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Comparison of patients with fulminant versus near-miss fulminant drug-induced hepatitis.

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Abstract

This study aimed to investigate and compare clinical and laboratory properties of patients with fulminant versus near-miss fulminant drug-induced hepatitis and the effect of these properties on mortality. Drug-induced hepatitis is the most common cause of acute liver failure in western countries. In severe drug-induced hepatitis, once encephalopathy develops, prognosis is poor without liver transplantation. Therefore, it is important to predict prognosis and know the clinical differences between patients developing encephalopathy and patients without encephalopathy. Patients with severe drug-induced hepatitis were researched retrospectively. The identified patients were divided into two groups: with encephalopathy (fulminant hepatitis; 25 patients) and without encephalopathy (near-miss fulminant hepatitis; 48 patients). The clinical properties and biochemical results of the two groups were compared, and parameters that could have an effect on mortality were evaluated. Hemoglobin, platelet count, albumin, and fibrinogen levels were found to be decreased, whereas, International Normalized Ratio (INR), total bilirubin, AST, LDH, lactate, and ammonia levels were found to be increased significantly in the fulminant hepatitis group. Creatinine, Model for End-Stage Liver Disease (MELD) score, and platelet count were found to be independent risk factors on mortality. The development of hepatic encephalopathy negatively impacts patient survival. Therefore, the prediction of a progression to fulminant hepatitis before hepatic encephalopathy develops and the clinical follow-up of patients accordingly are important issues. This study can provide significant insight into patients with severe drug-induced hepatitis.

Keywords: Drug-induced, Fulminant hepatitis, Hepatotoxicity, Near-miss fulminant hepatitis.

Abbreviations:

DILI: Drug-induced Liver Injury; DIH: Drug-induced Hepatitis; ALF: Acute Liver Failure; CIOMS: Council for International Organizations of Medical Science; ALT: Alanine Transferase; AIH: Autoimmune Hepatitis; ALP: Alkaline Phosphates; RUCAM: Roussel Uclaf Causality Assessment Method; NAC: N-acetyl cysteine; FH: Fulminant Hepatitis; WBC: White Blood Cell; INR: International Normalized Ratio; aPTT: activated Partial Thromboplastin Time; BUN: Blood Urea Nitrogen; AST: Aspartate Transaminase; GGT: Gamma Glutamyltransferase; LDH: Lactate Dehydrogenase; MELD: Model For End-Stage Liver Disease; NSAID: Nonsteroidal Anti-Inflammatory Drug.

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Introduction

Drug-Induced Liver Injury (DILI), also known as Drug-Induced Hepatitis (DIH), has a wide clinical spectrum, ranging from asymptomatic abnormal liver function tests to severe life-threatening Acute Liver Failure (ALF) [1]. It is the leading cause of ALF, accounting for about half of the cases in western countries [2]. When symptomatic, the symptoms range from non-specific symptoms of nausea, vomiting, and anorexia, to specific symptoms of right upper quadrant pain, skin rashes, itching, jaundice, ascites, and encephalopathy. The diagnosis of severe DILI is often clinical, such that patients require hospitalization [3,4]. Many drugs can cause DILI, and different drugs have led to varying disease time courses [5]. In western countries, the most common drugs that lead to idiosyncratic DILI are antimicrobials, central nervous system drugs, herbal/dietary supplements, and immunomodulatory agents [3].

DILI can be mediated by two mechanisms: intrinsic hepatotoxicity, which is predictable and dose-dependent, and idiosyncratic hepatotoxicity, which is unpredictable and not dose-dependent [6]. The former depends on the dose and becomes manifested within a few days. It mainly results from the direct toxicity of a drug or its metabolites when individuals are exposed to an intentional and deliberate overdose of drugs [1,2]. Idiosyncratic hepatotoxicity does not necessarily depend on the dose and occurs with variable latency [2]. It is the most common form and can further be caused by metabolic or immunological mechanisms, with the immunological effect resulting from a hypersensitivity reaction [7]. Approximately 25-30% of patients who develop DILI display symptoms of an allergic drug reaction, such as fever, rash, and eosinophilia [8]. The biochemical pattern of DILI is classified according to the Council for International Organizations of Medical Sciences (CIOMS). Based on the level of elevation of alanine amino transaminases (ALT) or alkaline phosphates (ALP) from the upper limit of normal and the ratio (R) of elevation of ALT to ALP (ALT/ALP), DILI is classified as either hepatocellular (ALT $\geq$ 3 times; R $\geq$ 5), cholestatic (ALP $\geq$ 2 times; R $\leq$ 2), or mixed types (ALT>3 times; ALP>2 times; R: 2-5). The degree of elevation in liver enzymes has a poor correlation with the severity of liver disease [9-11].

