International Journal of Advances in Medicine
Nabi T et al. Int J Adv Med. 2019 Apr;6(2):515-520
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20191168

Original Research Article

Clinical features, laboratory characteristics and outcome of patients with drug-induced acute liver failure

Tauseef Nabi[1], Nadeema Rafiq[2]*, Imran Jamil[3], Quratul Ain Arifa[4]

[1]Department of Endocrinology, Govt. Medical College, Srinagar, J&K, India
[2]Department of Physiology, Govt. Medical College, Baramulla, J&K, India
[3]Department of Medicine, MMU, Ambala, Haryana, India
[4]Department of Community Medicine, Govt. Medical College, Baramulla, J&K, India

Received: 08 February 2019
Accepted: 12 March 2019

***Correspondence:**
Dr. Nadeema Rafiq,
E-mail: dr.nadeema@gmail.com

ABSTRACT

Background: Acute liver failure (ALF) is a rare medical emergency. Its rapid progression and high mortality demand early diagnosis and expert management. Drug-induced ALF (DI-ALF) remains the uncommon cause of ALF in India. Clinical and etiological profile varies with geographical area and time. A prospective study of DI-ALF was carried with the aim to determine the clinical features, laboratory characteristics, outcome and hospital course.
Methods: A total of 15 patients with a diagnosis of DI-ALF were included in the study. The variables evaluated were demographic, signs and symptoms, biochemical parameters [bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT), internal normalization ratio (INR) etc.], outcome and course during hospitalization.
Results: Out of 15 DI-ALF patients, 12 had Anti-tuberculosis therapy (ATT) induced ALF and 3 patients had ayurvedic induced ALF. Majority of the patients were females (73.3%) and middle-aged (42.60±14.30 years). Coma grade at the time of admission showed that majority of patients (66.8%) had grade I and II encephalopathy. Depending on the pattern of liver injury, hepatocellular pattern was most common (53.3%) followed by mixed and cholestatic pattern. 40% of patients died with DI-ALF complications of which ATT induced ALF contributed 41.7%. Mean AST was more increased as compared to ALT. Development of ascites (P = 0.030) and mannitol use (P = 0.025) was significantly more common in non survived group than survived group. Length of hospital stay was significantly more in non survived group than survived group (P = 0.009).
Conclusions: ATT was the class of drugs most frequently associated with DI-ALF. DI-ALF disproportionately affected middle-aged women. Most DILI ALF patients had hepatocellular injury pattern. 40% of patients died with DI-ALF complications. Development of ascites, mannitol use and length of hospital stay was significantly more in non survived group than survived group.

Keywords: Acute Liver failure, Anti-tuberculosis therapy induced ALF, Drug-induced liver injury, Drug-induced ALF, Hepatic encephalopathy

INTRODUCTION

The liver has a central function in the metabolism of drugs, and as a result may be susceptible to its toxic or idiosyncratic effects. Acute liver failure (ALF) is a rare liver disorder that often leads to devastating consequences. ALF is a syndrome characterized by the development of hepatic encephalopathy (HE) together with signs of hepatocellular insufficiency, especially jaundice and coagulation disorders, in patients without

previous liver disease.[1] Fortunately, it is a rare disease with 2000 to 3000 reported cases in the United States per year.[2]

Etiology of ALF is diverse and shows wide geographical variation. The main etiological factor includes: viral, drugs including herbal and traditional medications, autoimmune, toxin and indeterminate.[3] Viral hepatitis is the commonest cause of acute liver failure in the Indian subcontinent and it accounts for 90% of cases.[4]

Drug-induced liver injury (DILI) is classified as either predictable or unpredictable (idiosyncratic).[5] The vast majority of DILI are idiosyncratic. DILI includes the whole spectrum from an asymptomatic elevation in liver tests to ALF. In fact, Drug-induced ALF (DI-ALF) remains the most common cause of ALF in the UK[6] and USA.[7] Specifically, in the UK, paracetamol overdose causes approximately 57% of all ALF with non-paracetamol drugs accounting for a further 11%.[6] DI-ALF is largely a diagnosis of exclusion because there are no laboratory, imaging, or biopsy findings that are specific for hepatotoxicity from a particular drug.[8]

