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RESEARCH ARTICLE

TO STUDY THE HEMATOLOGICAL PROFILE IN PATIENTS WITH ALCOHOLIC LIVER CIRRHOSIS IN A TERTIARY CARE HOSPITAL IN MANIPUR

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Abstract

Introduction: Alcoholic liver disease or alcohol-related liver disease (ALD) is damage to the liver caused by excessive alcohol consumption, resulting in serious and life-threatening complications such as cirrhosis, gastrointestinal bleeding, hepatic failure, hepatic encephalopathy and malignancy. Liver cirrhosis is defined as diffuse hepatic fibrosis with replacement of normal liver architecture by nodules. There are also lesser known sequalae including suppression of hematopoiesis due to its toxic effects, hypersplenism and nutritional deficiencies of folic acid and other vitamins. Anemia, leukocytosis, leucopenia and thrombocytopenia occurs in ALD. Most of these hematological parameters are underdiagnosed and understudied. Hence, Manipur being a high ALD prevalence state necessitates this study to evaluate the hematological profile in patients with alcoholic liver cirrhosis and to determine the association between various hematological parameters and different Model of End stage Liver Disease (MELD) scores.

Methods: This cross-sectional study was conducted in Regional Institute of Medical Sciences (RIMS), Imphal, Manipur from January 2021 to October 2022.Alcoholic liver cirrhosis patients above 18 years attending Medicine OPD, Liver clinic and those admitted in Medicine ward were enrolled. Blood samples for complete Hemogram, liver function test, kidney function test, prothrombin time, INR, serology (HbsAg, Anti HCV Ab, HIV 1&2) and ANA were collected. Ultrasound whole abdomen and Chest X ray were done whenever indicated. Different types of anemia, leucopenia, leukocytosis, thrombocytopenia in different groups of MELD scores were studied.

Result: A total of 146 alcoholic liver cirrhosis patients were enrolled in our study. The mean ± SD age of the patients was 48.63±10.00 years with majority males (91.8%). Anemia detected in >95% of the patients. Severe anemia was detected in 31.5%, moderate anemia in 49.3% and mild anemia in 15.1%. Most of them (47.9%) had leucocytosis and thrombocytopenia was seen in 78.1% patients. Prolonged PT was seen

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in 89.1% of the patients and elevated INR present in 69.9% of patients. Majority of patients had MELD score between 10-19 and 20-29 (34.2% each). Only 4.1% had MELD score > 40. There is statistically significant association between MELD score of the patients with severity of anemia ($p<0.05$) and leucocyte count while it is not significant with thrombocytopenia ($p=0.139$).

Conclusion: The prevalence of anemia in the present study was found to be 94.9% with predominant normocytic normochromic anemia (71.2%). There is significant association between MELD score of the patients with severity of anemia and leukocytosis while association with thrombocytopenia was insignificant. This study can now determine the stage at which emergent intervention could help in the recovery and effectively reduce morbidity and mortality of alcoholic cirrhosis patients.

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Introduction:-

Alcohol is the world's third largest risk factor for most disease burden. Harmful use of alcohol results in about 3.5 million deaths worldwide each year, most of the mortality attributed to alcohol is secondary to cirrhosis.[1]Its toxic effects are dose dependent and usually occurs only in people with prolonged alcoholism. These patients also may suffer from nutritional deficiencies of folic acid and other vitamins that play a role in hematopoiesis. As a result, alcoholics may suffer from moderate to severe anemia, characterized by enlarged, structurally abnormal red blood cells (RBC's), mildly reduced numbers leukocytes and neutrophils and moderately to severely reduced numbers of platelets. Although this generalized reduction in blood cell numbers (i.e., pancytopenia) usually is not progressive or fatal and is reversible with abstinence, complex aberrations of hematopoiesis can develop over time that may cause death.[2]

Anemia of diverse etiology occurs in about 75% of patients of chronic liver disease (CLD). The frequent association of anemia with ALD and/or hepatocellular failure provides a rationale for examining the role of the liver in the formation and destruction of RBCs. Mechanism responsible may be iron deficiency, hypersplenism, anemia due to chronic disease, folic acid and vitamin B12 deficiencies. [3]Anemia was associated with hepatic decompensation, hospitalization and a higher incidence rate of acute-on-chronic liver failure. Anemic patients had worse overall survival and increased liver-related mortality.[4]

Alcohol has direct bone marrow suppressive effect leading to a variable manifestation of leucocytosis and leukopenia resulting in high rate of infections and impaired defence mechanism.There also occur alterations in primary platelet haemostasis (platelet adhesion, activation and aggregation), decreased aggregability attributable to defective (trans-membrane and intracellular) signalling, a storage pool defect and an up regulation of the inhibitory pathways.[5]An increased intra-splenic platelet breakdown with variable roles of decreased platelet production and splenic pooling appear to be the most important determinant of reduced platelet counts.