One of the most difficult issues in the diagnosis of DILI is the determination of causality. There are many approaches to the assessment of causality. The most widely used approach is the Roussel Uclaf Causality Assessment Method (RUCAM) scale. RUCAM is a semi-quantitative scale, and it contains seven domains, including the onset and ending of the injury after the initiation or discontinuation of the suspected agent; progression and course of the reaction; risk factors; concomitant medications; causes of liver injury other than drugs; previous information on the medication; and response to readministration, if any. This scale assesses causality through assigning a score (range: -3 and +3 points) to each domain. A score >8 for an implicated drug suggests a highly probable relationship between the drug and liver injury. Other scores include probable (6-8), possible (3-5), unlikely (1-2), or excluded (<0) [12,13]. Despite the development of scoring systems and scales in the evaluation of DILI, DILI is still a diagnosis of exclusion. The definite diagnosis of DILI is supported by the exclusion of other causes of liver injury, such as autoimmunity and viral hepatitis [14]. A detailed clinical history, including those of herbs and complementary medicines, is of paramount importance for establishing a diagnosis of DILI [1].

Elevated transaminase or ALP alone without jaundice or hyperbilirubinemia qualifies as mild disease. The presence of hyperbilirubinemia with a bilirubin of >2 mg/dl qualifies as moderately severe disease. The presence of prolonged INR (>1.5), encephalopathy, or ascites with or without hospitalization, accompanied by hyperbilirubinemia or jaundice, connotes severe disease [1]. Once DILI is suspected or identified, management begins with the prompt discontinuation of the suspected agents along with supportive measures and monitoring [6]. Antioxidants have been used for the treatment of severe DILI, and, specifically, N-acetyl cysteine (NAC) is considered the treatment of choice for acetaminophen-induced liver injury [15]. Plasma exchange is another therapeutic modality that has been used for the treatment of ALF [16]. In order to provide adequate supportive care and management in acute fulminant hepatic failure, patients should be cared for in the setting of an intensive care unit in a liver transplant center.

Once DILI patients develop or present with coagulopathy and encephalopathy (fulminant hepatitis), the prognosis is very poor, with approximately 60-80% mortality in the absence of a liver transplantation (LT) [17]. Severe DILI patients without encephalopathy (near-miss hepatitis; please see Method section for detail) have a generally better prognosis than fulminant cases. Once fulminant liver failure develops, LT may be the sole treatment option [18]. Herein, we aimed to compare and investigate the clinical and laboratory properties of patients with fulminant versus near-miss fulminant DIH and the effect of these properties on mortality.

Material and Methods

Data in the files of 227 patients who had been hospitalized at Inonu University Medical School Gastroenterology Clinic between November 2009 and October 2015 with drug-related liver injury were scanned retrospectively. With the purpose of evaluating the relation between drug exposure and liver injury in patients, the international consensus criteria of RUCAM were used [19,20]. 73 patients with RUCAM scores of possible, probable, and highly probable were considered as meeting the criteria for inclusion in the study. These patients were divided into two groups: fulminant (n=25) and non-fulminant (n=48). Patients with encephalopathy who had been diagnosed with ALF based on clinical and biochemical findings were included in the fulminant patient group, while patients with findings of ALF in whom encephalopathy had not developed were included in the non-fulminant patient group. The non-fulminant patient group included in this study was rather close to the fulminant patient group in the clinical sense. That is, they were close to the encephalopathy limits, but encephalopathy had not developed yet. Therefore, we preferred to define this group as the “near-miss fulminant” group. Characteristic data, including age, sex, White Blood Cell (WBC), hemoglobin, platelet, INR, aPTT, BUN, creatinine, albumin, total bilirubin, direct bilirubin, AST, ALT, ALP, GGT, LDH, lactate, ammonia, past transplantation, past high-volume plasmapheresis, survival, co-morbid diseases, fibrinogen, fibrinogen groups, nr (AST or ALT/ALP), r(ALT/ALP), r groups, AST/ALT, AST/ALT group, number of hospital stay days, presence of eosinophilia, and MELD scores, of patients in both groups were investigated. We will now outline some of the rates we have tested in this study. The AST/ALT ratio is a marker used in the differential diagnosis of some liver diseases. This marker is used as AST/ALT<1 and >1 in some studies [21]. In this study, we divided each patient group (FH versus near-miss FH) into two groups (AST/ALT <1 and >1) and compared them. The nR ratio (AST or ALT/ALP) is a

