control Programme Guidelines in the country. Patients were contacted at the end of Intensive Phase(IP), extended IP, if any and Continuation Phase(CP),accordingly.

Long term treatment outcome was decided at the end of treatment period.

Regarding alcohol abuse by patients, the different categories that were outlined were: 'Hazardous': AUDIT score 8-16; 'Harmful': Score 16-20; 'Dependence': Score >20. Alcohol drink of 30 milliliter measure each was taken as standard for AUDIT score.

Patients with sputum negative pulmonary TB and extra pulmonary TB were excluded from the study.

Prior approval for this prospective study was granted by the Institutiional Ethics Committee (IEC).

RESULTS:

THE TABLE 1: AGE DISTRIBUTION OF THE SAMPLE POPULATION

AGE CATEGORY	n (%)
10 – 19	3 (1.5)
20 – 29	44 (22)
30 – 39	44 (22)
40 – 49	41 (20.5)
50 – 59	49 (24.5)
60 – 69	19 (9.5)
Total	200 (100)

Age of the participants ranged between 18 and 63. The mean ± SD of the age was 40.9 ± 12.8.Majority of the study population was from the age group 50-59 years,n=49(24.5%)[TABLE 1][FIG1]

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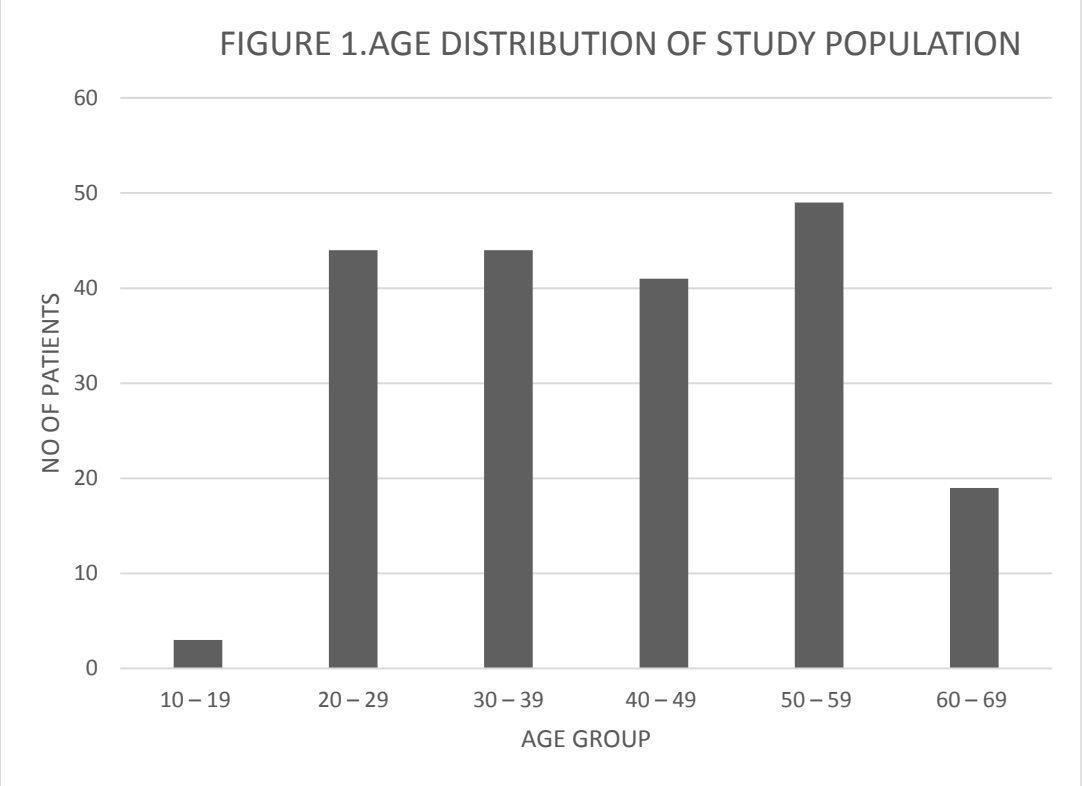

TABLE 2: DISTRIBUTION OF THE SAMPLE BASED ON SEVERITY OF ALCOHOL USE.

