INTRODUCTION

Cirrhosis is an end-stage liver disease having reported global prevalence of 4.5% to 9.5%.\textsuperscript{1,2} Cirrhosis of liver with its well-known complications, contributes significantly to overall mortality worldwide.

Haemorrhagic versus non haemorrhagic ascites in cirrhosis: Their relationship and impact on prognosis of liver cirrhosis

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ABSTRACT

Objectives: To evaluate the impact of haemorrhagic ascites on prognosis of patients with advance cirrhosis, this study was further aimed to assess the relationship between haemorrhagic ascites and advance cirrhosis and its effect on prognosis.

Methods: Eight hundred and thirty-eight patients having liver cirrhosis with ascites were analyzed retrospectively (over three years) while segregated into two groups haemorrhagic and non haemorrhagic ascites. Patient outcome variables were identified among both groups and independent predictors for survival were analyzed. Kaplan-Meier survival estimates determined survival rate comparison between groups.

Results: Haemorrhagic ascites was detected in (26.6%) patients. Spontaneous haemorrhagic ascites (79%) was the main cause of haemorrhagic ascites followed by hepatocellular carcinoma (14%) and iatrogenic (7.6%). Spontaneous bacterial peritonitis and acute kidney injury were statistically significant (p= 0.0001, 0.0001) among groups. Overall mortality at year three was higher (83%) in haemorrhagic ascites group. Survival among both groups (haemorrhagic versus non haemorrhagic) at one month, one year and three year was found to be significant (p= 0.000, 0.000 and 0.000).

Conclusion: Haemorrhagic ascites impact overall survival with more mortality in comparison to non haemorrhagic ascites. Haemorrhagic ascites was an independent predictor of survival. Haemorrhagic ascites is possibly considered another predictor of survival among advance cirrhosis.

KEYWORDS: Ascites, Hemorrhagic, Cirrhosis, Portal hypertension, Spontaneous bacterial peritonitis.

Haemorrhagic ascites being most frequent complication of cirrhosis of liver is also the commonest reason for hospital admission in cirrhotic patients.\textsuperscript{3} Presence of ascites profoundly impacts survival of cirrhotic patients as evidenced by reported mortality of 15% and 44% within one and five year respectively.\textsuperscript{4} Hemorrhagic ascites defined as red blood cell (RBC) count greater than 10,000/mm\textsuperscript{3} against normal RBC count (< 1000/mm\textsuperscript{3}) in ascitic fluid, is less frequent yet challenging complication among cirrhotic patients with ascites.\textsuperscript{5} Haemorrhagic ascites has 5% reported prevalence among cirrhotics with atypical features in comparison to usual ascites.\textsuperscript{6} Haemorrhagic ascites with its enhancing impact on morbidity and mortality of cirrhotic patients in relation to hepatocellular carcinoma, ruptured varices and trauma has been elaborated in earlier studies.\textsuperscript{6,7} The importance of routine ascitic fluid analysis in hospitalized patients with cirrhosis...
Cirrhosis: Cirrhosis of liver was confirmed on patient’s history related to cirrhosis, clinical features (ascites, hepatic encephalopathy and esophageal varices), imaging (ultrasonography and computed tomography showing small shrunken liver) and biochemical parameters. Histopathology also confirmed cirrhosis wherever required.12

Hepatic encephalopathy: Hepatic encephalopathy and its various grades were labeled according to West Haven Criteria and graded 1-4.13

Acute Kidney injury: Acute Kidney injury (AKI) is determined where ascites persists in cirrhosis even after withholding all diuretics and adequate fluid resuscitation whereas serum creatinine remained $> 1.5 \text{ mg/dL}$.14

Haemorrhagic ascites: Haemorrhagic ascites is defined when ascitic fluid contains $> 10,000/\text{mm}^3$ RBC as by earlier published data on the subject.8,9

Non Haemorrhagic ascites: Non haemorrhagic ascites is defined when ascitic fluid contains $< 10,000/\text{mm}^3$ RBC which is well in accordance to the earlier published data on the subject.8,9

Causes of haemorrhagic ascites:
1. Hepatocellular carcinoma (HCC) related
2. Hemoperitoneum where no cause is identified.

Iatrogenic hemorrhagic ascites:
Hemoperitoneum detected in the patient after paracentesis, either diagnostic or therapeutic or liver biopsy.

Spontaneous hemorrhagic ascites:
Hemoperitoneum where no cause is identified.16,17

Statistical Analyses: Data were analyzed through Statistical analyses SPSS software version 21 (SPSS Inc.; Chicago, Illinois, USA). Standard deviation and mean were used for descriptive analyses. Patients’ outcome variables were identified between haemorrhagic and non-haemorrhagic groups by univariate analysis and investigated through Chi square, Fisher exact, Student t and Mann-Whitney U tests, as required. Independent predictors for variables were analyzed by multivariate regression. Survival rate comparisons between both groups were determined using Kaplan-Meier survival estimates. To infer statistical significance A 5% type-I error level was used.