The drugs responsible vary by location and prevailing drug use. The drugs most commonly implicated in ALF include antituberculosis therapies (ATT), HDS, sulpha-containing drugs, nitrofurantoin, phenytoin, sodium valproate, flutamide and amoxicillin-clavulanate.[9,10] Herbal or adulterated traditional or complementary medications are also a notable cause in east Asia.[11,12] Liver damage induced by drugs other than paracetamol has been the most frequent cause of safety-related marketing withdrawals in the past 50 years.[13] Fewer than 10% of DILI progress to ALF failure.[10] However, up to 70% of patients who develop liver failure might die or require transplantation.[10,12]

There are no characteristic features that differentiate DI-ALF from other causes. Nevertheless, DI-ALF can be distinguished from other causes of ALF by the drug history and subacute course. Typical allergic signature drug reactions are less frequently noted in DI-ALF patients than suggested by a survey.[9]

Mortality related to ALF can be attributed to three complications in particular: cerebral edema, multiorgan dysfunction syndrome, and sepsis. The overall management strategy starts with the identification of cause and an initial assessment of prognosis. Because there is no specific therapy for ALF, treatment is limited to supportive measures that anticipate complications, allowing the liver time to regenerate. Treatment of suspected DI-ALF is to stop using the drug before the development of irreversible hepatic failure.

Therapies that have been directed at reducing tissue injury, removing accumulated toxins, and promoting hepatocyte regeneration (include interferon, insulin and glucagon, prostaglandin E1, charcoal hemoperfusion, exchange transfusion, and hyperimmunoglobulin infusion) have proven ineffective and are under trials.[14-17] Although many people recover with supportive treatment; Orthotropic liver transplantation (OLT) remains the only definitive therapy for patients with ALF. OLT has made a significant impact on survival of patients with ALF.[7]

There is limited availability of specific antidotes to DI-ALF. Two studies showed no benefit of corticosteroids in ALF and even demonstrated a poorer outcome in those with DI-ALF.[18,19] NAC has a well-established role in paracetamol-induced ALF although it is now also recommended in selected cases of non-paracetamol ALF.[20-23]

The present study was carried out to determine the clinical features, laboratory characteristics, outcome and hospital course of DI-ALF in Kashmir (North India), an endemic zone viral ALF.

METHODS

It was a single centre prospective study of adult patients with DI-ALF. This study was carried out in the Department of Gastroenterology of Sher-i-Kashmir Institute of Medical Science (SKIMS), Soura, J&K. The study was approved by the institutional ethical committee (SKIMS).

Study subjects

Total of 15 consecutive patients with diagnoses of DI-ALF who fulfilled eligibility criteria were recruited in the study. This study was conducted from 2011 to 2014. Information regarding various demographics characteristics was taken through well structured questionnaires from all subjects. Besides a detailed history, physical examination and biochemical workup which included baseline investigations, liver function test (LFT), coagulogram of subjects were carried out. Informed consent was obtained from all the recruited subjects.

Eligibility criteria

Inclusion criteria include patients having age >18years and DI-ALF was defined as biochemical evidence of acute liver injury with INR ≥1.5 and any degree of encephalopathy caused by the illness of duration <26 weeks in a patient with no prior known liver disease with history of hepatotoxic drug intake, including homeopathic, herbal medications at least for >1wks. Exclusion criteria include i) Viral ALF, ii) Autoimmune ALF, iii) Acute on chronic liver failure, iv) ALF during pregnancy, iv) Hepatic shock.

Detailed study design

After ALF was diagnosed, a detailed history was taken for any hepatotoxic drug intake, including homeopathic,

herbal medications and intravenous drug abuse. DI-ALF is largely a diagnosis of exclusion because there are no laboratory, imaging, or biopsy findings that are specific for hepatotoxicity from a particular drug. Blood samples of all the patients were taken for exclusion of other etiological diagnoses, which included hepatitis B surface antigen (HBsAg), hepatitis B core IgM (HBc-IgM), hepatitis A virus IgM (HAV-IgM), and hepatitis E virus IgM (HEV-IgM), hepatitis D virus (IgG and IgM anti-HDV), anti HCV (hepatitis C virus), ANA (anti nuclear antibody), ASMA (anti smooth muscle antibody), Wilson profile (serum ceruloplasmin, serum copper) and iron profile.