Initially, Model of End stage Liver Disease (MELD) score (variables -bilirubin, creatinine, INR) was designed for assessing the prognosis of cirrhotic patients undergoing trans jugular porto-systemic intrahepatic shunt (TIPS)[6]andMELD score for organ allocation to patients listed for liver transplantation [7]Nowadays, MELD score is use for standardization of the degree of liver disease and prognostication.

Alteration in the hematological indices is a tell-tale sign of chronicity of ALD. This could also extend help in increasing the longevity in patients awaiting liver transplantation. We, through our study, have tried to group the patients with deranged hematological indices using MELD score and analyse the variation of these indices in accordance. This could have clear therapeutic implications in managing these patients and reducing the adverse events.[7]

Materials And Methods:-

This cross-sectional study was conducted in Regional Institute of Medical Sciences (RIMS), Imphal, Manipur for a period of 2 (two) years, from January 2021 to October 2022.Chronic alcoholic liver cirrhosis patients attending Medicine OPD, Liver clinic and those admitted in Medicine ward, RIMS, Imphal were enrolled in the study after informed consent.

Inclusion Criteria

Included patients >18 years age diagnosed as chronic alcoholic liver cirrhosis according to the working definition with evidence of presence of underlying liver cirrhosis in clinical examination and imaging.

Exclusion Criteria

Included chronic liver disease due to other etiologies, comorbid illness- Diabetes mellitus, Hypertension, Chronic kidney disease, Hepatocellular cancer**,**history of hepatotoxic drug intake andpatients with anaemia due to other causes

Outcome variables

Included different types of anemia, leucopenia, leukocytosis, thrombocytopenia in different groups of MELD scores in alcoholic liver cirrhosis patients

Operational Definitions:

Significant alcohol consumptionwas >14 standard drinks per week in men and >7 per week in women[1]**.**Chronic alcoholic liver cirrhosis occurred when there was 40-80g/d for men and >20g/d for women for 10-20 years.[1]Alcohol intake will be calculated in standard units(drinks)/week.1 standard drink =10-12g of alcohol was equivalent to 340 ml (12 oz) of beer**,**115 ml (4 oz) of non-fortified wine,43 ml (1.5 oz) (a shot) of 80 proof beverage (e.g. whisky)**,**0.5 L (1 pint) of 80 proof beverage contains approximately 160g of ethanol (about 16 standard drinks) and 750 ml of wine contains approximately 60g of ethanol.[1]

Liver cirrhosis:

Diagnosis of cirrhosis will be based on clinical findings, biochemistry (low serum albumin, AST/ALT ratio >1), imaging (heterogeneous echo texture of liver with irregular outline, altered liver size, Portal vein > 13, Porto systemic collateral), endoscopy (esophageal varices) or documentation suggestive of prior decompensation.[8]

Anemia

Is defined when Hb<13 in males and <12 in females.[9]
Mild:11-12.9(males) and 11-11.9 (females)
Moderate:8-10.9 (males) and 8-10.9 (females)
Severe:<8 (males and females)

Leukopenia

Is when total count <4000 cells/cumm while leucocytosis is total count >11000 cells/cumm. **Thrombocytopenia** is platelets <1.5 lakhs cells/cumm[1]

The normal range of total bilirubin (0.1-1mg%),AST(5-40 IU),ALT (5-30 IU),serum albumin (3.5-5.5g/dl), serum urea (18-40mg/dl) and serum creatinine(0.6-1mg/dl).[1]

MELD score of cirrhosis will be used to assess the prognosis in liver disease

MELD = 3.78×ln [serum bilirubin (mg/dL)] + 11.2×ln [INR] + 9.57×ln [serum creatinine (mg/dL)] + 6.43[.10]

The estimated 3-month mortality is based on the MELD score.[10]

MELD Score	Mortality Probability
40 and above	71.3% mortality
30-39	52.6% mortality

MELD Score	Mortality Probability
20-29	19.6% mortality
10-19	6.0% mortality
9 or less	1.9% mortality

Study Tools:
Complete Hemogram was done by Haematology automated analyser, Liver Function test (LFT) by enzymatic analyser, Prothrombin Time (PT) and International Normalised ratio (INR) done by Haemostaticsanalyser, Kidney function test (KFT) by Kinetic method for Blood Urea and Jaffe's method for S. Creatinine, Hepatitis C serology by Flaviscreen method, Hepatitis B serology by Viruschek rapid test, HIV I & II serology by Retrogine HIV kit.