parameter that has been used to show drug-related toxicity in some studies [22]. This value is calculated as the ratio of the highest transaminase value to ALP. The R ratio (ALT/ALP) is calculated as the ratio of ALT to ALP and has been defined to show the type of injury in the liver. Accordingly, R<2 shows cholestatic injury, R between 2 and 5 shows mixed-type injury, and R>5 indicates hepatocellular injury. In this study, we divided both patient groups (FH versus near-miss FH) based on the R value into three groups and compared them. Eosinophilic group: In our center, the value of 550 is accepted as the upper limit of normal in the kits used to measure eosinophils. Therefore, we evaluated the patients in both groups based on the eosinophil count (<550 or >550). Data were statistically summarized as median (min-max) or count and percentage. Mann Whitney U, Pearson Chi-square, Fisher's exact chi-square, and Yate's adjusted chi-square tests were used for the analyses of data as appropriate. Multiple logistic regression analysis was used to determine factors related to mortality. IBM SPSS statistics 23.0 program was used in analyses. P<0.05 values were accepted for the statistical significance limit.

Table 1. *Demographic and clinical characteristics of study groups.*

Parameters	Near-Miss Fulminant (n=48)	Fulminant (n=25)	p
Age (years)	33(17-80)	35(17-81)	0.34
Sex			0.22
(n: female /male)	(22/26)	(16/9)	
(%:female/male)	(45.8/54.2)	(64/36)	
WBC (× 10^3/mL)	8.6 (3.3-61.9)	9 (2.5-20.7)	0.38
Hemoglobin (g/dL)	13.4 (8.1-17.5)	11.5 (6.4-17)	0.006
Platelet (× 10^3 /mL)	253 (67-428)	126 (8-382)	0.001
INR	1.4 (0.8-6.3)	3 (1.5-8.1)	0.0001
aPTT (seconds)	35.3 (19.9-136.6)	44.5 (28.5-181)	0.13
BUN (mg/dL)	10.5 (4-72)	10 (3-84)	0.52
Creatinine (mg/dL)	0.7 (0.5-4.5)	0,6 (0.3-2.9)	0.052
Albumin (g/dL)	3.3 (2-4.2)	2.9 (1.3-4.1)	0.034
Total Bilirubin (mg/dL)	8.8 (4-32.9)	13.3 (4.1-29.5)	0.019
Direct Bilirubin (mg/dL)	5.3 (2.5-24.6)	9.8 (2.3-20.7)	0.24
AST (U/L)	413 (26-4147)	1030 (71-7897)	0.047
ALT (U/L)	622 (18-4565)	891 (36-10631)	0.37
ALP (U/L)	146 (49-580)	179 (31-331)	0.11
GGT (U/L)	105 (12-924)	97 (25-433)	0.56
LDH (U/L)	447 (173-2886)	569 (245-7158)	0.03
Lactate (mg/dL)	15 (8-38)	29 (13-93)	0.0001
Ammonia (µg/dl)	75 (32-256)	205 (71-662)	0.0001
Transplantation (+/-)	0/48	8/17	0.001
Plasmapheresis (+/-)	9/39	11/14	0.02
Death (+/-)	0/48	15/10	0.001
Comorbid disease (+/-)	18/30	7/18	0.58
Fibrinogen (mg/dL)	272 (156-425)	130 (80-210)	0.0001
Fibrinogen groups			0.0001
Decreased	4	24	
Normal	44	1	

nR (ALT or AST/ALP)	3.6 (0.1-30.3)	5.2 (0.6-84.4)	
R (ALT/ALP)	3.7 (0.1-37.1)	4.9 (0.3-84.4)	0.67
R (ALT/ALP)			0.35
<2	13	9	
2-5	15	4	
>5	20	12	
AST/ALT			0.028
AST/ALT			0.34
<1	30	12	
>1	18	13	
Hospitalisation (days)	10 (3-70)	18 (2-59)	0.079
Peripheral blood Eosinophils /mm^3			0.087
<550	41	25	
>550	7	0	
MELD score	19 (6-40)	30 (17-42)	0.0001