HSV (herpes simplex virus), CMV (cytomegalovirus) and EBV (Epstein barr virus) serology were done if non hepatotropic viruses were suspected as a cause of ALF in immunocompromised patients. Imaging was obtained to rule out biliary processes, hepatic vascular abnormalities, and intrahepatic lesions. Patients were given the option of liver transplant (to be done at the hospital with transplantation facility) at various stages of study when indicated. Liver injury pattern can be hepatocellular, cholestatic and mixed. Calculation of *R* value.[24]

ALT/AST value divided by its ULN = fold elevation/fold elevation above ULN for alkaline phosphatise.

Definitions

- Hepatocellular injury = $R>5$
- Cholestatic injury = $R<2$
- Mixed injury = $R>2<5$

Supportive treatment

All patients were managed with the standard supportive care treatment with stoppage of the offending drug.[25] The patients received treatment of and prevention for the complications of ALF.[26]

The treatment mainly involved continuous intravenous dextrose to prevent hypoglycemia; proton pump inhibitors for stress-related ulcers and lactulose enema. With the development of advanced HE, intensive care management, fluid and electrolyte balance, midazolam sedation and mannitol infusion in case of raised intracranial pressure. Fresh frozen plasma and vitamin K was given in only those patients who had a spontaneous bleed. Blood and urine cultures were obtained in suspected cases of sepsis, which were then treated as per sensitivity. Renal impairment was defined as serum creatinine level of more than 1.5mg/dl.

Monitoring

Patients were monitored clinically (Grade of HE) and biochemically (bilirubin, PT, INR etc.). In addition, morbidity and mortality were also assessed.

Statistical analysis

Frequency distribution was assessed in terms of means ± SD for quantitative variables and number (percentages) for categorical variables. In univariate analysis, the categorical variables were compared by using $\chi 2$ test or Fisher exact test where appropriate. For continuous variables, the independent sample t-test was used. *P* values <0.05 was considered statistically significant. All the analyses were performed by the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA, version 21.0).

RESULTS

In our study out of 15 DI-ALF patients, 12 (80%) had Anti-tuberculosis therapy (ATT) induced ALF and 3 (20%) patients had ayurvedic induced ALF.

Table 1: Baseline characteristics of drug-induced ALF.

Characteristics	Drug-induced ALF n=15
Categorical variables [n (%)]	
Female gender	11 (73.3%)
Hepatic- encephalopathy	
Grade I	7 (46.7%)
Grade II	3 (20%)
Grade III	2 (13.3%)
Grade IV	3 (20%)
Fever	6 (40%)
Vomiting	4 (26.7%)
Rash	2 (13.3%)
Hepatocellular pattern of liver injury	8 (53.3%)
Cholestatic pattern	1 (6.7%)
Mixed pattern	6 (40%)
Mortality	6 (40%)
Continuous variables [Mean±SD]	
Age (Years)	42.60±14.30
INR	2.57±1.19
Bilirubin (mg/dl)	16.4±8.50
AST (mg/dl)	1320±534
ALT (mg/dl)	990.62±623
Albumin (g/dl)	2.13±0.42
Creatinine (mg/dl)	1.23±0.70
Interval between jaundice and encephalopathy (days)	28±18.30
MELD Score	27.45±5.85

Table 1 shows the distribution of baseline characteristics (both categorical and continuous) of DI-ALF. All the patients were of Kashmiri ethnicity. Majority of the patients were females (73.3%). Coma grade at the time of admission showed that majority of patients (66.8%) had grade I and II encephalopathy. 2 (13.3%) patients had a rash at presentation. Depending on the pattern of liver

injury, hepatocellular pattern was most common (53.3%) followed by mixed and cholestatic pattern. A total of 6 (40%) patients died with DI-ALF complications of which ayurvedic induced ALF contributed 1 (33.3%) and ATT induced ALF 5 (41.7%). The mean age of DI-ALF patients was 42.60±14.30 years. Mean AST was more increased as compared to ALT 1320±534 and 990.62±623 mg/dl respectively. Mean MELD score was 27.45±5.85.

Table 2: Hospital course of drug-induced ALF.

