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Predictors of Complicated Withdrawal in Patients with Alcohol Dependence Syndrome

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Abstract: *Alcohol withdrawal is a common condition in alcohol dependence patients and complicated withdrawal is important as it is associated with seizures and delirium tremens and is reported to have high mortality. Identification of risk factors contributing to the development of complicated withdrawal will help in improving the clinical outcome by providing preventive and early management.*

Aim: *To assess the risk factors for the development of complicated withdrawal in patients with alcohol dependence syndrome.*

Materials and Methods:*This is a cross sectional study. The study subjects included are outpatients and inpatients having alcohol dependence syndrome at Government Hospital for Mental Care, Visakhapatnam.30 male patients diagnosed with alcohol withdrawal seizures and delirium tremens were compared with 30 patients with uncomplicated alcohol withdrawal. The subjects are assessed for sociodemographic profile,drinking characteristics, medical and psychiatric comorbidity.*

Results:*Correlation analysis of sociodemographic and clinical variables across two groups of complicated and uncomplicated alcohol withdrawal were done using MATLAB.Among socio demographic variables, education of the subjects had a statistically significant relationship with the nature of withdrawal with a p-value of 0.0086.Among alcohol use related variables, maximum units of alcohol consumed per dayhas a statistically significant relationship with the nature of withdrawal with a p-value of 0.0083.Finally, among clinically measure variables,Erythrocyte sedimentation rate (ESR) has a statistically significant effect on the nature of withdrawal with a p-value of 0.0357.*

Conclusion: *Maximum units of alcohol consumed, past history of seizure, low education, elevated erythrocyte sedimentation rate and elevated differential count of polymorphs are found to be risk factors for complicated withdrawal. Further prospective study is recommended.*

Keywords:*Alcohol Dependence Syndrome, Complicated Withdrawal, Delirium Tremens, Withdrawal Seizures, Uncomplicated Withdrawal.*

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I. Introduction

Alcohol withdrawal syndrome (AWS) is a common condition that frequently encounters in clinical practice. It arises in alcohol dependent individuals, usually within 24 to 48 hours of last consumption of alcohol.Though many individualspresent with mild symptoms and they can be managed in an outpatient setting, however, some individuals have more severe symptoms [1]. According to [3], 5-20% of alcohol dependent individuals report complicated withdrawal and there are several risk factors associated with complicated withdrawal. Severe alcohol withdrawal includes delirium tremens (DT) and withdrawal seizures (WS)[2]. WS was reported to occur in 6-15% of alcohol dependent individuals [3]. DT is reported to occur in 24 to 33% of hospitalized patients treated for AWS. Also, [2] reports a mortality rate of 0 to 8% among AWS patients in USA. Complicated withdrawal in known to increase morbidity and mortality, worsening of cognitive functioning among persons experiencing withdrawal, associated with longer hospital stay, higher costs, increased the burden on nursing and medical staff [4]. Thus, identification of risk factors contributing to the development of complicated withdrawal will help in improving the clinical outcome by providing preventive and early management. Those having high risk for AWS include high total ethanol consumption, previous history of withdrawal seizures and multiple previous detoxifications. DT risk factors include longer duration

since last alcohol intake, past history of DT, co-morbid medical illness, low albumin, high urea, tachypnea, hypotension [1]. Eyer et al [3] report that significant predictors of WS during alcohol withdrawal syndrome therapy were a delayed climax of withdrawal severity since admission prevalence of structural brain lesions in the patient's history and WS as the cause of admittance. Significant predictors at admission for the occurrence of DT a lower platelet count and structural brain lesions. Sarkar et al., [5] heavy drinking,continuous pattern of drinking, past history of delirium, alcohol‐ induced psychosis, and presence of cognitive deficits emerged as strong predictors of alcohol withdrawal delirium. The purpose of this study is to identify the possible predictors for complicated withdrawal which might have important preventive and therapeutic implications.