Based on addiction severity the sample was classified to three groups.

SEVERITY OF ALCOHOL USE	**n (%)**
Hazardous	169 (84.5)
Harmful	28 (14)
Dependence	3 (1.5)
Total	200 (100)

The AUDIT score of the participants ranged from 8 to 21 with median (Interquartile range IQR) as 10.5 (9, 12.5).

Majority of the study group belonged to hazardous use group n=169(84.5%)[TABLE 2]

TABLE 3: DISTRIBUTION OF THE SAMPLE BASED ON DURATION OF SYMPTOMS.

SYMPTOM DURATION	**n (%)**
Less than 15 days	4 (2)
15 days to 2 Months	83 (41.5)
2 Months to 6 Months	108 (54)
More than 6 Months	5 (2.5)
Total	200 (100)

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The most common time period of reporting symptoms was between 2 months and 6 months,n=108(54%)[TABLE 3]

TABLE 4: ADDICTION SEVERITY AND NUTRITIONAL STATUS

ADDICTION SEVERITY	UNDERWEIGHT (%)	NORMAL (%)	OVERWEIGHT (%)	TOTAL (%)
Hazardous	107 (63.3)	60 (35.5)	2 (1.2)	169 (100)
Harmful	25 (89.3)	3 (10.7)	0 (0)	28 (100)
Dependence	3 (100)	0 (0)	0 (0)	3 (100)

Undernourishment was seen in majority of population across all three groups 63.3,89.3,100%.

Nutritional status varied significantly between the different groups with different alcohol abuse severity, more proportion becoming under nourished as the severity of alcohol use increases.

Fisher exact p value = 0.036.[TABLE 4][FIG2]

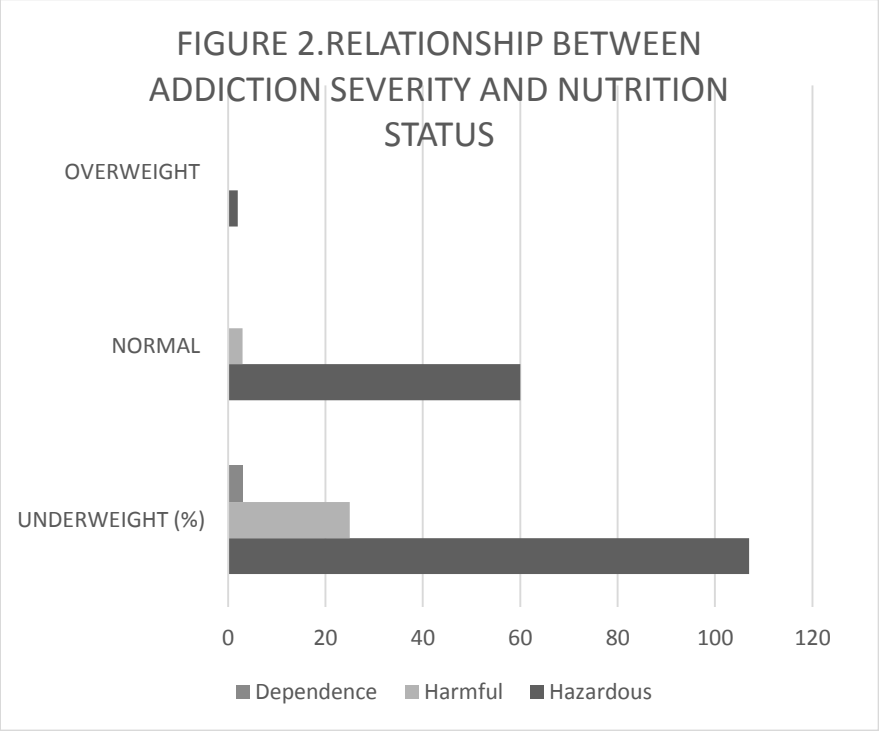

TABLE 5: ADDICTION SEVERITY AND PRESENCE OF HAEMOPTYSIS

Addiction Severity	No (%)	Yes (%)	Total (%)
Hazardous	157 (92.9)	12 (7.1)	169 (100)
Harmful	23 (82.1)	5 (17.9)	28 (100)
Dependence	0 (0)	3 (100)	3 (100)

