Original Article

Prediction of Low Factor V Levels in Patients with Herbal Medicine Related Acute Liver Injury

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ABSTRACT

Background: Prior epidemiologic studies predicted a rapid rise in herbal medicine-related acute liver injury (HILI) and liver transplantation (LT) as trading of traditional herbal medicine drugs is expanded. HILI is the leading cause of liver transplantation in the world. The indication for LT was defined as acute liver failure (ALF) with the factor V (FV) level below 35%. Objective: To explore the possible impact of herbal medicine-related to the liver failure on the laboratory parameters and to determine if simple laboratory values play a role in determining lower FV levels. Materials and methods: Totally, 38 HILI cases who were admitted to a tertiary care hospital between May 2016 and May 2018 were scanned, retrospectively. Need for LT was assessed by the determination of FV levels. Results: The mean age of participants was 37±13 years where 27 (71%) were female while the rest were male and 81% of the total populations were farmers. Total 78% patients were reportedly consuming herbal medicine pills, and 22% reported consuming traditional Turkish herbs. Among 38 cases with HILI in critical care, 2 (5.2%) have died, 3 (7.8%) underwent LT and 33 (87%) were recovered and discharged. Results of 38 patients with available data also showed that factor V levels were positively correlated with the hemoglobin and platelet levels ($p<0.05$) and negatively correlated with prothrombin time ($p<0.05$). **Conclusion**: These findings suggest that detecting anemia and thrombocytopenia could be an important, economically feasible strategy for improving outcomes in HILI.

Key words: *Liver Transplantation, Acute liver Failure, Factor V, Herbal medicine-related acute liver injury.*

Acute liver failure (ALF) is the combination of acute liver injury, hepatic encephalopathy and elevated prothrombin time in a person with no prior history of liver disease. It is also referred to as fulminant hepatic failure [1]. A wide scale of causes can result in ALF including drugs, herbal products, toxins, viral hepatitis, varicella zoster virus (VZV), herpes simplex virus (HSV), autoimmune hepatitis, mushroom poisoning (Amanita phalloides), Reye's syndrome, acute fatty liver of pregnancy, Budd-Chiari syndrome, hypoperfusion, HELLP syndrome, heatstroke, Wilson disease and tumoral infiltration etc [2.3].

Patients with ALF can apply to the hospital with nonspecific symptoms but then jaundice, encephalopathy, coagulopathy, metabolic abnormalities, renal dysfunction, ascites, sepsis, lung injury, hemodynamic instability, are developed by the time [4]. Management of ALF includes intensive care support, treatment of specific etiology if it is known, and early determination of the candidates for liver transplantation (LT). Prognostic scoring systems mostly used in ALF are King's College criteria, Clichy-Villejuif criteria and Model for end-stage liver disease (MELD). These systems have been used to assess the severity of ALF and to identify candidates of transplantation [5].

Herbal medicines have gained popularity among individuals worldwide because it is considered to be natural and safe. In contrast to this idea, herbs may cause adverse reactions of variable severity and numerous

organs; specifically, the liver can be affected [6-8]. Nonscientific usage of herbal products can accompany ALF and which may lead to the need of transplantation. The aim of this study is to evaluate the correlation of hematologic parameters in herb induced liver injury (HILI) and to make some suggestions for their prognostic value.

METHODS

This retrospective study was conducted in a tertiary care hospital for a period of 2 years i.e. from May 2016 to May 2018. The study was conducted after getting the ethics committee approval and after getting consent from the patients. Total 38 cases, who were admitted with a diagnosis of herb induced ALF, were included in this study. Their demographic and clinical data were collected by reviewing electronic medical records of the hospital.

Those patients were included in the study who were reportedly having hepatotoxicity due to herbs, herbal drugs and herbal dietary supplements. Patients with acute or chronic viral hepatitis, metabolic liver diseases, Wilson's disease, and autoimmune hepatitis were excluded from the study. In addition, patients with malignancies including hepatocellular carcinoma, were also excluded..

Need for LT was assessed by the determination of Factor V levels. Descriptive statistics, Chi-squared and t-tests were used for analysis. Multi-variable logistic regression was used to identify laboratory parameters associated with FV levels. SPSS program and Pearson correlation were used to investigate the relation between the biochemical parameters.

RESULTS

Out of the total 38 patients, 27 (71%) were female and 11 (29%) were male. Mean age of the participants was 37±13 years. The occupational data shows that among the study participants, 81% were farmers. A total of 78% of patients were reported of consuming herbal medicine pills; and 22% reported consuming traditional Turkish herbs. Among 38 cases with HM- related ALF in critical care, 2 (5.2%) participants died, 3 (7.8%) underwent LT and 33 (87%) recovered during the study and were discharged.