WBC: White Blood Cell; INR: International Normalized Ratio; aPTT: activated Partial Thromboplastin Time; BUN: Blood Urea Nitrogen; AST: Aspartate Transaminase; ALT: Alanine Transaminase; ALP: Alkaline Phosphatase; GGT: Gamma Glutamyltransferase; LDH: Lactate Dehydrogenase; MELD: Model For End-Stage Liver Disease.

Results

Patients were divided into two groups: fulminant (n=25) and near-miss fulminant (n=48). In the analyses carried out using different univariant analysis methods, the following values were found to be significantly low in the fulminant group: hemoglobin (p<0.006), platelet (p<0.001), albumin (p<0.034), fibrinogen (p<0.0001), and fibrinogen group (p<0.0001). The following were significantly higher in the fulminant group: INR (p<0.0001), total bilirubin (p<0.019), AST (p<0.047), LDH (p<0.03), lactate (p<0.0001), ammonia (p<0.0001), transplantation (p<0.001), plasmapheresis (p<0.002), mortality (p<0.001), AST/ALT group (p<0.027), and MELD (p<0.0001) score. In contrast, no statistically significant differences were found in the following: age, etiology, sex, WBC, aPTT, BUN, direct bilirubin, ALT, ALP, GGT, co-morbid diseases, nR, R, R groups, AST/ALT group, number of hospitalization days, and eosinophilia. While the blood creatinine value was statistically insignificant, the p value (p=0.052) was very close to 0.05, which was the limit of statistical significance (Table 1). In our study, we found that fulminant hepatitis developed in 12 patients out of 32 patients with hepatocellular-type DILI (37.5%), in nine patients out of 21 patients with cholestatic-type DILI (42.8%) and in four patients with mixed-type DILI (19.7%). Although the mixed-type DILI appeared less risky as regards the fulminant course as compared to the other two types of DILI, we could not find any statistically significant differences (p<0.35). While the first four causes were antibiotics (22.9%), natural drugs (12.5%), ecstasy (8.3%), and paracetamol (8.3%) in near-miss FH, the first four causes were paracetamol (20%), natural drugs (12%), antibiotics (8%), and NSAIDs (8%) in the FH group. There were no statistically significant differences when we compared both patient groups as regards etiology (p<0.5) (Table 2). With the purpose of showing if some parameters with statistical significance in the univariate analysis were effective risk factors on mortality, a multivariate analysis was carried out. It was found, based on the multiple logistic regression, that creatinine (p=0.034), MELD score (p=0.047), and platelet count (p=0.011) were independent risk factors on mortality.

Table 2. *The drugs that was thought as causative agent of toxic hepatitis in study groups.*

Etiology	**Near-Miss Fulminant n=48-(%)***	**Fulminant n=25-(%)***	**p**
Antibiotic	11-(22.9)[1]	3-(8)[3]	0.5
Natural drug	6-(12.5)[2]	4-(12)[2]	
Extacy	4-(8.3)[3]	2	
Paracetamol	4-(8.3)[4]	5-(20)[1]	
NSAID	3	3-(8)[4]	
Antibiotic plus NSAID	2	2	
Antitubercular drugs	2	1	
Antidepressant drugs	0	1	
Oral contraceptive drugs	2	0	
Statin	1	0	
Statin plus antidepressant	1	0	
Antihipertansive plus oral antidiabetic drugs	1	0	

Antiepileptic drug	1	0
Antiepileptic plus antifungal	1	0
Antihypertensive drug	1	1
Antipsychotic	1	0
Antipsychotic plus antibiotic	1	0
Halothane	0	1
Levothyroxine	1	0
Methotrexate	1	0
Paracetamol plus NSAID	0	1
Protein	1	0
Psorcutan beta	1	0
Infliximab plus azothiopurine	0	1
Rituximab	1	0
Agricultural drug	1	0