Characteristics	Survived group N=9	Non survived group N=6	P-value*
	N (%)	N (%)	
Renal failure	3 (33.3%)	1 (16.7%)	0.491
Development of ascitis	1 (11.1%)	4 (66.7%)	0.030
Infection	7 (77.8%)	2 (33.3%)	0.095
Mannitol	2 (22.2%)	5 (83.3%)	0.025
Hypotension	1 (11.1%)	2 (33.3%)	0.308
Mechanical ventilation	2 (22.2%)	1 (16.7%)	0.801
UGI bleeding	2 (22.2%)	1 (16.7%)	0.801

*P-value <0.05 is considered statistically significant

A total of 4 patients developed renal failure during the hospital course with 3 (33.3%) in survived group versus 1 (16.7%) in non survived group (P=0.491). The other complication included infections in 7 (77.8%) patients in survived group versus 2 (33.3%) patients in non survived group (P=0.095). Mannitol was used in 46.7% of patients with 22.2% in non survived group versus 83.3% in non survived group and the difference was statistically significant (P = 0.025). Development of ascites was also significantly higher in non survived group than non survived group (P=0.030). Complication like hypotension and UGI bleed were similar between both groups (P = ns) (Table 2).

The mean number of days of admission in hospital in the survived group was 8.90±2.20 versus 12.3±2.10 in non survived group. The difference between the two groups was statistically significant (P = 0.009) (Table 3).

DISCUSSION

ALF is severe hepatic dysfunction that is characterized by rapid onset, hepatic encephalopathy, and coagulopathy, in the absence of preexisting liver disease.[27] Drug-induced ALF (DI-ALF) remains the most common cause of ALF in the UK and USA.[6,7] DI-ALF is largely a diagnosis of exclusion because there are no laboratory, imaging, or biopsy findings that are specific for hepatotoxicity from a particular drug.[8] Each different etiology leads to a similar final common pathway. Trying to determine etiology is essential, however, as outcomes and the use of antidotes depend on the identification of the causative process. OLT has remained the treatment of choice for DI-ALF.[28,29] So the prospective study was carried out to determine the clinical characteristics and hospital course and outcome of DI-ALF in Kashmir (North India).

Table 3: Length of hospital stay in survived group and death group.

	Survived group Mean±SD (range)	Non survived group Mean±SD (range)	P-value*
Duration of hospital stay (days)	8.90±2.20 (6-13)	12.3±2.10 (10-14)	0.009

In this study out of 15 DI-ALF patients, 12 (80%) had ATT induced ALF and 3 (20%) patients had ayurvedic induced ALF. ATT also topped the list of DI-ALF in India as studied by Devarbhavi H et al.[30,31] where acetaminophen use is rare and tuberculosis is prevalent. In India, antituberculosis drugs account for nearly three-quarters of all DI-ALF cases.[32,33]

Majority of the patients in our study were middle-aged (42.60±14.30 years) and females (73.3%). Which is similar to the ALFSG study, where the average age of subjects was 44 years and the majority were women (71%).[9] In a case series of 128 patients with ALF (including 21 children <18 years old) from Bangalore, India, the mean age was 38 years.[31,32] While in India, 53% of ALF cases were seen in females.[34] The higher female incidence could be attributed to a higher likelihood of hepatotoxicity from drugs.[11,35,36]

Coma grade at the time of admission in our study showed that the majority of patients (66.8%) had grade I and II encephalopathy. Devarbhavi H et al, in his study showed 59.7% patients had grade I and II encephalopathy in DI-ALF.[32] While other study showed majority of patients (68%) had grade 2 or higher encephalopathy.[9] The higher grade of encephalopathy in their study may be because their patients had more complicating factors than ours like one-half of patients had some degree of renal impairment (Creatinine ≥1.5mg/dl) and MELD score was 33.