II. Methodology

The study was a cross-sectional comparative study conducted in Government Hospital for Mental Care, Visakhapatnam. The subjects included were inpatients diagnosed with alcohol dependence syndrome in withdrawal state according to International Classification of Diseases-10 (ICD-10) criteria, undergoing detoxification treatment. Sampling method is convenience sampling. Inclusion criteria for selecting subjects consisted of choosing individuals with AWS, who are above 18 years and had given consent to participate in the study. No specific exclusion criteria were considered, except for those who had not consented to participate in the study. The subjects were divided into 2 groups: Group A and Group B. Group A consists of 30 subjects with complicated alcohol withdrawal. This group included those presenting withDT and/orWS. Group B consists of 30 subjects presenting with uncomplicated alcohol withdrawal. A structured self socio-demographic pro-forma was used to record socio-demographic profile with age, gender,education, employment, socioeconomic status, religion, marital status, and domicile.Other important variables like, family history of substance use, alcohol use parameters, hematological and biochemical data at the time of assessment were also recorded for each subject. The whole dataset was de-identified to preserve privacy of the subjects. Correlation analysis of sociodemographic and clinical variables across two groups of complicated and uncomplicated alcohol withdrawal were performed by evaluating Pearson's correlation coefficients. Statistical significance was determined based on p-values less than 0.05.Apart from correlation analysis, we also used least absolute shrinkage andselection operator (LASSO) for variable selection and logistic regression for building our predictive model. We used tenfold cross validation to evaluate the sparsest model within one standard error of the minimum mean squared error.All statistical calculations and operations were carried out using MATLAB (2014a).

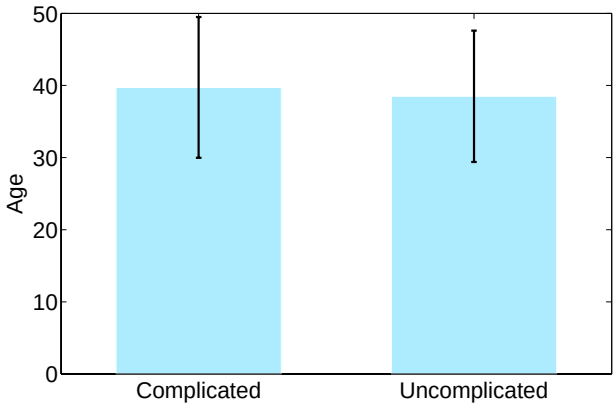


Figure 1: Comparison of age across two groups

III. Results

All the subjects in our study were male and they were between the ages of 25 and 67 years. The mean age of subjects with complicated withdrawal was 39.73 years (standard deviation (SD)of 9.76 years), whereas the mean age of subjects with uncomplicated withdrawal was 38.5 years (SDof 9.11 years). Comparison of two groups with respect to age is shown in figure 1. Age of subjects had no statistically significant influence on the nature of withdrawal as the p-value was 0.6149> 0.05.**Education** of the subjects had a statistically significant relationship with the nature of withdrawal with a p-value of 0.0086. Education level of the subjects was discretized into two categories as: *Middle school and below, High school and above*. Majority of the subjects with complicated withdrawal had belonged to the *Middle school and below*category. Majority of subjects with uncomplicated withdrawal had higher education levels and belonged to the *High school and above* category. Thus, establishing education level as a good predictor of nature of alcoholic withdrawal. Most of the subjects from both groups A and B, belonged to a rural background and had lower socio-economic status. Majority of the

subjects from both groups were employed and married.Distribution and comparison of all the socio-demographic variables measured are presented in Table 1.

The mean age of initiation of alcohol consumption for subjects with complicated withdrawal was 24.6 years (SD of 9.90 years) and that of subjects with uncomplicated withdrawal was 23.83 years (SD of 7.21 years). Mean duration of alcohol intake for subjects with complicated withdrawal was 14.43 years (SD of 6.54 years) and the mean duration of alcohol intake for subjects with uncomplicated withdrawal was 14.96 years (SD of 7.34 years). Mean duration of daily alcohol intake for subjects with complicated withdrawal was 7.51 years (SD of 4.70 years) and the mean duration of daily alcohol intake for subjects with uncomplicated withdrawal was 7.51 years (SD of 6.38 years). Mean duration of early morning alcohol intake for subjects with complicated withdrawal was 4.55 years (SD of 4.02 years) and for subjects with uncomplicated withdrawal was 3.25 years (SD of 3.26 years). Mean duration of experiencing previous withdrawal syndrome for subjects with complicated withdrawal was 5.05 years (SD of 4.11 years) and for subjects with uncomplicated withdrawal was 4.18 years (SD of 3.23 years). It can be observed that all the above mentioned alcohol use related variables have similar means and standard deviations across both groups. Hence, none of these variables are good indicators or discriminating between complicate or uncomplicated withdrawals. This observation can be substantiated by their p-values, which were all higher than 0.05. However, the variable: **maximum units of alcohol consumed per day**has a statistically significant relationship with the nature of withdrawal with a p-value of 0.0083. It can be observed that mean value of maximum units of alcohol consumed per day for complicated withdrawal is 18.48 units (SD 10.14 units) and the mean value of maximum units of alcohol consumed per day for uncomplicated withdrawal is 11.83 units (SD 8.65 units). Hence, higher the maximum units of alcohol consumed per day for an individual, higher are the chances that the individual will have complicated withdrawal symptoms. This trend is illustrated through a boxplot in Figure 2. All these alcohol use related variables which have numerical values are compared in in Table 2.

