DISCUSSION

Ascitic decompensation is a common major complication of cirrhosis and a sign of advanced liver disease because the prognosis becomes poorer after ascitic decompensation.[186] Once cirrhosis is clinically confirmed, nearly 60% of patients experience ascitic decompensation within 10 years, and eventually ascites becomes resistant to medical treatments in 5-10% of the patients, which is called refractory ascites.[187]

A significant increase in sodium excretion cannot be achieved because patients with refractory ascites either do not respond to a high dose of diuretics or they suffer from side effects related to the use of diuretics, such as hyperkalemia, hyponatremia, hepatic encephalopathy (HE), and renal failure. Thus, refractory ascites is closely related to high morbidity and mortality with a 2-year survival rate of less than 50%.[188]

This study was carried out on 60 patients who were admitted to the Hepatobiliary Unite; Alexandria Main University Hospital. All patients were cirrhotics and suffering from refractory ascites.

The diagnosis of ascites was made based on physical examination and ultrasonography results, and that of refractory ascites according to the International Ascites Club diagnostic criteria as follows: "ascites that cannot be mobilized, or early recurrence of ascites which cannot be satisfactorily prevented by medical therapy".[187]

Accordingly, there were two types of refractory ascites: "diuretic-intractable ascites" which could not be mobilized or its early recurrence could not be prevented because the development of diuretic-induced complications such as hyperkalemia, hypokalemia, hyponatremia, hepatic encephalopathy, or renal failure precluded the use of an effective diuretic dosage, and "diuretic-resistant ascites", which is induced by failure of a significant increase in sodium excretion because patients do not respond to high doses of diuretics (spironolactone 400 mg/day and furosemide 160 mg/day) and sodium restriction.[187]

The aim of this study was to evaluate the precipitating factors for refractory ascites in patients with cirrhosis.

The mean age of the studied patients was 57 years and 40 patients were males; while 20 patients were females.

The type of refractory ascites in our patients was diuretic-intractable in 52 patients (86.7%) and diuretic-resistant in 8 patients (13.3%).

This was nearly in agreement with Ennaifer R, et al (2014)190 who found refractory ascites type was diuretic intractable in all cases. In contradictory to Seo JH, et al (2013)[189] who found diuretic-resistant ascites in 68.7% and diuretic-intractable ascites in 31.3% of patients with refractory ascites.

History of hematemsis and/or melena was obtained in 28 patients (46.7%); while history of previous paracentesis was obtained in 43 patients (71.7%).

Seo JH, et al (2013) 189 found history of variceal bleeding in 6 patients (3%) and history of paracentesis in 12.5% of his studied patients. Ennaifer R et all (2014) found history of variceal bleeding in 41 patients (33.1%).

Refractory ascites is observed in 5%-10% of advanced cirrhosis cases and has a one-year mortality rate of 20%-50%.[191]

Liver transplantation is the only definitive treatment for these patients, but the procedure is limited by donor liver resources and high cost. Repeated large-volume or total-volume paracentesis with intravenous albumin infusion is currently recommended as the firstline treatment for patients with refractory ascites.[192] To date, large volume paracentesis, peritoneo-venous shunt, and Transjugular Intra- Hepatic Portosystemic Shunt (TIPS), combined with diuretics, have widely been used to control ascites, so as to improve their quality of life and help ease the waiting time for liver transplantation. However, these interventions have failed to significantly improve survival, and the prognosis of refractory ascites has been demonstrated to be related more to the severity of underlying liver disease, regardless of treatment modalities. Thus, liver transplantation has been strongly recommended for patients with refractory ascites to improve survival.[193]

Consequently, it is meaningful to investigate predictors of refractory ascites development in cirrhotic patients with ascetic decompensation, because these patients will benefit from prompt liver transplantation. However, there have been few investigations identifying predictors of refractory ascites development in cirrhotic patients.