Data collection:
A detailed structured proforma including age, sex, detailed clinical history, physical examination and biochemical profile (complete Hemogram, LFT,KFT),PT and INR, serology(HbsAg, anti HCV Ab, HIV 1 &2) and ANA of subjects were recorded. Chest xray, usg abdomen and CECT abdomen were done when indicated. Ascitic fluid analysis was done. Upper GI endoscopy was done whenever necessary.

Statistical Analysis:
Data was entered in Microsoft Excel and analyzed using statistical package for social sciences version 26 (SPSS V.26). Descriptive statistics like mean, standard deviation, percentages etc. were used. Chi square test was used to check the significance of categorical variables and ANOVA test was used to compare the means along multiple groups. P value of <0.05 was considered significant.

Approval of Research Ethics Board and Informed consent:
The study was approved by Research Ethics Board Regional Institute of Medical Sciences, Imphal. (Reference No-A/206/REB-Comm (SP)/RIMS/2015/697/39/2020).

Results:-

A total of 146 alcoholic liver cirrhosis patients were included in the study. The baseline characteristics of the study subjects were given in table I.The mean ± SD age of the patients was 48.63±10.00 years majority belonged to 40-49 years age group (35.6%). Majority were males (134, 91.8%) while females were 12 (8.2%). All the patients (100%) consumed alcohol,most of them consumed 501-1000 ml per day. Most of the patients (95.8%) consumed locally brewed alcohol. Maximum of them took alcohol for last 15-19 years (62,42.5%) and mean duration of consumption was 18.2±5.6 years. Smokers were 8.2% and there were no IV drug users. Majority of the patients presented with jaundice followed by abdominal distension due to ascites and 32 patients had encephalopathy. Only 2 each of the patients were reactive for hepatitis B and C and none were reactive for HIV 1 and 2 or ANA positive. Among the patients only 6 (4.1%) had normal hemoglobin (Hb) level. Anemia detected in >95% of the patients (mean Hb - 8.89±1.98g/dl, minimum level was 3.08g/dl). Moderate anemia was noted in 72 patients (49.3%), severe anemia in 46 patients (31.5%) and mild anemia in 22(15.1%). Out of the 140 patients with peripheral smear (P.S) showed 71.2% had normocytic normochromic blood picture and 17.8% of patients had macrocytic anemia. Majority of study subjects (47.9%) hadleucocytosis and 8.2% had leucopenia (mean leucocyte - 12210±7247/cu.mm). Thrombocytopenia was seen in 78.1% patients (mean platelet count - 1.08±0.46 lakh/cu.mm, minimum platelet count - 35,000). 89.1% of the patients had prolonged PT and 69.9% of patients had elevated INR. More than 50% of the patients had elevated blood urea and serum creatinine. Serum Albumin level was low in 91.8% of the patients and there was A/G reversal in 80.8% of the patients. 98.6% had elevated bilirubin and ALT and AST were elevated in most of the participants. Majority of patients had MELD score between 10-19 and 20-29 (34.2% each). Only 4.1% had MELD score ≥40. There is significant association between MELD score of the patients with severity of anemia ($p<0.05$) given in table II. Compared to patients with mild anemia, those having moderate to severe anemia had higher MELD scores (score>20). The mean Hb did not show any specific trendacross MELD scores. The mean leucocyte count of the patients increased (5.84 to 22.33) as MELD score increased, and it is statistically significant ($p=0.000$).There is no significant association between MELD score of the patients with presence of thrombocytopenia ($p<0.016$). Mean level of platelet was less than one lakh in patients with higher MELD scores

(98,000 in patients with score 30-39 and 75,000 in score ≥40) but this association was not statistically significant (p=0.139) given in table III. Association between MELD scores with mean level of hematological parameters was given in table IV.

Table I:- Baseline characteristics of the study subjects (N = 146).