RESULTS

Demographic, clinical and biochemical profile: Out of 838 cirrhotic patients analyzed, haemorrhagic ascites was detected in 223 (26.6%) patients whereas
non haemorrhagic ascites was found in 615 (73.3%). Age, gender, aetiology of cirrhosis and its severity among groups are highlighted in Table-I. Liver chemistries like ALT, bilirubin, albumin and INR among both groups with their statistical significance (p values of 0.01, .0001, 0.0001 and 0.000) have shown in Table-I. Severe liver disease as evidenced by MELD and CTP score was found in the patients with haemorrhagic ascites where mean CTP score was 10±1.7 and 9.1±1 (p=0.000) and MELD score was 23.1±9 and 19.2±6 (p= 0.000) in both groups respectively as shown in Table-I.

**Portal hypertension indices and complications:** Spleen had a mean size of 16±3 cm in the haemorrhagic ascites group and 15±3 cm in controls with statistical significance (p=0.0001). Stage of ascites with their frequency among both groups have statistical significance (p=0.18) in Table-II. Degree of varices with their frequency among the groups having statistical significance (p=0.0001) Table-II. Various complications of cirrhosis among both groups showed only SBP and AKI to be statistically significant (p= 0.0001, 0.0001) as shown in Table-II.

**Causes of haemorrhagic ascites:** Spontaneous haemorrhagic ascites 176 (79%) was the main cause of haemorrhagic ascites followed by HCC 30(14%) and iatrogenic 17 (7.6%) in this study.

| Biochemical parameter | Mean ± SD | Mean ± SD |
|-----------------------|-----------|-----------|
| ALT iu/ml             | 68±6.9    | 55.5±6.2  | 0.01 |
| Creatinine mg/dl      | 1.5±0.8   | 1.28±0.7  | 0.000 |
| Bilirubin mg/dL       | 6.1±0.3   | 4.8±0.3   | 0.000 |
| INR                   | 1.8±0.4   | 1.5±0.3   | 0.000 |
| MELD Score            | 23.1±9    | 19.2±6    | 0.000 |
| CTP Score             | 10±1.7    | 9.1±1     | 0.000 |
| Hb% gm/dL             | 7.3±1.2   | 8.7±1.1   | 0.000 |
| WBC /mm3              | 8±1.3     | 6.4±3.4   | 0.000 |
| Platelets/mm3         | 121±29    | 127±49    | 0.062 |
Survival analysis: Overall mortality at year 3 was 83% in comparison to 70% among non-haemorrhagic ascites. From the haemorrhagic ascitic group 71% survived one month, 17% survived 1 year and 13% patients survived 3 year with survival probability estimates (0.73, 0.18 and 0.135) respectively. Whereas, from non haemorrhagic ascites group 87% survived one month, 50% survived 1 year and 27% patients survived 3 year with survival probability estimates (0.87, 0.51 and 0.28) respectively was found significant (p = 0.000, 0.000 and 0.000) as shown in Fig-1.

Predictors of mortality: Among various parameters only haemorrhagic ascites (Odd ratio=0.45, P=0.000, CI = 0.31-0.734), hepatic encephalopathy (Odd ratio=0.347, P=0.000, CI = 0.214-0.563) and SBP (Odd ratio 6.07, p=0.000,CI = 2.6-14.2) qualified as independent predictors of mortality. Table-III

Ascitic RBC’S range: Patients of haemorrhagic ascites were grouped on the basis of ascitic RBC’S count where 16 (7.3%) patients had ascitic RBC’S count > 50,000/mm3 while majority had ascitic
DISCUSSION

Haemorrhagic ascites was present in 223 (26.6%) in this study whereas earlier studies\textsuperscript{8,9} have 25% and 35.5% patients with haemorrhagic ascites. Most patients in this study had viral related (Chronic HCV and HBV) as the cause of cirrhosis whereas study by Yıldız et al.\textsuperscript{9} showed chronic HBV followed by HCV mainly causing cirrhosis. Urrangana et al.\textsuperscript{8} showed alcohol as a cause of cirrhosis followed by chronic HCV and HBV.

Hyponatremia, raised creatinine, hypotension and advance severity of liver disease (High CTP and MELD score) are well established poor prognostic indicators among patients with liver cirrhosis.\textsuperscript{4,19,20} Spontaneous hemorrhagic ascites was found incidentally among cirrhotics presents without signs of haemorrhage (hypotension, tachycardia and syncope). Earlier studies\textsuperscript{6,10} suggest that hemorrhagic ascites may indicate poor prognosis among cirrhotics due to increased risk of AKI, HE and high mortality. Two possible mechanisms related to development of spontaneous haemorrhagic ascites have been proposed.\textsuperscript{10} First proposed mechanism is of intra-abdominal bleeding from an organ or a small peritoneal vessel, or a varix,\textsuperscript{13} whereas second is related to raised portal or splenic pressure causing diapedesis of erythrocytes within peritoneum.