In the literature, we identified only three studies which principal aim was to determine the predictor's factors of refractory ascites development in patients with cirrhosis: the Spanish study of Planas et al.[194] A Korean study of Seo et al. [189] and the study of Ennaifer R et al.[190]

The liver failure was probably sufficient for refractory ascites development in patients with Child-Pugh C liver function.[195]

In our study Child class C cirrhosis was present in 42 patients (70%). Jaundice as a sign of decompensation was found in 52 patients (86.7%); hepatic encephalopathy in 37 patients (61.6%); and tense ascites in 49 patients (81.7).

In the prospective study of Planas et al,[194] the score Child-Pugh >8 at inclusion was an independent predictor factor of refractory ascites with an OR of 1.4.[192]

In the study done by Ennaifer R et al,[190] Child-Pugh class, MELD score and MELD/Na score were found to be a significant predictor of refractory ascites development in the univariate analysis but not in multivariate analysis. These was in agreement with our results. This can suggests the independent role that may have liver failure in occurrence of refractory ascites.

Electrolyte imbalances in patients with liver cirrhosis, such as hyponatremia or hyperkalemia, are associated with severe ascites, as indicated by high prevalence of refractory ascites.[196]

In our study hyponatremia was present in 16 patients (26.6%) and hyperkalemia in 12 patients (20%).

Bernardi, et al.[197] and Angeli, et al.[198] showed a relationship between serum electrolyte levels and responsiveness of ascites to diuretic therapy.

They found that patients who do not respond to diuretics have lower serum sodium and higher potassium concentrations than those who do respond to diuretics. Additionally, several reports have proposed that serum potassium level may affect refractory ascites development in part.[199]

Similarly, the results of Seo JH, et al [189] showed that the risk of developing refractory ascites was significantly related to a higher serum potassium level in patients with ascetic decompansation.

Although serum sodium concentration is known to have a significant correlation with the survival of cirrhosis patients awaiting for liver transplantation,[200] its role in the prediction of refractory ascites development has not been clear.

In our study diuretic intractable refractory ascites with inability to increase the dose of diuretics because of the occurrence of side effects was found in 52 patients (86.8%). Hypotension was the cause in 28 patients (46.6%); hepatic encephalopathy in 20 patients (33.3%) and renal impairment in 4 patients (6.6%).

In the study done by Seo H, et al [189], hepatic encephalopathy was the cause of intractable ascites in 14 patients (25%). This was in agreement of our results. Also, in the study done be Ennaifer R, et al [190] hepatic encephalopathy was a precipitating factor in 42 patients (33.9%).

Renal failure due to the complication of hepatorenal syndrome occurred in 4 patients (2%) of the studied patients of Seo H, et al [189]. This also was in agreement with our results.

Bacterial infections are a leading cause of acute on chronic liver failure and are associated with high mortality in end-stage liver disease. Dysfunction of the defensive mechanisms against bacterial or fungal infections makes patients with cirrhosis prone to the development of sepsis.[201]

By reviewing the studies reporting on the clinical course of cirrhosis after infectious episodes, the overall mortality of infected patients is reportedly around 38% with 30.3% of cases occurring at 1 month and 63% at 12 months, with the pooled odds ratio for death of infected versus non infected of 3.75 (95% confidence interval 2.12–4.23). [202]

Spontaneous bacterial peritonitis represents one of the most common infectious complications in patients with cirrhosis. The median mortality in 7062 such patients was

43.7%, with 31.5% of the cases occurring at 1 month and 66.2% at 12 months. Moreover, severe renal failure is common in patients with spontaneous bacterial peritonitis and is associated with a poor outcome.[203] Urinary tract infection, pneumonia and bacteraemia represent 20%, 15% and 12% of infections, respectively, while soft tissue infections had a lower and variable prevalence. [204]

C-reactive protein (CRP) is a reliable marker of bacterial infections in cirrhosis. However, the accuracy of CRP decreases in advanced disease or in the presence of ascites. The combination of CRP with pro-calcitonin (PCT) slightly increases the diagnostic accuracy. Elevated CRP level in patients without overt infection, is a useful predictor of clinically significant bacterial infections in the next weeks or months. [205]

In our study, high CRP with a cut off value 12 mg/ml was found in 11 patents (16.6%). Spontaneous bacterial peritonitis as diagnosed by ascetic fluid polymorph nuclear leucocytic count more than 250/HPF, was diagnosed in 9 patients (15%).

