Original Paper

ETIOLOGICAL STUDY OF ACUTE ON CHRONIC LIVER FAILURE AMONG PATIENTS ADMITTED IN MEDICINE WARD IN CHITTAGONG MEDICAL COLLEGE HOSPITAL

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Abstract

Introduction: Acute on chronic liver failure (ACLF) is defined as acute hepatic insult manifesting as jaundice and coagulopathy complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease. It has various etiology and manifestations, as well as high mortality. These etiologies vary depending on geographical region - from east to west. For example, infectious etiologies predominate in the east whereas alcohol and drugs constitute the majority of acute insults in west. In Asian region, reactivation of hepatitis B virus and superinfection with hepatitis E virus are more common among the infectious etiologies.

Objective: As the incidence of chronic liver disease is increasing day by day and the etiology of acute decompensation of underlying chronic liver disease varies depending on geographical location, so it may be different in Bangladesh from other Asian countries. A very few studies have been published so far showing etiological prevalence of Acute on Chronic Liver Failure (ACLF) in Bangladesh. This study has been conducted to address the etiology of ACLF in our perspective.

Methods: A cross sectional longitudinal study carried out in the department of Medicine, Chittagong Medical College Hospital. Thirty patients admitted with ACLF as defined by Asia Pacific Association for Study of Liver Disease (APASL) were consecutively included. Detailed history, complete physical examination and laboratory investigations were done for each patient.

Results: From January 2009 to December 2009, among thirty patients 6 cases (20%) of ACLF was caused by HEV super infection followed by Sepsis (16.67%), variceal bleeding (13.33%) and hepatotoxic drugs (3.33%) respectively. Multiple factors were found in (16.67%) cases while no cause could be identified in (30%) cases. In our study common causes of chronic liver diseases were hepatitis B (50%), hepatitis C (26.67%) and alcohol (16.67%). Among thirty patients five died within forty eight hours of hospital admission. In hospital mortality was 16.67%.

Conclusion: Acute on Chronic Liver Failure (ACLF) is one of the commonest causes of mortality, morbidity and socio-economic burden particularly in Bangladesh. Early detection and proper management of acute events that lead to ACLF would alleviate mortality and morbidity. However due to high treatment cost, proper management of chronic liver diseases as well as ACLF cannot be afforded by most people in our country.

Key-words: Acute on Chronic Liver Failure, Sepsis, Hepatitis B virus, Hepatitis E virus.

Introduction

Liver failure can develop as Acute Liver Failure (ALF) in the absence of any preexisting liver disease, or a chronic decompensation of an end-stage liver disease naming Chronic Liver failure (CLF), or an acute deterioration of known or unknown chronic

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liver disease known as Acute-on-Chronic Liver Failure (ACLF)[1]. The terminology, Acute-on-chronic liver failure (ACLF) was first used in 1995 to describe a condition in which two insults to liver are operating simultaneously, one of them is ongoing and chronic and the other one is acute[2]. Current recommendation by APASL (Asian Pacific Association for the study of liver) in defining acute on chronic liver failure is: Acute hepatic insult manifesting as jaundice (serum bilirubin>5 mg/dl) and coagulopathy (INR >1.5), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease[1]. ACLF has various etiology and manifestations, as well as high mortality. Acute insults that lead to acute decompensation of underlying chronic liver disease (CLD) vary depending on the geographical location and the population under study. They include both infectious and non-infectious causes. Infectious etiologies predominate in the east whereas alcohol and drugs constitute the majority of acute insults in the west. Among the infectious etiologies, reactivation of hepatitis B virus (HBV) infection is one of the major causes of ACLF in the Asian region[3,4]. The other very important infectious etiology of the acute event is superinfection with hepatitis E virus, predominantly in patients in the Indian subcontinent[5,6,7]. Whereas HAV infection have been found as the root of acute decompensation in some western trials. But we are in the endemic zone for HAV and infection occurs at a very early age which provides long-time possibly life-long immunity. So HAV is less likely to be a cause of acute decompensation in our country. Various bacterial, parasitic, fungal, protozoal and spirochetal infections may also affect the liver[8]. These infections may lead to liver failure in patients with underlying chronic liver disease. Sepsis plays an important role in the progression and management decisions of ACLF and it also has been recognized as an integral cause for the development of ACLF. Among the noninfectious etiologies hepatotoxic drugs, herbal indigenous medicines, variceal bleeding, major surgical procedure are important causes of ACLF[9,10,11]. As the incidence of chronic liver disease is increasing day by day and the etiology of acute decompensation of underlying chronic liver disease varies depending on geographical location, so it may be different in Bangladesh from other countries. Some causes of this acute decompensation are preventable if patients can be made aware of these factors and reversible if treated with appropriate liver support. To our knowledge, studies published showing etiological prevalence of ACLF in Bangladesh very scares. So to know the etiology of ACLF in our perspective will be very helpful to prevent, treat and hence to reduce mortality and morbidity of patients with ACLF.