Increased splenic size and higher degree of varices in patients with haemorrhagic ascites in this study validates the role of raised portal or splenic pressure as a cause of haemorrhagic ascites. This is similar to the earlier studies.\textsuperscript{6,10} Complications like haematemesis, AKI and SBP occur frequently with haemorrhagic ascites as compared to non haemorrhagic ascites. Earlier studies\textsuperscript{8,9} have also endorsed SBP and AKI as frequently reported problem with haemorrhagic ascites whereas HE was also found significantly.

This study showed high mortality rate at 1 month, 1 year and 3 year among patients with haemorrhagic ascites like large earlier published studies.\textsuperscript{8,9} This study has tested various determinants like Haemorrhagic ascites, HE, portal vein thrombosis, SBP as an independent predictor of mortality among patient of cirrhosis with ascites and found haemorrhagic ascites, SBP and HE as an independent predictor of mortality. Yildiz et al.\textsuperscript{9} had shown haemorrhagic ascites along with hepatorenal syndrome and HCC as an independent predictor for mortality in large cohort at Turkey. Urrunaga et al.\textsuperscript{8} in their study had also shown similar results where multilogistic regression determined haemorrhagic

Table-III: Determination of independent predictors of mortality (multinomial logistic regression analysis).

| Variable             | Odds Ratio | P Value | Confidence Interval |
|----------------------|------------|---------|---------------------|
| Age                  | 1.00       | 0.216   | 0.997-1.021         |
| Gender               | 1.143      | 0.449   | 0.809-1.614         |
| Haemorrhagic ascites | 0.45       | 0.000   | 0.31-0.734          |
| MELD Score           | 0.994      | 0.645   | 0.969-1.019         |
| Hepatic encephalopathy | 0.347     | 0.000   | 0.214-0.563         |
| Hematemesis          | 0.499      | 0.263   | 0.147-1.686         |
| Portal vein Thrombosis | 0.659    | 0.405   | 0.247-1.757         |
| SBP                  | 6.07       | 0.000   | 2.6-14.2            |
| AKI                  | 1.685      | 0.07    | 0.959-2.961         |

RBC’S count between 10,000/mm\(^3\) – 50,000/mm\(^3\). Statistical significance is not evidenced as p values shown (0.73, 0.60, 0.32 and 0.80). Table-IV.

Table-IV: Comparison of complication of cirrhosis among subgroups of haemorrhagic ascites.

| Complications of cirrhosis | Haemorrhagic ascites (RBC’S > 50,000/mm\(^3\)) N (%) | Non haemorrhagic ascites (RBC’S 10,000-50,000/mm\(^3\)) N (%) | P Value |
|----------------------------|------------------------------------------------------|---------------------------------------------------------------|---------|
| HDU admission              | 10 (65%)                                             | 139 (67%)                                                     | 0.73    |
| AKI                        | 07(43.7%)                                            | 109 (52.6%)                                                   | 0.60    |
| SBP                        | 09(55%)                                              | 87(42%)                                                       | 0.32    |
| Hepatic encephalopathy     | 09 (55%)                                             | 108(52%)                                                      | 0.80    |
ascites as an independent predictor of mortality along with HCC and high MELD score. Current study also tested range of ascitic RBC’S count among haemorrhagic ascites either having 10,000 – 50,000/mm3 or > 50,000/mm3 as earlier determined by Yildiz et al.3 and found same results. This further validates earlier study that 10,000/mm3-50,000/mm3 ascitic RBC’S count can be considered for haemorrhagic ascites. Among types of haemorrhagic ascites spontaneous haemorrhage was the most common cause in this study with abdominal distension. Haemorrhagic ascites presenting with worsening ascites and shock is always related to ruptured varices or HCC have been reported in about 0.5% patient.6,10,21 This study had shown 07 (3.1%) patients who died with HCC related haemorrhage which is quite high as compare to earlier study.8

Limitations of the study: It was retrospective design and missing of iatrogenic hemorrhagic ascites at first paracentesis. However, imploring design and missing of iatrogenic hemorrhagic ascites. Clinical presentation and outcomes in patients with cirrhosis. J Hepatol. 2013;58:1113-1118. doi: 10.1016/j.jhep.2013.01.015

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Authors Contribution:

IHN: Conceived, designed and did statistical analysis & editing of manuscript.

IHN & AT: Did data collection and manuscript writing.

KM: Did review and final approval of manuscript.