Socio-Demographic Variables	Complicated (N=30)	Uncomplicated (N=30)	p-value
Education			
• Middle school and below	22	12	0.0086*
• High school and above	8	18	
Domicile			
• Rural	22	22	1.0000
• Urban	8	8	
Socioeconomic status			
• Lower	22	20	1.000
• Middle	6	10	
• Upper	2	0	
Employment status			
• Employed	21	23	0.5670
• Unemployed	9	7	
Marital status			
• Unmarried	2	1	0.7948
• Married	28	26	
• Separated	0	2	
• Divorced	0	1	

Table 1: Distribution and comparison of socio-demographic variables across two groups

Clinical Variables (Numerical)	Complicated (N=30)	Uncomplicated (N=30)	p-value
Age of initiation (years)	24.60 (9.90)	23.83 (7.21)	0.7330
Duration of alcohol intake (years)	14.43 (6.54)	14.96 (7.34)	0.7676
Duration of daily intake (years)	7.51 (4.70)	7.51(6.38)	1.0000
Duration of early morning intake (years)	4.55 (4.02)	3.25 (3.26)	0.1744
Maximum units of alcohol consumed perday	18.48 (10.14)	11.83 (8.65)	0.0083*
Duration of withdrawal Syndrome	5.05 (4.11)	4.18 (3.23)	0.3709

Table 2: Distribution and comparison ofnumerical alcohol use variables across two groups

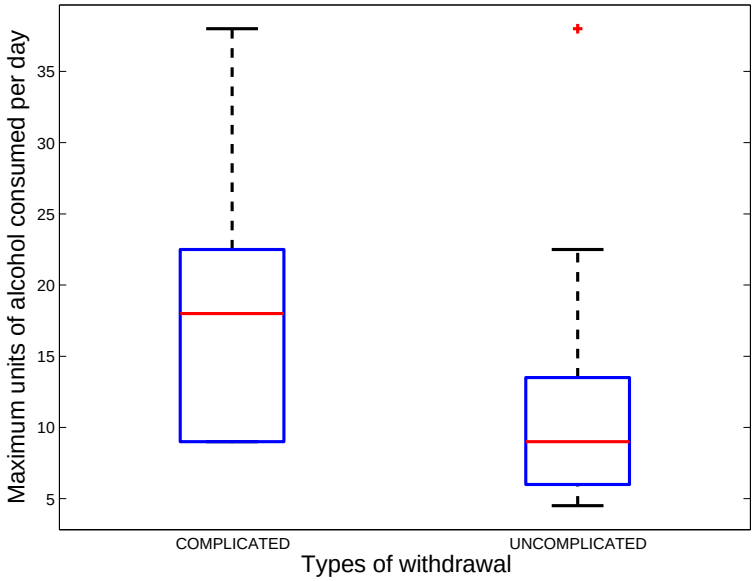


Figure 2: Boxplot showing alcohol consumption for both COMPLICATED and UNCOMPLICATED withdrawal symptoms

All the alcohol use related variables which have categorical values are compared for both groups in Table 3.For the complicated withdrawal group, 53.33% subjects had a family history of alcohol intake and the rest did not. For the uncomplicated withdrawal group, 56.67% subjects had a family history of alcohol intake and the rest did not. For the complicated withdrawal group, 33.33% subjects had an episodic pattern of alcohol intake and the rest had a continuous pattern of alcohol intake. For the uncomplicated withdrawal group, 20% subjects had an episodic pattern of alcohol intake and the rest had a continuous pattern of alcohol intake. For the complicated withdrawal group, 43.33% subjects had a history of withdrawal seizures and the rest did not. For the uncomplicated withdrawal group, 20% subjects had a history of withdrawal seizures and the rest did not. For the complicated withdrawal group, 16.67% subjects had a history of delirium tremens and the rest did not. For the uncomplicated withdrawal group, 6.67% subjects had a history of delirium tremens and the rest did not.