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Haemoptysis was present in all 3 patients of alcohol dependence. The presence of haemoptysis varied significantly between different addiction severity groups with a fisher exact p value P < 0.001. The groups with more severe addiction showed more incidence of haemoptysis.[TABLE 5]

TABLE 6: DISTRIBUTION OF THE SAMPLE BASED ON ADHERENCE TO ATT.

ADHERENCE	N (%)
Yes	163 (81.5)
No	37 (18.5)
Total	200 (100)

The total adherence among the study population was 81.5 %(n=163)

The number of missed doses ranged from 0 to 16 with median (IQR) of 3 (2, 5).[TABLE 6]

A simple linear regression was calculated to predict number of missed doses based on AUDIT score. A significant regression equation was found (F(1,198) = 213.43, p < 0.001) with an R2 of 0.5187. The predicted number of missed doses is equal to -4.74 + 0.78 x AUDIT Score. The number of missed doses increased 0.78 for each unit increase in AUDIT Score.

ASSOCIATION BETWEEN AUDIT SCORE AND ADHERENCE

Results of the Spearman correlation indicated that there was a significant positive association between AUDIT score and being non adherent to ATT. (rho = 0.5561, p < .001).Results of the logistic regression indicated that there was a significant association between AUDIT Score and being non adherent in treatment ($\chi 2$ (1) = 103.38, p < .001). The odds ratio calculated from the logistic regression model was 2.17 with 95% CI [1.73, 2.73] and p value < 0.001.Which means a unit increase in AUDIT score increases a person's chance to be non-adherent by 2.17 times.

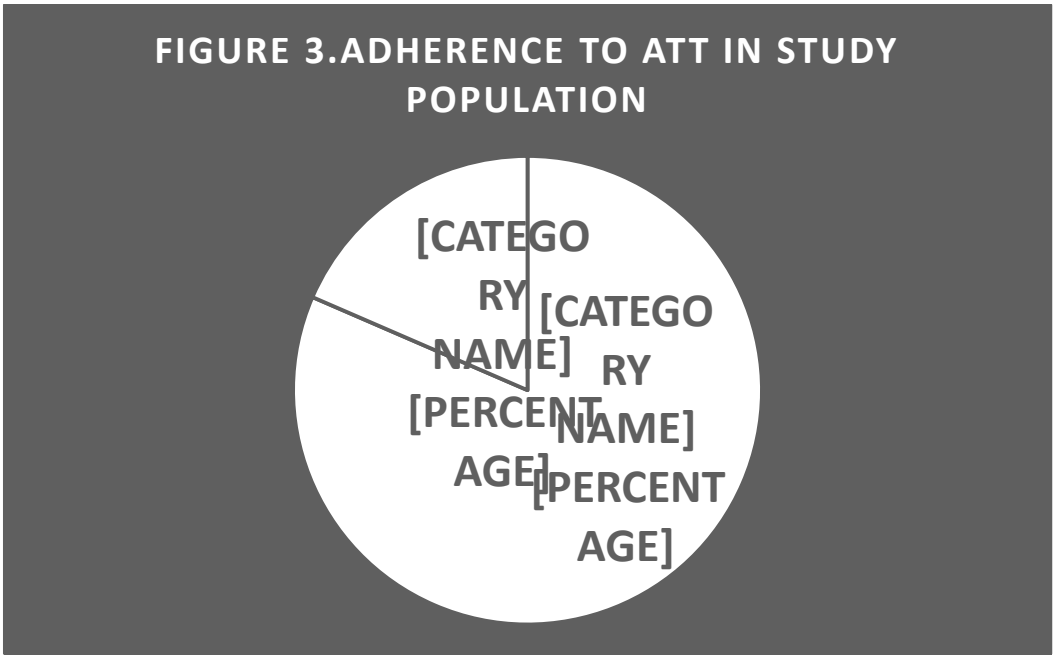

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TABLE 7: DISTRIBUTION OF THE SAMPLE BASED ON LONG TERM OUTCOME.