The descriptive statistics of the patients and the comparison in the result groups are shown in Table 1. Results of the 38 patients with available data shows that Factor V levels were positively correlated with hemoglobin and platelet levels ($p<0.05$) and negatively correlated with prothrombin time ($p<0.05$). Factor VIII levels were strongly and positively correlated with prothrombin time ($p<0.01$), and positively correlated with total bilirubin levels ($p<0.05$), while it was negatively correlated with platelet levels ($p<0.05$). All the patients who underwent LT or died, had a Factor V levels below than 30% compared to discharged counterparts ($p<0.005$).

Table 1: Descriptive statistics and comparison results by groups

Lab Testing Parameters	N	Mean	Std. Deviation	Minimum	Maximum
Aspartate transaminase IU/ml	38	137.60	257.78	15.0	1240.0
Alanine transaminase IU/ml	38	171.52	255.73	7.0	1172.0
Glucose (mg/dl)	38	108.26	116.98	65.0	800.0
Alkaline phosphatase IU/ml	38	165.47	230.13	47.0	1408.0
Gamma-glutamyltransferase IU/ml	38	136.32	222.88	0.9	873.0
Albumin (mg/dl)	38	3.51	0.97	0.25	4.90
Globulin (mg/dl)	31	3.21	0.84	1.90	5.20
Total Bilirubin (mg/dl)	38	3.22	5.50	0.32	24.12
Direct Bilirubin (mg/dl)	36	2.56	4.75	0.04	20.0
Leukocyte count(cells×10^3/mm^3)	38	7.13	2.48	2.9	13.5
Neutrophils (cells×10^3/mm^3)	38	4.30	2.16	0.2	11.9
Hemoglobin (gm/dl)	38	12.97	2.41	6.4	16.8
Platelet Count (cells×10^3/mm^3)	38	199.55	83.05	27.0	393.0
Factor V	37	61.43	33.03	15.0	191.0
Factor VIII	18	77.94	74.74	14.0	300.0
PH	20	7.40	0.05	7.24	7.55
HCO3	20	21.22	3.25	12.0	27.0
Prothombin time	36	15.97	4.39	11.7	28.6

DISCUSSION

While there may be a number of possible explanations for the increase in HILI, our data highlight urgent need for the simple diagnostic tools to predict ALF. The diagnosis of drug-induced liver injury (DILI) relies on compatible history, liver function tests and exclusion of other causes. DILI is attributed to any drug or herbal and dietary supplement within 6 months of liver injury onset [9]. Liver injury associated with the consumption of herbal

medicines is defined as HILI, which is almost similar to those of DILI [10].

Most of the cases of ALF have an identifiable etiology. In the US reports, approximately 12% of cases were considered indeterminate ALF (IND-ALF) which has mostly caused by occult viruses or toxins. All the patients were presented with hepatocellular injury but were misdiagnosed usually due to lack of hepatitis E virus (HEV) Ig M testing at the time of liver injury onset. These findings indicate that exclusion of acute HEV requires anti-HEV Ig M testing in patients with suspected HILI [11]. In compared to this finding, our study had nil patients who were found to be positive in the test for acute HEV infection.

In a study by Teschke R et al [12], all the patients presented with hepatocellular injury but were misdiagnosed usually due to lack of hepatitis C virus (HCV) RNA testing, at the time of liver injury onset. These findings also indicate that exclusion of acute HCV requires HCV RNA testing in patients with suspected DILI [12]. In the current study, all the patients were tested negative for HCV- RNA with PCR technique. Anti-tuberculosis drugs are the most common cause of DILI and the cases of drug-induced ALF are more common in middle and low income countries. Although, in a study by Cao J et al [13], more subjects developed DILI in the study population, due to extensive usage of the anti-tuberculosis drugs. In our study, there were no patients with DILI amid study population.

Recent reports have suggested that the incidence of DILI from herbal and dietary supplement has increased in the past years. In addition, women and persons older than 60 years are more likely to present with HILI. Furthermore, Szantova M et al [14] suggested that sex differences in absorption, distribution, metabolism and excretion (ADME) should be investigated to understand the increased pre-disposition of HILI in women. In the current study, nearly 75% of the study subjects were women and our findings were in line with the other studies.

Clichy Villejuif (CV) criteria is one of the most widely used tools worldwide to determine a prognosis for ALF or FH. The CV criteria is mainly used in Europe, and they include grade 3 or 4 hepatic encephalopathy and factor V levels less than 20% in patients below than 30 years of age and less than 30% in patients above than 30 years of age [15]. Our data strongly support the routine assessment of factor V-related hematologic parameters to enhance the care of patients awaiting liver transplantation. In addition, our findings also uncover anemia and thrombocytopenia as simple markers for predicting lower factor V levels and open perspectives for novel liver transplantation strategies based on the simple field tests. The limitation to this study was that the results may not generalized entire population of the region with ALF due to small sample size.

CONCLUSION

In this study, we assessed the simple hematologic parameters in HILI patients. Our findings point to a critical role of hemoglobin and platelet levels in HILI development in rural areas of Asia. Better and simpler methods to identify ALF, will diminish the high-cost tests for developing countries. It may be also concluded that the performance of the CV criteria could be improved by the integration of hemoglobin and platelet levels into the prediction of outcomes for HILI.

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