Characteristics	Study patients (N = 146), n (%)
Age (in years)	
<40	20.5%
40-49	35.6%
50-59	30.1%
>60	4.5%
Gender	
Male	134(91.8%)
female	12 (8.2%)
Addictions	
Alcohol	100%
Smoking/tobacco	8.2%
IVDUs	0%
Variables related to alcohol	
Types of alcohol	
Local	140(95.8%)
Rum	4(2.8%)
Whisky	2(1.4%)
Duration of consumption	
<15 years	26(17.8%)
15-19 years	62(42.5%)
20-24 years	36(24.7%)
25-29years	16(11%)
>30 years	6(4.1%)
Amount consumed/day(ml)	
500	14(9.6%)
501-1000	48(32.9%)
1001-1500	72(49.3%)
>1500	12(8.2%)
Clinical features	
Jaundice	134(91.8%)
Ascites	124(84.9%)
Pallor	122(83.6%)
Pedal edema	118(80.8%)
Hepatic encephalopathy	32(21.9%)
Others *	34(23.2%)
Grades of hepatic encephalopathy (West Haven classification)	
0	114(78.1%)
1	8(5.5%)
2	10(6.8%)
3	12(8.2%)
4	2(1.4%)
Serology	
Hep B	2(1.4%)
Hep C	2(1.4%)
HIV	0
ANA	0
Anemia (Hb<13g/dl in males,<12g/dl in females)	
Present	

Absent	95.9% 4.1%
Severity of anemia	
Mild	22(15.1%)
Moderate	72(49.3%)
Severe	46(31.5%)
Anemia base on P.S.	
Normocytic normochromic	71.2%
Macrocytic	17.8%
Microcytic hypochromic	11%
Leucocyte count	
Normal	43.9%
Leucopenia	8.2%
Leukocytosis	47.9%
Thrombocytopenia (<1.5lakh/cumm)	
Present	78.1%
Absent	21.9%
Clotting profile	
Elevated Prothrombin time	89.1%
Elevated INR	69.9%
Renal function test	
Elevated blood urea	52%
Elevated serum creatinine	52%
Liver function test	
Serum albumin	
Normal	12(8.2%)
Low	134(91.8%)
Albumin/globulin ratio	
Normal	28(19.2%)
Reversal	118(80.8%)
Total bilirubin	
Normal	2(1.4%)
High	144(98.6%)
ALT(Alanine transaminase)	
Normal	34(23.3%)
Elevated	112(76.7%)
AST(Aspartate transaminase)	
Normal	8(5.5%)
Elevated	138(94.5%)
AST/ALT ratio	
<1	6(4.1%)
>1	140(95.9%)
MELD score	
<9	22(15.1%)
10-19	50(34.2%)
20-29	50(34.2%)
30-39	18(12.3%)
>40	6(4.1%)

Table II:- Association between MELD scores with severity of anemia (N=146).

Severity of anemia	**MELD scores, n (%)**				
	<9	**10-19**	**20-29**	**30-39**	**>40**
No anemia	0	2(33.3)	2(33.3)	0	2(33.3)
Mild	8(36.4)	4(18.2)	8(36.4)	2(9.1)	0
Moderate	10(13.9)	30(41.7)	22(30.6)	8(11.1)	2(2.8)

Severe	4(8.7)	18(39.1)	14(30.4)	8(17.4)	2(4.3)
Chi – square test: p value :0.007					

Table III:- Association between MELD score and platelet count (N=146).

Platelet counts	**MELD scores, n (%)**					Total
	≤9	**10-19**	**20-29**	**30-39**	**≥40**	
Normal	6 (18.8%)	8 (25.0%)	12 (37.5%)	6 (18.8%)	0	32 (100.0%)
Reduced	16 (14.0%)	42 (36.8%)	38 (33.3%)	12 (10.5%)	6 (5.3%)	114 (100.0%)
Chi-square test, p value: 0.33						

Table IV:- Association between MELD scores with mean level of hematological parameters (N=146).

Hematological parameters (Mean ± SD)	**MELD scores, n (%)**					**p-value**
	≤9	**10-19**	**20-29**	**30-39**	**≥40**	
Hb (g/dl)	9.55±1.70	8.61±1.73	8.90±2.27	8.51±1.65	9.97±3.07	0.204
Leucocytes (cells/cumm)	5.84±2.83	11.91±5.78	12.31±4.87	17.28±11.61	22.33±8.31	0.000
Platelets (cells/cumm)	1.07±0.35	1.07±0.35	1.09±0.33	0.98±0.52	0.75±0.28	0.139
***Anova test**						

Discussion:-

Abnormalities in hematological parameters are common in patients with alcoholic liver cirrhosis. The pathogenesis of abnormal hematological parameters in cirrhosis is multifactorial and includes portal hypertension-induced sequestration, alterations in bone marrow stimulating factors, bone marrow suppression. Excess alcohol intake itself causes direct bone marrow suppression leading to toxic effects on the blood cell lines including pancytopenia.[11.] Indirectly, it affects the nutritional biology of the patient resulting in production of functionally immature cells. Alcohol causes complex aberrations in hematological parameters leading to fatal complications, increasing the mortality rate in these patients. Abnormalities in hematological parameters are associated with an increased risk of complications including bleeding and infection.