LONG TERM OUTCOME	N (%)
Treatment completed	97(48.5)
Cured	77 (38.5)
Failed	4 (2.0)
Loss to follow up	16 (8.0)
Regimen Changed	3 (1.5)
Died †	3 (1.5)
Total	200 (100)

Long term outcome: Treatment completed, n=97(48.5 %) followed by cured,n=77(38.5%)[TABLE 7].

† All deaths (n=3) occurred during intensive phase (IP) of treatment regimen.

[FIGURE 4]

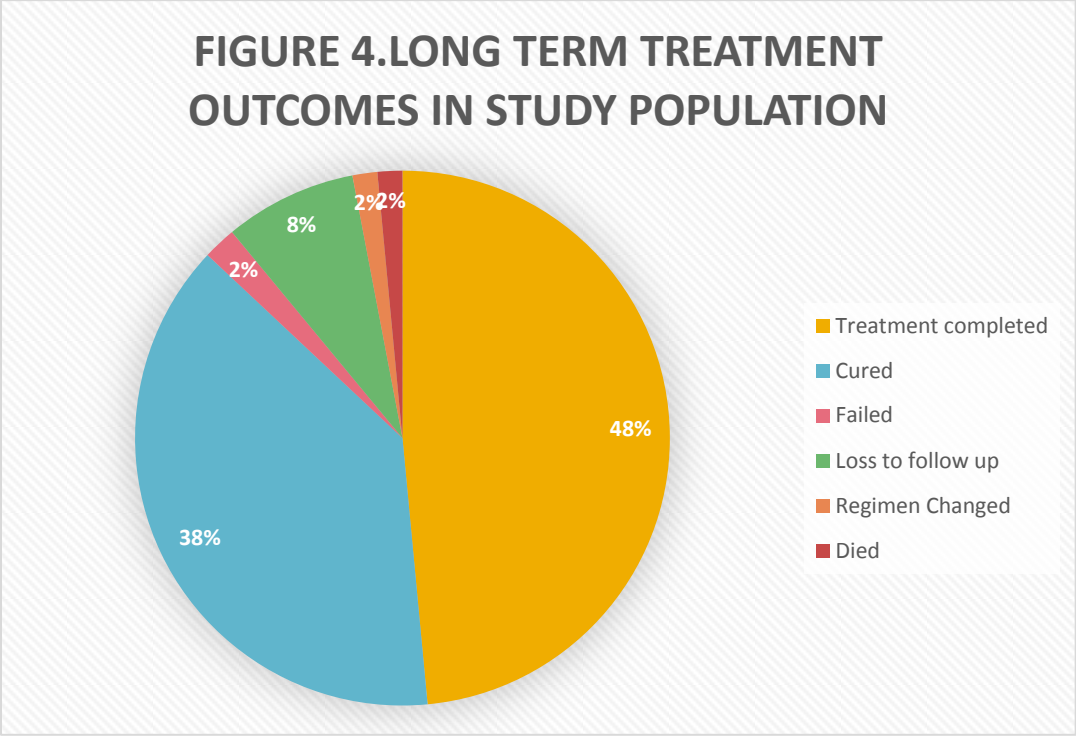

TABLE 8: ASSOCIATION BETWEEN ALCOHOL USE PATTERN AND ADHERENCE TO TREATMENT

ADDICTION SEVERITY	NON ADHERENT (%)	ADHERENT (%)	TOTAL (%)
Hazardous	10 (5.9)	159 (94.1)	169 (100)
Harmful	24 (85.7)	4 (14.3)	28 (100)
Dependent	3 (100)	0 (0)	3 (100)

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Fisher's exact test revealed a significant difference in distribution of adherent and non-adherent participants in the different addiction categories with p value < 0.001, with increased proportion of non-adherence in people with more severe alcohol use pattern.[TABLE 8][FIG5]