Depending on the pattern of liver injury in this study, hepatocellular pattern was most common (53.3%) followed by mixed and cholestatic pattern. 40% of patients died with DI-ALF complications of which ATT induced ALF 5 (41.7%) contributed the most followed by ayurvedic induced ALF contributed 1 (33.3%). In the ALFSG study, 78% had hepatocellular injury, 13% had cholestatic injury, and 10% had mixed pattern.[9] Suggesting hepatocellular pattern was most common. Studies from India showed mortality ranged between 67.1% to 70% which is higher than ours.[33,37] The reason for higher mortality in their study is because their patients had more severe disease as suggested by higher MELD,

INR, and higher grade of HE. Studies from US and Spain reported 72% mortality/liver transplantation.[38,39] While Devarbhavi H et al, in other study reported 65.6% in DI-ALF in adults and children.[32]

In our study mean AST was more increased as compared to ALT. Mannitol was used during the hospital course in 46.7% of DI-ALF patients with 22.2% in non survived group versus 83.3% in non survived group and the difference was statistically significant (P=0.025). Development of ascites was also significantly higher in non survived group than non survived group (P = 0.030). Length of hospital stay was significantly more in non survived group than the survived group. Other study also showed that AST levels were higher in ALF patients.[28] Reuben A et al, also reported ascites in 25% of patients while in our study 33.3% of DI-ALF patients had ascites.[9,7]

CONCLUSION

ATT was the class of drugs most frequently associated with DI-ALF and to a lesser extent by ayurvedic medication. DI- ALF disproportionately affected middle-aged women. Most DI-ALF patients have hepatocellular injury pattern. Ascites was the most serious complications of DI-ALF. 40% of patients died with DI-ALF complications. Mortality was higher in ATT induced ALF as compared to ayurvedic induced ALF. Length of hospital stay was significantly more in non survived group than the survived group.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of Sher-i-Kashmir Institute of Medical Science (SKIMS), Soura, J&K, India

REFERENCES

1. Trey C, Davidson CS. The management of fulminant hepatic failure. Prog Liver Dis. 1970;3:282-98.
2. Hoofnagle JH, Carithers RL Jr, Shapiro C, Ascher N. Fulminant hepatic failure: summary of a workshop. Hepatol. 1995;21(1):240-52.
3. Ostapowicz G, Fontana RJ, Schiodt FV. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med. 2002;137:947-54.
4. Acharya SK, Dasarathy S, Kumer TL, Sushma S, Prasanna KS, Tandon A, et al. Fulminant hepatitis in tropical population: clinical course, cause, and early predictors of outcome. Hepatol. 1996;23:1448-55.
5. Kaplowitz N. Drug-induced liver injury. Clin Infect Dis. 2004;38(Suppl 2):44-8.
6. Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2013;369:2525-34.
7. Lee WM. Acute liver failure in the United States. Semin Liver Dis. 2003;23:217-26.
8. Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, et al. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. Gastroenterol. 2015;148(7):1340-52.
9. Reuben A, Koch DG, Lee WM. Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a US multicenter, prospective study. Hepatol. 2010;52:2065-76.
10. Andrade RJ, Lucena MI, Fernandez MC, Pelaez G, Pachkoria K, García-Ruiz E, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterol. 2005;129(2):512-21.
11. Bjornsson E, Olsson R. Suspected drug-induced liver fatalities reported to the WHO database. Dig Liver Dis. 2006;38:33-8.
12. Wai CT, Tan BH, Chan CL, Sutedja DS, Lee YM, Khor C, et al. Drug-induced liver injury at an Asian center: a prospective study. Liver Int. 2007;27:465-74.
13. Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med. 2006;354:731-39.
14. Woolf GM, Redeker AG. Treatment of fulminant hepatic failure with insulin and glucagon: a randomized, controlled trial. Dig Dis Sci. 1991;36:92-6.
15. Sinclair SB, Greig PD, Blendis LM, Abecassis M, Roberts EA, Phillips MJ, et al. Biochemical and clinical response of fulminant viral hepatitis to administration of prostaglandin E: a preliminary report. J Clin Invest. 1989;84:1063-9.
16. O'Grady JG, Gimson AE, O'Brien CJ, Pucknell A, Hughes RD, Williams R. Controlled trials of charcoal hemoperfusion and prognostic factors in fulminant hepatic failure. Gastroenterol. 1988;94(1):1186-92.
17. Redeker AG, Yamahiro HS. Controlled trial of exchange-transfusion therapy in fulminant hepatitis. Lancet. 1973;1:3-6.
18. Randomised trial of steroid therapy in acute liver failure. Report from the European Association for the Study of the Liver (EASL). Gut. 1979;20:620-3.
19. Karkhanis J, Verna EC, Chang MS, Stravitz RT, Schilsky M, Lee WM, et al. Steroid use in acute liver failure. Hepatol. 2014;59:612-21.
20. Polson J, Lee WM. American Association for the Study of Liver Disease. AASLD position paper: the management of acute liver failure. Hepatol. 2005;41:1179-97.
21. Nabi T, Nabi S, Rafiq N, Shah A. Role of N-acetylcysteine treatment in non-acetaminophen-induced acute liver failure: A prospective study. Saudi J Gastroenterol. 2017;23(3):169-75.
22. Chughlay MF, Kramer N, Spearman CW, Werfalli M, Cohen K. N-acetylcysteine for non-paracetamol drug-induced liver injury: a systematic review. Br J Clin Pharmacol. 2016;81(6):1021-9.