Clinical Variables (Categorical)	Complicated (N=30)	Uncomplicated (N=30)	p-value
Family history of alcohol intake			
• YES	16	17	0.7994
• NO	14	13	
Pattern of drinking			
• Episodic	10	6	0.2502
• Continuous	20	24	
History of withdrawal seizures			
• YES	13	6	0.0533
• NO	17	24	
History of delirium tremens			
• YES	5	2	0.2347
• NO	25	28	
Medical Comorbidity			
• YES	8	6	0.5495
• NO	22	24	

Table 3: Distribution and comparison of categorical alcohol usevariables across two groups

For the complicated withdrawal group, 26.67% subjects had medical comorbidity and the rest did not. For the uncomplicated withdrawal group, 20% subjects had medical comorbidity and the rest did not.

Clinical Measurements (Numerical)	Complicated (N=30)	Uncomplicated (N=30)	p-value

Systolic BP (mm of Hg)	136.3 (23.5597)	129.0 (16.2629)	0.1659
Diastolic BP (mm of Hg)	87.3 (14.6059)	85.3 (12.2428)	0.5677
Pulse rateper minute	93.9 (13.8910)	89.9 (14.7436)	0.2839
Respiratory rate per minute	21.1 (4.0321)	20.2 (1.9667)	0.2427
Temperature (F)	99.2 (1.2542)	98.9 (0.4747)	0.1327
Hemoglobin (%)	12.3 (1.4943)	12.3 (1.4379)	0.8885
Total WBC count	8046.7 (838.6086)	8013.3 (752.8032)	0.8719
Differential count			
Polymorphs	60.73(4.28)	58.76 (3.35)	0.0526
Lymphocytes	34.9(7.7431)	37.2 (4.0179)	0.1600
Eosinophils	5.2 (2.3693)	4.2 (1.5906)	0.0686
Erythrocyte sedimentation rate	27.3 (20.6346)	17.2 (15.2098)	0.0357*
Random blood sugar (mg/dl)	128.4 (36.5822)	133.5 (51.9235)	0.6638
Serum creatinine (mg/dl)	1.0 (0.1012)	1.0 (0.1188)	0.4856
Total bilirubin (mg/dl)	0.5 (0.2976)	0.5 (0.3229)	0.5353
SGOT (IU)	79.3 (71.4978)	61.5 (67.1559)	0.3244
SGPT (IU)	76.0 (72.7997)	59.3 (73.7705)	0.3811