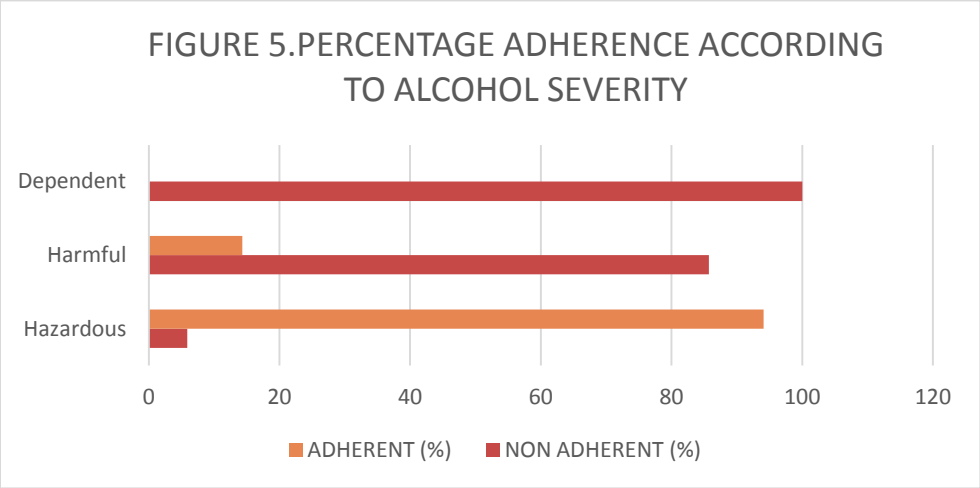


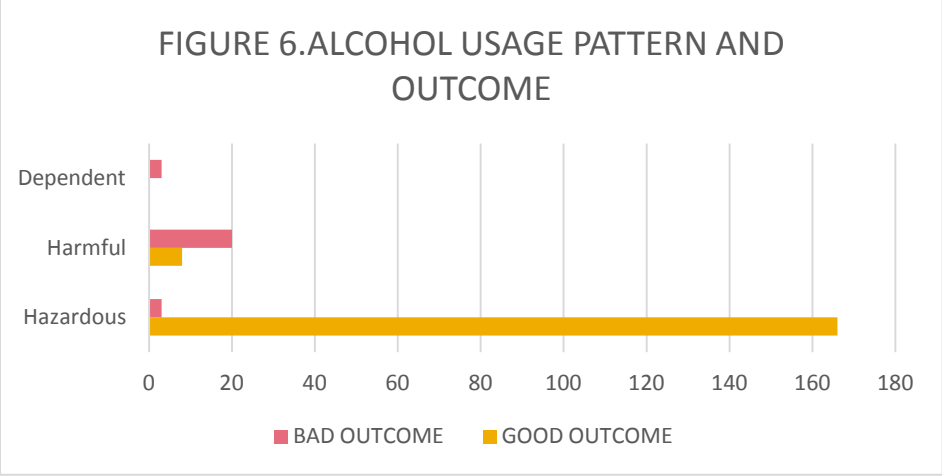
TABLE 9: ASSOCIATION BETWEEN ALCOHOL USE PATTERN AND LONG TERM OUTCOME

ADDICTION SEVERITY	GOOD OUTCOME (%)	BAD OUTCOME (%)	TOTAL (%)
Hazardous	166 (98.2)	3 (1.8)	169 (100)
Harmful	8 (28.6)	20 (71.4)	28 (100)
Dependent	0 (0)	3 (100)	3 (100)

Fisher's exact test revealed a significant difference in distribution of participants with good and bad outcomes in the different addiction categories with p value < 0.001, with increased proportion of bad outcomes in people with more severe alcohol use pattern.