Materials & Methods

It was a cross sectional longitudinal study carried out in the department of Medicine, Chittagong Medical College Hospital during the period of January 2009 to December 2009. Thirty patients admitted with ACLF as defined by Asia Pacific Association for Study of Liver Disease (APASL) were consecutively included. Patients of Acute viral hepatitis, drug Induced hepatitis, patient suffering from Hepatocelluar Carcinoma, and obstructive biliary disease were excluded. Ethical clearance was taken prior to commencing this study. Detailed history, complete physical examinations and laboratory investigations were done for each patient. The diagnosis of underlying cirrhosis was made based on clinical, biochemical, endoscopic (oesophageal varices at least grade-II in size), ultrasonographical (presence of nodular irregular liver with portosystemic collaterals) findings. Endoscopy was carried out after hospital admission and initial stabilization, in some cases recent past endoscopy were considered. Hepatitis viral markers (HBsAg, IgM Anti-HEV, Anti-HCV, IgM Anti-HAV) were carried out by enzyme linked immunosorbant assay (ELISA). Sepsis was defined as the presence of raised temperature of 100^0F, neutrophilic leucocytosis and sometimes evidences of focus of infection like specimen culture. Combination of factors like sepsis, dyselectrolytaemia, variceal bleeding was defined as multiple factors. All the patients were treated conservatively. Oral antiviral agents were used in patients with HBV infection. Supportive measures like albumin infusion, broad spectrum antibiotics, mannitol infusion, lactulose and proton pump inhibitor, glucose and vitamins were given as needed. In some cases intravenous vasopressor agent such as vasopressin was used and endoscopic variceal ligation was performed in patients with variceal bleeding.

Results

In our study males are more frequently affected (86%) than female in all age group. Bulk of the study population 9 (30%) were between 45-54 years followed by 6 (20%) were between 55-64 years of age. Majority of the study population belongs to low (upto BDT.60,000 per annum) socioeconomic (83.33%), primarily educated (40%) and illiterate (36.67%) group. Jaundice (100%), ascites (100%), leg oedema (80%) and encephalopathy (100%), were presenting features and oliguria, abdominal pain, fever, features of variceal bleeding and constipation were the additional features. HEV superinfection is most frequently occurring causes 6 (20%) of acute decompensation of chronic liver disease followed by sepsis 5 (16.67%). Variceal bleeding contributes to 4 (13.33%) cases, hepatotoxic drugs (NSAIDS) responsible in only 1 (3.33%) case and others unidentified causes responsible in about 9 (30%) cases. It is mentionable that in a significant proportion of patients (16.67%), multiple factors were found to be responsible for acute decompensation of chronic liver disease (Table-I).

Table-I: Etiology of acute decompensation among patients with ACLF (n=30)

Precipitating factors	Frequency of Occurrence	Percentage
HEV superinfection	6	20
Multifactorial	5	16.67
Sepsis	5	16.67
Variceal bleeding	4	13.33
Drugs	1	3.33
Unknown	9	30
Reactivation of hepatitis B or C virus	0	0
HAV super infection	0	0
Alcohol	0	0
Total	**30**	**100**

Among thirty patients five (16.67%) died within forty eight hours of hospital admission. In hospital mortality was 16.67% which was related to higher grades of encephalopathy at presentation, HEV super-infection and variceal bleeding and presence of multi-factorial etiology for acute decompensation (Table-II).