Table 4: Distribution and comparison of clinical variables across two groups

All the clinical variables are compared in Table 4. The mean value of systolic BP for subjects with complicated withdrawal is 136.3mm of Hg (SD of 23.5597) and that of subjects with uncomplicated withdrawal is 129.0 mm of Hg (SD of 16.2629).The mean value of diastolic BP for subjects with complicated withdrawal is 87.3 mm of Hg (SD of 14.6059) and that of subjects with uncomplicated withdrawal is 85.3 mm of Hg(SD of 12.2428). The mean value of pulse rate per minute for subjects with complicated withdrawal is 93.9 (SD of 13.8910) and that of minute for subjects with uncomplicated withdrawal is 89.9 (SD of 14.7436). The mean value of respiratory rate per minute for subjects with complicated withdrawal is 21.1(SD of 4.0321) and that of subjects with uncomplicated withdrawal is 20.2 (SD of 1.9667). The mean value of body temperature for subjects with complicated withdrawal is 99.2 F (SD of 1.2542) and that of subjects with uncomplicated withdrawal is 98.9 F (SD of 0.4747). The mean value of haemoglobin for subjects with complicated withdrawal is 12.3 % (SD of 1.4943) and that of subjects with uncomplicated withdrawal is 12.3 % (SD of 1.4379). The mean value of total WBC count for subjects with complicated withdrawal is 8046.7 (SD of 838.6086) and that of subjects with uncomplicated withdrawal is 8013.3 (SD of 752.8032).For the group with complicated withdrawal, the mean values of the differential counts for polymorphs, Lymphocytes, Eosinophils are 60.73 (SD of 4.28), 34.9 (SD of 7.7431) and 5.2 (SD of 2.3693) respectively. For the group with uncomplicated withdrawal, the mean values of the differential counts for polymorphs, Lymphocytes, Eosinophils are 58.76 (SD of 3.35), 37.2 (SD of 4.0179)and 4.2 (SD of 1.5906) respectively. The mean value of random blood sugarfor subjects with complicated withdrawal is 128.4 mg/dl(SD of 36.5822) and that of subjects with uncomplicated withdrawal is 133.5 mg/dl(SD of 51.9235). The mean value of serum creatininefor subjects with both complicated withdrawal and uncomplicated withdrawaluncomplicated withdrawal is 1mg/dl (with SD of 0.1012 and 0.1188 respectively). The mean value of total bilirubinfor subjects with complicated withdrawal is 0.5mg/dl (SD of 0.2976) and that of subjects with uncomplicated withdrawal is 0.5mg/dl (SD of 0.3229). The mean value of SGOT for subjects with complicated withdrawal is 79.3 (SD of 71.4978) and thatof subjects with uncomplicated withdrawal is 61.5 (SD of 67.1559). The mean value of SGPT for subjects with complicated withdrawal is 76.0 (SD of 72.7997)and that of subjects with uncomplicated withdrawal is 59.3 (SD of 73.7705).**Erythrocyte sedimentation rate (ESR)**has a statistically significant effect on the nature of withdrawal with a p-value of 0.0357. Higher values of ESR indicates higher chances of complicated withdrawal and it is illustrated in the boxplot in Figure 3. In our study, the mean value of ESRfor subjects with complicated withdrawal is 27.3 (SD of 20.6346) and the mean value of ESR for subjects with uncomplicated withdrawal is 17.2 (SD of 15.2098).

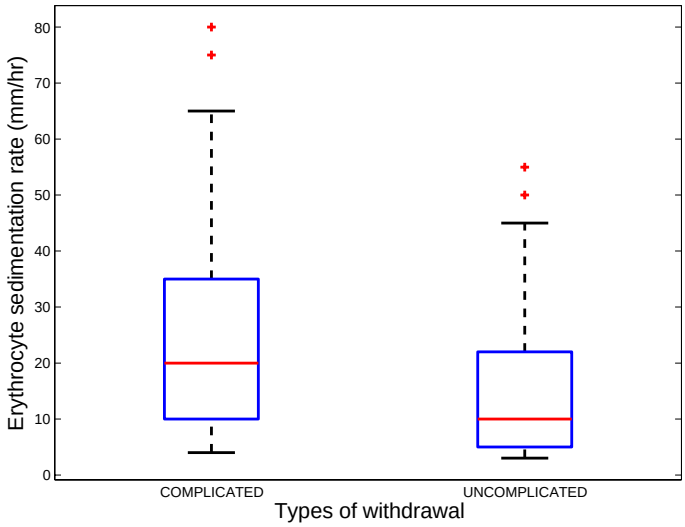
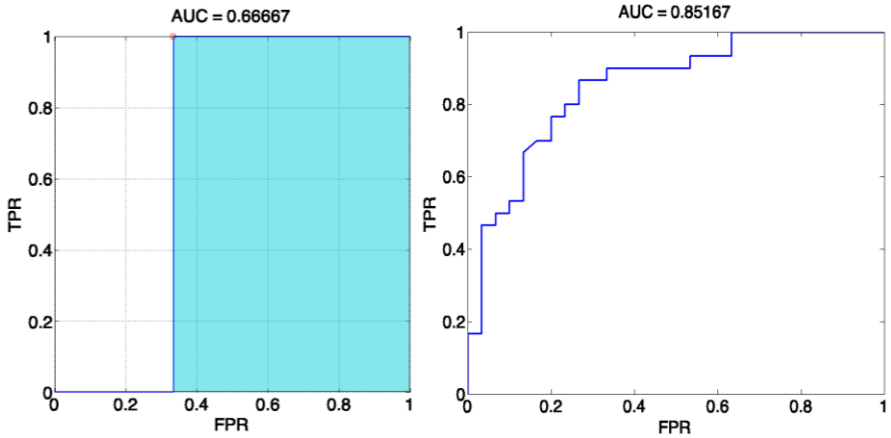