ASSOCIATION BETWEEN AUDIT SCORE AND LONG TERM OUTCOME

Results of the Spearman correlation indicated that there was a significant positive association between AUDIT score and the long term outcome of treatment being bad. (rho = 0.5316, p < .001).Results of the logistic regression indicated that there was a significant association between AUDIT Score and having a bad long term outcome (χ^2 (1) = 103.27, p < .001). The odds ratio calculated from the logistic regression model was 2.53 with 95% CI [1.86, 3.44] and p value < 0.001Which means a unit increase in AUDIT score increases a person's chance to have a bad outcome by 2.53 times.



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About 16% amongst the alcohol abusers (all males) were detected having history of other substance misuses including opium- in form of opium husk (bhukki),cannabis(bhang),heroine, tobacco products(cigarettes, bidis, tobacco chewing, zarda), and injectable drug misuse.

AUD may lead not only to delay in diagnosis of this disease but to the initiation of its treatment at the patient level, ultimately leading to increased TB mortality and morbidity.

DISCUSSION

The role of alcohol in influencing the treatment outcome among tuberculosis treatment has not yet been fully studied. Limited data exist on this correlation of alcohol abuse with treatment adherence and outcome in Indian subcontinent inspite of its hazardous and harmful effects. Such persons are also known to be involved in other 'substance misuse' including opium, cannabis, heroin, cocaine(smack) etc. along with tobacco products including smoking.

As revealed in a report released by the National Crime Record Bureau(NRCB) of the country, this state registered the highest number of drug smuggling cases in the country accounting for one fourth of total drug traffickers caught in 2017.[25]

Sociodemographic parameters

In the present study majority of patients belonged to age group 50-59,whereas in a study conducted by **Kumar S G et al in 2013** [26] it was found that most common age group of alcohol abuse is 15–44 years.The observation reflects that alcohol screening should involve all age groups of population.

Most of the patients reported their symptoms within a duration of 2 to 6 months, n=108(54%).This points towards the time delay for recognition of symptoms by the patient, late reporting to clinician and hence delayed TB diagnosis; increasing disease burden, its severity thus further escalating the financial cost of treatment to patient/family. In a similar alcohol abuse related study by **ELN Maciel in 2010** conducted over 304 patients, 80% patients reported cough of more than 3 weeks duration, with median health care delay being 30 days (5- 68) and median total delay of 110 days.[27] In Ethiopa in **2014 by SA Yimer** et al in another study, detected median time of patients delay in diagnosis as 21 days with patients residing in rural areas having more delay in diagnosis compared to rural area.[28] The findings are well consistent with our study and obviously highlight this delay related to alcohol abuse.

The median AUDIT score calculated from the present study was 10.5, with majority of population being male. **Shin S et al in 2012** calculated the mean AUDIT score to be 14.7 for men which was more than that of women.[29];conforms to our study findings. This depicts the heavy alcohol use pattern amongst males, with the need for targeted interventions.

Haemoptysis was found to be significantly associated with severity of alcohol intake as all the 3 patients having the 'alcohol dependence' in our study presented with this feature. Haemoptysis is unambigiously an indicator of severity of lung involvement as alcohol significantly impairs immune response of a person and can lead to widespread involvement with destructive changes in addition to increasing the chances of person to person droplet nuclei transmission of the disease. The detrimental effects of alcohol on immunity have been elaborated in detail by **Ramakrishnan C V et al in 1961** and **Yamanaka et al in 2001** also .[6,7]

In our study 'hazardous drinking' was the most common drinking pattern, comprising 169 out of 200 patients (84.5%).Whereas the prevalence of hazardous and harmful use of alcohol in the study conducted by **Sau. A in 2017** was 34.5% (95% CI 24.5% to 44.5%) .[30]However, this points towards the rising trends of alcohol use over the the passage of time. That study also revealed that habit and pattern of drinking in high risk level(alcohol dependence) was much higher among men, being hazardous and harmful with statistically significant association.

Development, implementation and enforcement of alcohol control policies have a potential to alleviate harmful use of alcohol, TB associated mortality, TB treatment non adherence has been documented in an increasing number of countries in different continents, including India.[31] Systematic screening for alcohol use and early identification of alcohol use disorders in all patients engaged with prevention and treatment services for TB.