*in order of frequency, NSAID: Nonsteroidal Anti-Inflammatory Drug

Discussion

In contemporary hepatology, DILI is in first place among the issues not solved yet. New and different drugs are produced in parallel with technological advancements, and hepatotoxicity can develop with varying rates in relation to these drugs. In other words, exposure to hepatotoxicity increases day by day, and increases are observed in morbidity-mortality risks related to liver failure paralleling such exposure. The main important issue that restricts us is the inability of predicting which drug will cause liver injury in which patient. Although genetic and environmental factors are indicted in this issue, no definite evidence has been found yet. Herbal products are commonly used for a healthy life and alternative medicine. Herbal products cause 16% of DILI cases in the USA and 71% in Far East countries including Singapore [23,24]. Amoxicillin clavulanic acid is among the most common causes of DILI in many countries and causes idiosyncratic-type injury [8,25]. In our study, we could not find any statistically significant differences when we compared both patient groups as regards etiology. However, while the first four causes in near-miss FH were antibiotics (22.9%), natural drugs (12.5%), ecstasy (8.3%), and paracetamol (8.3%), the same were paracetamol (20%), natural drugs (12%), antibiotics (8%), and NSAIDs (8%) in FH.

In a study, Russo et al. found that the female sex dominated in FH development in relation to both acetaminophen and non-acetaminophen (77% and 75%, respectively) [26]. Likewise, in a study carried out on patients with ALF related to DILI, it was reported that ALF developed more frequently in the female sex (71%) [27]. It was found that fulminant hepatitis developed in 16 patients out of the 38 females included in our study (42.1%), while fulminant hepatitis developed in only nine males out of 35 included (25.7%). However, no statistically significant differences were found. Likewise, histology of the liver differs according to the liver injury caused by the drug. While it has been reported in the literature that a liver biopsy is performed in half of the patients with suspected DILI, a liver biopsy is not required for diagnosis [8]. A correlation has been found between drugs causing hepatocellular injury in DILI and some biochemical tests including high levels of ALT and R value and the histologic properties in the liver. Presumably, it is the correlation that was insufficient, in which case this should be singular [28]. Screening of the Spanish DILI network had revealed that cases with pure hepatocellular injury had more mortal courses as compared to the cholestatic and mixed-injury types [8]. In this study, we grouped the patients as mixed-, cholestatic-, and hepatocellular-injury groups, and found that the rate of advancement to FH was higher in hepatocellular and cholestatic DILI than mixed DILI, but the difference was not statistically significant. Also, we did not find a relation between the cholestatic, mixed, and hepatocellular types and mortality based on the R value. We think that these results are related to the closeness of our cases to each other in clinical findings other than encephalopathy and laboratory findings.

Drug-related immune-mediated hepatotoxicity differs from drug-related hepatotoxicity without immune-mediation with the togetherness of fever, eosinophilia, and other allergic reactions [29]. DILI is a common disease that can mimic all the forms of liver diseases and threaten life. The main drug or its metabolite can cause liver injury through cytokines or immune response [30]. It has been observed that the chance of healing was better in patients with biopsies with hypersensitive reactions with eosinophilia and/or granuloma [28]. Rashes, eosinophilia, atypical lymphocytes, and high levels of liver enzymes related to Type IV allergic reactions are seen in liver injuries resulting from some drugs [31]. In our study, we did not find any differences between the fulminant hepatitis and the near-miss FH group as regards eosinophilia. Prothrombin time and INR are important parameters in fulminant hepatitis to indicate the severity of disease [32,33]. In a study evaluating patients with FH related to paracetamol, it was reported that high levels of prothrombin were effective on mortality [34]. Both the INR and aPTT can be prolonged in liver failure in concordance with the severity of failure. In this study, the INR was prolonged significantly, whereas aPTT was prolonged non-significantly in the fulminant group when both groups compared. The PT or INR assesses factor VII, which is the coagulation factor with the shortest half-life. So, the first test to become abnormal in liver failure is PT or INR. Then later, as the other coagulation factors start to become noticeably less abundant, the aPTT becomes prolonged too. Also, the increased level of factor VIII may delay aPTT being prolonged. All of these may explain the statistical differences of INR and aPTT [35].