Figure 3: Boxplot showing Erythrocyte sedimentation rate for both COMPLICATED and UNCOMPLICATED withdrawal symptoms

IV. Variable selection and model performance

All the data was randomly split into training dataset (80%) and test dataset (20%). The training set was used for variable selection and model training. Prediction accuracy was assessed on the test set. Using LASSO, we chose the sparsest possible model within one standard deviation of the minimum mean squared error. In total five variables with non-zero coefficients were chosen as predictor variables: {Education (EDU), Maximum units of alcohol consumed per day (MAXAMT), History of seizures (HOWSEIZ), Differential countof Polymorphs (P), Erythrocyte sedimentation rate (ESR} for a logistic regression model. From our correlation analysis, we can observe that EDU, MAXAMT and ESR already exhibited a statistically significant relationship with the nature of withdrawal. However, LASSO variable selection approach also chooses the variables HOWSEIZ and P. Selection of these variables is not spurious, because their p-values (0.0533 for HOWSEIZ and 0.0526 for P) were relatively closer to 0.05.

The logistic regression model for classification of subjects with AWS into groups of complicated and uncomplicated was built using the five variables from the train dataset and it was tested on the test dataset. Receiver operating characteristics (ROC) curve were plotted as shown in Figure 4 a. The area under the curve (AUC) for the classification model was 0.6667. For an optimal threshold of 0.0245, sensitivity of the model was 100% specificity was 66.67%, accuracy was 83.33%, positive predictive value (PPV) was 75% and negative predictive value (NPV) was 100%. ROC curve for the logistic regression model built on the entire dataset, resulting in AUC of 0.8518, is also plotted Figure 4 b. All the five predictor variables were individually analysed for their effect on the nature of withdrawal during our correlation analysis and their p-values are: {Education (EDU) : 0.0086, Maximum units of alcohol consumed per day (MAXAMT) : 0.0083 , History of seizures (HOWSEIZ) : 0.0533,Differential countof Polymorphs (P) : 0.0526, Erythrocyte sedimentation rate (ESR) : 0.0357}. We also analyzed each of one these variables for their discriminative power by calculating AUC for each predictor variable when used alone. Their individual AUC values are:{Education (EDU): 0.6667, Maximum units of alcohol consumed per day (MAXAMT): 0.7466, History of seizures (HOWSEIZ): 0.6167,Differential countof Polymorphs (P): 0.6455, Erythrocyte sedimentation rate (ESR): 0.6577}.



(a) (b)

Figure 4: ROC curves for models built on training dataset and the entire dataset.

V. Discussion

Severe form of alcohol withdrawal syndrome in which, those presenting with alcohol withdrawal seizures and DT are reported to be associated with significant morbidity and mortality. Hence early identification and pharmacological intervention will help in reducing these conditions. Complicated alcohol withdrawal is a difficult variable to predict. Several studies have exploredthe association between complicated withdrawal and measured variables like *clinical*, *biochemical* and *sociodemographic* factors.

In this study, age was not a significant factor in determining the severity of withdrawal. Subjects in this study have approximately similar ages (mean ages of 39.73 years and 38.5 years in group A and B respectively). This is in accordance with a number of previous studies [2,3,6,7,8,10,11]. This is in conflict with some of the studies [12,13,14]. Lukan et al., state that higher age can be a significant risk factor because it may indicate tolerance, longer duration and higher amount of alcohol intake, and may be associated with medical co-morbidities worsened physical condition [13]. Bower et al.[14], reported that elderly patients had significantly more severe alcohol withdrawal symptoms, that lasted longer compared to younger population. Other socio-demographic variables of domicile, socioeconomic status, marital status and employment status were not found to be predictive of complicated withdrawal. This finding is similar to that of several studies. However, in this study education is found to be a significant predictor of complicated withdrawal. Individuals with lower education levels have complicated withdrawal symptoms. Similar results were reported by Prior et al., [15], whereby statistically significant relationship was observed between education levels anda predisposition to alcohol dependence.Illiterate individuals, subjects with lower education levels and early dropouts may not have an exposureto an anti-drug or an anti-alcohol perspective and that can be a reason for higher rates of substance abuse. Schnohr et al., [16] reported a relationship between education level and substance abuse and state that individuals with low levels of educations often suffer from heavy dependence on smoking, drinking, physical inactivity and obesity.