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Prevalence of alcohol use disorders among TB patients have ranged from 10% to 50% in studies carried out in Australia, Canada, Russia, Switzerland, and the USA [32]. There are only a few studies which have assessed alcohol use disorders in tuberculosis patients in low and middle income countries: India 14.9–32% alcohol abusers/alcoholics [33,34]

Health professionals in these settings should be trained to identify not only alcohol use disorders, but also patterns associated with increased risk of negative health consequences including TB-related risks and appropriate interventions and treatment modalities implemented. These may include simple advice and brief interventions or expand to pharmacotherapy of alcohol dependence and referral to specialists for support in organising and implementing structured treatment. Active screening and identification of TB cases among this population, these people should be enrolled in special treatment programmes for alcohol dependence. In a study conducted by **Thomas et al in 2017** The proportion of patients with favourable treatment outcomes was higher in the intervention group.[(35)]

We observed that patients with greater degree of alcohol abuse had greater non adherence to anti tuberculous medication, all patients in alcohol 'dependence group' were non adherent, and 85.7% amongst 'harmful group' were found to be non adherent. A recent study in India also found that persons who consumed alcohol during treatment missed on average 18 doses more (95%CI 13–22) during their intensive phase than those who did not.[36]The possible causes of non adherence could be pre-existing alcoholic liver disease, increased chances of drug induced hepatotoxity, alcohol induced gastritis; all resulting in ATT drug intolerance. Increased alcohol dependence can lead to decreased patient approach to health services; with increased incidence of drug induced liver injury (DILI) as reported in the study conducted by **Abbara A et al** in 2017.[37]

Treatment outcomes when compared with severity of alcohol abuse it was found that 1.8% of patients of hazardous alcohol abuse had bad outcome , with 71 % of patients with harmful alcohol abuse and all the patients(n=3) having alcohol dependence had bad outcome. Three patients of the 'dependence group' i.e. with excessive alcohol intake died while during intensive phase of the treatment.

The findings are in accordance to results acquired from previous studies which highlights the increased chances of bad outcome in patients having greater levels of alcohol abuse. **B E Thomas et al in 2019** found that combined effect of alcohol misuse and smoking had unfavorable treatment outcomes with significantly higher values.[38]This also points out to need to identify the coexistent addictions like smoking. In a study conducted in Kerala by **Duraisamy K in 2014** among 179 MDR patients it was found that 37% had unsuccessful treatment outcomes and the hazard for unsuccessful outcome was significantly higher among alcoholic patients and they missed more doses during treatment [39]

Special attention would need to be paid to high risk groups for these conditions including the homeless, people released from prisons, and those misusing other psychoactive substances such as tobacco and illicit drugs.

CONCLUSION:

Unambiguously, unabated alcohol abuse is bad for health, especially so for a suspected diseased person. It not only leads to late reporting by the patient to the health system, thus delaying the diagnosis but also affects the treatment course and its outcome, especially so in tuberculosis disease. Because anti-tubercular treatment with multiple drug regimen is known for their multi-organotoxic effects on the body. Tolerance to increasing volumes of alcohol abuse is a proven phenomenon with its proportionate enhancing toxicity. Alcohol use disorders lead to noncompliance of the prescribed drug schedule regimen intake by the patient, enhances non adherence, resulting in poor treatment outcome; rather risking the development of drug resistant tuberculosisa serious concern for the patient, family and the community indeed! Associated substance misuse in the form of opium (poppy husk/'bhukki'), cannabis ('bhang', 'sukha'), heroin, cocaine ('smack'), compounded with tobacco addiction in any form (cigarette, 'bidi' ,'hookah', 'zarda') adds to the already worrysome state of affairs;along with poverty and malnutrition amongst such patients.

Therefore, a routine screening especially in high risk groups including homeless, people released from

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prisons, alcohol and drug addicts of all ages needs to be considered as a corrective measure so as to help in early diagnosis of this air borne infectious disease, with effective and early management thus to decrease the morbidity and mortality with the ultimate pan-global goal of End-TB.

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