In a study carried out to determine the early dynamic changes in ALF, it was reported that an INR level of over 5 together with hepatic encephalopathy is a poor prognostic factor [36]. In our study, INR was clearly longer in the FH group. However, we could not determine any effect on mortality. High levels of serum creatinine have been reported as a criterion for poor prognosis in several studies [37,38]. Although creatinine was

not significantly high in the FH group in our study, it was rather close to $p<0.05$, which is the limit of significance. At the same time, we determined that creatinine is an independent risk factor for mortality. It has been reported that high levels of blood lactate are related to poor prognosis in some critical illnesses and liver failure [39,40]. It has been reported recently that the blood lactate level in patients with FH is a prognostic marker for early mortality [40,41]. In another study, an early blood lactate measure is an early marker of the severity of liver injury [42]. In a study determining the early dynamic changes in ALF, it has been reported that an ammonia level higher than 123 together with hepatic encephalopathy is a poor prognostic factor [36]. Blood ammonia levels were found to be higher in patients with FH, and a positive relation was shown between these high levels and encephalopathy [41-43]. In our study, we found blood lactate and blood ammonia levels were significantly higher in patients with FH. That is, we found a direct relationship between FH development and blood ammonia and lactate levels. However, we could find no evidence that their parameters increase mortality in patients with FH.

It has been reported that fibrinogen levels are very low in the exacerbation of chronic hepatitis B, in severe acute hepatitis, and in patients with liver failure and also that prothrombin time elongates [44-46]. In our study, we found that the fibrinogen level was significantly lower in the FH group. However, we could not find any statistical relation between such a reduction in the fibrinogen level and mortality. It has been shown in some liver diseases, such as Wilson's disease, that a high AST/ALT ratio can predict FH [21]. We obtained similar results in our study also, and, in our opinion, one should pay attention to FH in case of a high AST/ALT ratio even if FH is not present at admission in patients with suspected DILI. It has been shown that the nr value, which shows the rate of higher value one of transaminases to ALP, of higher than 5 is better in the prediction of FH than both a high level of ALT and high level of bilirubin [22]. In contrast, no significant differences were detected in the nr value in our study between the FH and near-miss FH patient groups.

In a study determining the early dynamic changes in ALF, it has been reported that total bilirubin of over 15 together with hepatic encephalopathy is a poor prognostic factor [36]. The presence of jaundice in DILI patients indicates a higher possibility of death, this rate has been determined as 9-12% [3,8,47,48]. There are studies reporting that liver injury is greater with higher bilirubin levels. It has been reported that when the bilirubin level is over 2 mg/dl, liver injury is high, and the patient must be guided to a hepatologist [3,12,49]. In our study, we showed that the total bilirubin was markedly higher in the FH group. However, we could not find any relation between total bilirubin and mortality. Discussions on the use of the MELD score in FH are ongoing. It has been shown that the MELD score predicts a 30-day survival in non-acetaminophen FH when LT has been performed [50]. Likewise, it has been reported in another study that the MELD score is as good as the King's College criteria in non-acetaminophen FH [51]. In a prospective study carried out in Denmark, it has been reported that MELD is an important parameter for predicting FH in patients that have taken an overdose of acetaminophen [52]. In a study on early prognostic factors in FH, it has been shown that MELD is a good predictor. In the same study, it has been show that there was a relation between a poor prognosis and creatinine>1.5, age>50, the presence of grade III-IV encephalopathy, and MELD>33 [53]. In our study, a statistical difference favoring FH was found upon comparison of both groups as regards MELD. Furthermore, we found that MELD is an independent risk factor for mortality. We are aware that there are contradicting data in the literature. We, therefore, are avoiding giving powerful messages in the subject of MELD.

Conclusion

The mean survival in FH with conservative treatment is 30% [54]. However, severe DILI patients without encephalopathy have a generally better prognosis than fulminant cases. FH is a potentially reversible disease when diagnosed early [55]. Therefore, ensuring the treatment of the patient in an intensive care unit in the early period to improve survival is important for the prognosis. So, the prediction of progression to fulminant hepatitis before hepatic encephalopathy develops and the clinical follow-up of patients accordingly are important. According to the results of this study, Ammonia can be evaluated as a marker (significant; $P<0.0001$) from the list in Table 1. This study can provide significant insight into patients with severe DIH.

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