Principle cause (76.67%) of chronic liver disease of our study population is hepatitis virus infection. Among them HBV accounts for 15 (50%) cases and HCV accounts for 8 (26.67%) cases. Alcohol contributes in 5 (16.67%) cases, metabolic and cryptogenic causes accounts for only 3.33% in each case.

Table-II: Clinical profile of patients who succumbed to death.

Patients characteristic	Case 4	Case 7	Case 8	Case 22	Case 26
Age	55 years	54 Years	55 Years	45 Years	50 Years
Sex	Male	Male	Female	Male	Male
Grade of encephalopathy	Grade III	Grade IV	Grade IV	Grade III	Grade III
Past history of hospitalization for acute decompensation of CLD	Yes	Yes	Yes	Yes	Yes
Etiology of acute decompensation	Multifactorial	Multifactorial	Variceal bleeding,	Multifactorial	HEV superinfection
Time interval from admission to death	48 hours	48 hours	24 hours	24 hours	48 hours

Discussion

This cross sectional longitudinal study was carried out to determine and analyse the etiology of ACLF. Majority of the study population were above the 45 years of age. Ramachandran et al[2], Z Azam et al[12] and Krishna Y.R et al[13] in their study also showed similar age of presentation. In our study, male incidence is six times more than female. The reason for increased incidence may be more exposure of male to environmental contamination, accidental cuts, razor trauma of shaving and circumcision.

Our study showed that incidence of ACLF is the highest among low income group. Studies have found an association between low socioeconomic status and increased cirrhosis incidence[14,15], but it remains unclear whether low socioeconomic status is also associated with a worse prognosis in patients with cirrhosis[16]. Several factors might contribute to the worse prognosis of cirrhosis in patients with low socioeconomic status such as poor are poor in seeking medical advice, compliance and even presence of co-morbid diseases.

We found, jaundice, ascites, encephalopathy as presenting features which satisfied the APASL definition of ACLF. But in the study of Z Azam et al[12] serum bilirubin were adopted 2 mg/dl. It is mentionable that during our study period, we also found patients with similar characteristics but as we have adopted APASL criteria, we excluded those patients. So we feel whether APASL criteria for ACLF need to be redefined.

In our study, 20% patients were positive for Anti-HEV IgM. Mahtab et al[17] from Bangabandhu Sheik Mujib Medical University, Bangladesh, showed 21.7% (15/59) patients were positive for Anti-HEV IgM in his study which correlates well with our findings. In a study from New Delhi, India, 72 patients with acute decompensation of HBV related cirrhosis of liver were considered where HEV was identified as a major culprit with Anti-HEV IgM being positive in 8.64%[18]. Hepatitis E virus has also been implicated as a cause of acute decompensation of previously unrecognized asymptomatic patients with HBV related chronic liver disease[19]. In a different study from Karachi, Pakistan, also describes patients with recently decompensated cirrhosis of liver, who were tested positive for Anti-HEV IgM[12,20].

No patients were found positive for Anti-HAV IgM. In this study Alcohol intake does not contribute to any cases of acute decompensation though it is responsible for 16.67% (5/30) of underlying cirrhosis. Probably this is because patients become abstained from alcohol after developing chronic liver diseases. In our study 16.67% patients showed evidence of sepsis. Lack of personal hygiene, inadequate treatment of causal CLD and failure of early recognition may be the underlying cause of developing sepsis and consequently ACLF.

The present study showed variceal bleeding contributes 13.33% cases of acute decompensation which differs with that of Mahtab et al[17] where this factor contributes to only 4.3% case.