Among alcohol related variables maximum amount of alcohol consumed per day is found to be a significant predictor of complicated withdrawal. This finding is in agreement with previous studies [5,8,11,18,19]. There are other studies that did not show any such correlation [12,20]. Large quantities of alcohol disrupt neuronal stability leading to greater vulnerability for development of delirium. Also, exposure to high quantity of alcohol causes up-regulation of N- methyl- D- aspartate (NMDA) receptors, there-by leading to severe hyper-excitability of brain ending with delirium [5]. Toxic effects of alcohol acting over months to years on brain leads to lowering of person's seizure threshold [19].No relation between complicated withdrawal and pattern of drinking, duration (in years) of consumption of alcohol or duration of experience of withdrawal syndrome was found in this study.

History of withdrawal seizures was found to be a significant predictor of complicated withdrawal in this study. This is in accordance to a number of studies [2,3,8,9,17,20]. Monte R et al.[8], report that the presence of epileptic seizures at diagnosis of uncomplicated withdrawal syndrome and the number of seizures, was associated with eventual development of DTs. A study by Fiellin et al. [9], report that those who developed DT were more likely to report prior alcohol withdrawal seizures, a history of DT or both. Brown et al. [17] report past history of alcohol withdrawal seizures as a best predictor of susceptibility to subsequent withdrawal seizure [21]. Most frequently mentioned theories regarding this is kindling phenomenon, a condition where, following repeated sub threshold electrical stimulation sin the past, the brain is likely to demonstrate progressively more severe motor overactivity [22]. Both animal and human studies shown a higher chance of having severe AWS in individuals who had a greater number of withdrawal episodes in the past [3]. Pattern of

drinking is not found to be a significant predictor of complicated withdrawal, though a study done be Sarkar et al, report that continuous pattern of drinking is found to be predictive of occurrence of delirium in alcohol withdrawal [5]. A history of delirium tremens was shown to be predictive of complicated withdrawal in few studies [5,6,18,23], but not in this study. History of medical comorbidities is also not found to be predictive of complicated withdrawal. Fiellin et al.[9], report that individuals who developed delirium tremens were more likely to have medical comorbidity (diabetes mellitus, coronary artery disease, hypertension, and chronic obstructive pulmonary disease) compared to controls.

Among the vitals and biochemical parameters considered in the study, differential count of polymorphs, erythrocyte sedimentation ratewas found to be significant predictors of complicated withdrawal. Several other parameters have been found to be significantly predictive of complicated withdrawal in various other studies for example thrombocytopenia [2,3,10], low serum potassium level [2,12], lower mean sodium level [17], higher serum alanine transaminase level [2,11,12], elevated serum GGT [2,12], high blood homocysteine and low blood pyridoxine level [10] elevated systolic blood pressure [8,9], elevated pulse rate [6,17,23], elevated axillary temperature [8]. No such correlations were found in this study, and some of these parameters were not assessed in the current study.

The study has limitations of having a small sample. This study is a cross-sectional study; a prospective study would have been even more informative. More biochemical and other clinical parameter could be included in the assessment. Although the current study is more focused on identifying risk factors that can be easily identified in clinical history, thus helping in early identification, anticipation thus prevention and early management of complicated alcohol withdrawal.

VI. Conclusion

Complicated alcohol withdrawal is known to be associated with significant morbidity and mortality. Hence prevention is more preferable than management of such. This study is a cross-sectional study conducted in psychiatry department, included subjects admitted with alcohol withdrawal to assess for possible predictors that help anticipate the subsequent development of complicated withdrawal. Two separate groups consisting of those presenting with complicated (delirium tremens and/or alcohol withdrawal seizures) and those presenting with uncomplicated alcohol withdrawal were compared. Correlation analysis between the two groups revealed that low education, elevated erythrocyte sedimentation rate and maximum amount of alcohol consumed per day were found to be predictors. Logistic regression analysis added 2 other predictors i.e., past history of seizures and differential count of polymorphs.

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