The present study was conducted on 146 patients with chronic alcoholic liver cirrhosis and the prevalence of anemia was 94.9% which was almost similar to the finding of Kesavadas et al[12] (88%), Selvamaniet al[13](60%) and Kavitha[14] (80%) in patients having decompensated chronic liver disease (CLD). The Mean Hemoglobin (Hb) was found to be 8.89±1.98g/dl, the minimum Hb level of 3.8g/dl and maximum Hb level of 13.3g/dl in our study. Majority of them (49.3%) had moderate anemia, 31.5% patients had severe anemia, 15% had mild anemia and the rest had normal Hb (4.1%), whereas in a study conducted by Kavitha[14]mean Hb was 9.58g/dl in moderate alcoholics, 8.59g/dl among severe alcoholics and 11.63g/dl among non-alcoholics.Anbazhagan et al[15]reported in his study 80% anemia out of which 37.5%patients had severe anemia with Hb level <6gm/dl.

In our study, normocytic normochromic anemia was predominant among thepatients (71.2%) followed by macrocytic anemia in 17.8% and 11% having microcytic hypochromic picture. This was comparable with findings of the study conducted by Selvamani et al[13]where the most common was normochromic normocytic anemia (52%), Khare et al[3] , Patel et al[16] and Jha et al[17]. The prevalence of moderate-severe anemia (Hb <10 g/dL) increased with the degree of portal hypertension. The most common etiologies of anemia were gastrointestinal bleeding (25%)and iron deficiency (9%). Male gender, MELD, hepatic decompensation and HVPG were independent risk factors for anemia.

In this study, patients with end stage liver disease secondary to alcohol consumption were divided into various MELD score groups. The MELD score of the patients had significant association with severity of anemia ($p<0.05$) and leucocytosis. But MELD score did not have significant association with mean decline of Hb (p value-0.204)and severity of thrombocytopenia (p value-0.139).There was mean Hb declined from 9.55g/dl in patients with MELD

score <9 to 8.51g/dl in those with MELD score between 30-39, though it was not statistically significant(p value-0.204). There was a significant gradual rise in mean leukocyte count from lower to higher MELD scores (5840 cells/cu mm in MELD score ≤9, 11900 in MELD score 10-19, 12300 in MELD score 20-29, 17280 in MELD score 30-39 and 22330 in MELD score ≥40) and it was statistically significant (p value of- 0.000).Similarly platelet count dropped from around 1.07 lakh cells/cu mm in patients with low MELD scores to 75000 cells/cu mm in patients with MELD score ≥40, however it was not statistically significant (p value-0.139).However,it is believed that alcohol affects the production of thrombocytes and accelerates their degradation.Above mentioned findings were comparable with a study conducted by Jain et al[18], where there was a progressive fall in haemoglobin levels with increase in MELD score. All the patients with MELD score ≤9 had normal leukocyte count, leucocytosis predominated in those with MELD score 10-19 and 20-29. In patients with MELD score 30-39, leukopenia was more prevalent. All the patients MELD score ≥40 had leukopenia. Patients with MELD score ≤9 and 10-19 did not have thrombocytopenia. Thrombocytopenia was found in those with MELD score 20-29 and 30-39 while all the patients with MELD score ≥40 had thrombocytopenia.The statistically significant association between the variables and the groups shows that MELD score grouping system could be an important tool in the assessment of these patients. To the best of our knowledge, this is the first study in Manipur categorizing the MELD score into different groups and utilizing it for studying the hematological spectra and alcohol related complications in patients with alcoholic liver cirrhosis.

Conclusion:-

Our study found alcohol adversely affecting the production and functioning of virtually all types of blood cells, its production and maturation and if severe increases risk to anemia, bacterial infections and impaired blood clotting and fibrinolysis. The prevalence of anemia in the present study was found to be 94.9%.The rising MELD score has statistically significant association with severity of anemia and leukocytosis while no significant association was found with mean Hb decline and severity of thrombocytopenia.This association strongly depicts that the clinicians could effectively take precautions in preventing the further progression of the disease thus decreasing the mortality in these patients.

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Conflict of interest:
None declared

Ethical Approval:
The study was approved by the Institutional Ethics Committee.

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