But our figure is akin to previous study of Krishna Y. R.[13] et al where it was reported as 11.4% cases. Hepatotoxic drugs such as NSAIDs induced acute decompensation contributes to 3.33% (1/30) cases of ACLF in our study. Z Azam et al[12] reported 4.35% case (1/23) due to hepatotoxic drug which is close to our finding.

Reactivation of Hepatitis B or C virus is another strong possible cause of acute decompensation[1]. Study of Kumar M. et al[19] also addressed this. We strongly feel that this factor may also play a very great role in significant number of cases. But during hospital stay we could not perform HBV DNA and HCV RNA because of financial constraints of patients and unavailability of laboratory facilities in our hospital. This is one of the limitations of our study. In 16.67% (5/30) of patients, we found multiple etiological factors (e.g. sepsis, variceal bleeding, dyselectrolytaemia) causing acute decompensation and 3 out of 5 patients with this etiology ultimately died. Lack of health awareness, late reporting to hospitals and inadequate treatment may be the underlying causes of developing multiple etiologies in those patients. This issue of multifactorial cause of acute decompensation has not been focused in previous studies. So this may be an issue for future work. Reasons of acute decompensation could not be established in 30% cases of this study. This figure is close to the study of Z Azam et al[12] where they reported 43.48% (10/23) cases of ACLF of unknown etiology. The present study revealed that mortality is related to multifactorial etiology, HEV superinfection, higher grade of encephalopathy, variceal bleeding, history of repeated hospitalization for acute decompensation, and old age. This study also observed that mortality usually occurred within forty eight hours of hospital admission which may be due to late presentation to hospital consultation and advanced stage of disease with failure to respond to available treatment facility. Thus early recognition and referral, optimum treatment can improve the prognosis. However liver transplantation and liver support devices Molecular Adsorbent Recycling System (MARS) could improve the outcome.

In this study, HBV infection is the major cause 50% (15/30) of underlying chronic liver diseases which correlates with previous studies[21,22]. In Taiwan after universal vaccination program against HBV, incidence of HBV related chronic liver disease had been reduced significantly[23]. But in our country, possibly due to high cost of hepatitis B vaccination it can not be afforded by all people, so HBV related cirrhosis is still very high (50%). We are very much hopeful that as hepatitis B vaccination is integrated into the expanded program on immunization to interrupt prenatal and early horizontal transmission of HBV, the subsequent development of hepatitis B related chronic liver disease will be reduced.

This study showed HCV infection contributes 26.67% (8/30) cases of causal chronic liver diseases. Whereas a study in Egypt showed HCV is the main causes (73.5%) of chronic liver disease[24] which mirror the geographical variation in prevalence of hepatitis virus infection. Alcohol constitutes 16.67% (5/30) cases of causal CLD that is parallel to Krishna Y. R. et al[13] where it was 11%. This low percentage is due to our religious and conservative view of the society towards alcohol drinking. The present study shows Wilson's diseases contribute to 3.33% (1/30) patients of cirrhosis which is close to the study by Jeyamoni Ramchandra et al[2] at Christian medical college, Vellore, Tamilnadu who showed Wilson's diseases constituted 5% cases of chronic liver diseases. In 3.33% case no etiology of causal chronic liver diseases was found in this study. This is labeled as cryptogenic causes of cirrhosis. In the UK, this figure stands between 5% and 10%[25].

Conclusion

Acute on chronic liver failure is a separate clinical entity as its clinical features, diagnostic criteria and treatment aspects are different from those of other form of liver failure. ACLF is one of the common causes of mortality, morbidity and socio-economic burden particularly in Bangladesh. This study reflected that major part of the affected people belongs to poor economic class.As treatment cost is very high, proper management of chronic liver diseases as well as ACLF can not be afforded by this group of people. However many causes of acute decompensation can be prevented by improving sanitation, vaccination providing safe water supply, and early recognition of infection thus mortality and morbidity could be reduced. This study demands the redefinition of ACLF. As Z Azam et al[12] observed serum bilirubin level at lower level than APSAL criteria (<5mg/dl) in their study, so this level of serum bilirubin may be adopted in future study . As it is a small study, we recommend large and multi center study before drawing conclusion.

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