23. Darweesh SK, Ibrahim MF, El-Tahawy MA. Effect of N-Acetylcysteine on mortality and liver transplantation rate in non-acetaminophen-induced acute liver failure: a multicenter study. Clin Drug Investig. 2017;37(5):473-82.
24. Danan G, Benichou C. Causality assessment of adverse reactions to drugs-I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol. 1993;46:1323-30.
25. Lee WM, Larson AM, Stravitz RT. AASLD Position Paper: The Management of Acute Liver Failure: Update, 2011. Available at: http://www.aasld.org/practiceguidelines/Documents/AcuteLiverFailureUpdate2011.pdf. Accessed on January 2019.
26. Rolando N, Harvey F, Brahm J, Howard JP, Alexander G, Gimson A, et al. Prospective study of bacterial infections in acute liver failure: an analysis of fifty patients. Hepatol. 1990;11:49-53.
27. Bernal W, Lee WM, Wendon J, Larsen FS, Williams R. Acute liver failure: a curable disease by 2024? J Hepatol. 2015;62(Suppl 1):112-20.
28. Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug induced liver injury in the United States. Liver Transpl. 2004;10:1018-23.
29. Mindikoglu AL, Magder LS, Regev A. Outcome of liver transplantation for drug induced acute liver failure in the US. Analysis of the UNOS database. Liver Transpl. 2009;15:719-29.
30. Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. Am J Gastroenterol. 2010;105:2396-404.
31. Devarbhavi H. Acute liver failure induced by anti-infectious drugs: causes and management. Curr Hepatol Rep. 2017;16(4):276-85.
32. Devarbhavi H, Patil M, Reddy VV, Singh R, Joseph T, Ganga D. Drug-induced acute liver failure in children and adults: Results of a single-centre study of 128 patients. Liver Int. 2018;38(7):1322-9.
33. Kumar R, Bhatia V, Khanal S, Sreenivas V, Gupta SD, Panda SK, Acharya SK. Antituberculosis therapy-induced acute liver failure: magnitude, profile, prognosis, and predictors of outcome. Hepatology. 2010;51(5):1665-74.
34. Rathi C, Pipaliya N, Patel R, Ingle M, Phadke A, Sawant P. Drug induced liver injury at a tertiary hospital in India: etiology, clinical features and predictors of mortality. Ann Hepatol. 2017;16(3):442-50.
35. Andrade RJ, Lucena MI, Ferna´ndez MC, Kaplowitz N. Drug-induced liver disease. Chapter 1. In: Kaplowtiz N, DeLeve LD, editors. Drug-induced liver disease. 2nd ed. New York: Informa Healthcare; 2007:1-11.
36. Spanish Group for the Study of Drug-Induced Liver Disease. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish Registry over a 10-year period. Gastroenterology; 2005;129:512-21.
37. Devarbhavi H, Dierkhising R, Kremers WK. Antituberculosis therapy drug-induced liver injury and acute liver failure. Hepatol. 2010;52(2):798-9.
38. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. Lancet. 1993;342:273-5.
39. Tost JR, Vidal R, Caylà J, Diaz-Cabanela D, Jimenez A, Broquetas JM. Severe hepatotoxicity due to anti-tuberculosis drugs in Spain. Int J Tuberc Lung Dis. 2005;9:534-40.

Cite this article as: Nabi T, Rafiq N, Jamil I, Arifa QA. Clinical features, laboratory characteristics and outcome of patients with drug-induced acute liver failure. Int J Adv Med 2019;6:515-20.