This was in agreement with the results of Seo JH,[189] who found that spontaneous bacterial peritonitis was the complication at admission for refractory ascites in 27 patients (13.6%). Also, Ennaifer R, et al found SBP in 7 patients (25.9%).

Urinary tract infection as diagnosed by excess pus cells in urine was diagnosed in 8 patients (13.3%). Tandon P, et al [206] reported urinary tract infection in 20% of cases with refractory ascites.

Type 2 hepatorenal syndrome (HRS) is characterized by a moderate (serum creatinine lower than 2.5 mg/dl) and slowly progressive renal failure. Patients with type 2 HRS show signs of liver failure and arterial hypotension but to a lesser degree than patients with type 1 HRS. [207]

The dominant clinical feature is severe ascites with poor or no response to diuretics (a condition known as refractory ascites). The median survival of patients with type 2 HRS (6 months) is worse than that of patients with non-azotamic cirrhosis with ascites.[208]

In our study, elevated blood urea and serum creatinine sufficient to diagnose type 2 HRS was found in 4 patients (6.6%). Also hypotension was observed in 28 patients (46.6%). In addition, decreased urinary sodium excretion less than 10 mEq/liter was observed in 12 patients (20%).

PVT is most common in patients with pre-existing cirrhosis. The prevalence of PVT increases with the severity of the cirrhosis, being less than 1% in patients with compensated cirrhosis but 8%-25% in candidates for liver transplantation.[209] Ultrasound and ultrasound Doppler are almost always sufficient for diagnosis. Contrast-enhanced sonography was shown to be superior to sonography and colour Doppler sonography for the detection and characterization of PVT. The gold standard of invasive angiography such as portal venography or superior mesenteric arteriography is rarely necessary. Retrograde carbon-dioxide portography can make PVT more evident than conventional CT/MRI, especially when an important hepatofugal flow is present. However, CT and MRI are better for

determining the extent of thrombosis. Contrast-enhanced sonography or CT imaging can help differentiate benign from malignant PVT.[210]

Clinical findings of PVT in cirrhosis vary from asymptomatic disease to a life-threatening condition at first presentation. In a study of 79 patients with PVT and cirrhosis at diagnosis, 43% were asymptomatic, 39% had gastrointestinal bleeding because of varices or portal hypertensive gastropathy and rapidly accumulating ascites and 18% had acute abdominal pain of which 70% had intestinal infarction (10 of 79).[211]

In our study, portal vein thrombosis was diagnosed by Doppler ultrasound in 12 patients (20%). This complication of cirrhosis may be a precipitating factor for refractoriness of ascites in our patients.

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world, with over 600,000 new diagnoses per year. HCC generally occurs in association with cirrhosis, particularly due to hepatitis C, hepatitis B, alcohol, hereditary hemochromatosis, and primary biliary cirrhosis. This malignancy is becoming recognized as an early complication and the most frequent cause of death in persons with viral-associated cirrhosis.[212]

Patients who develop HCC usually have no symptoms other than those related to their chronic liver disease. Suspicion for HCC should be heightened in patients with previously compensated cirrhosis who develop decompensation such as ascites, encephalopathy, jaundice, or variceal bleeding. These complications are often associated with extension of the tumor into the hepatic or portal veins or arterio-venous shunting induced by the tumor.[213]

The American Association for the Study of the Liver Diseases (AASLD) and the National Comprehensive Cancer Network guidelines support diagnosing HCC based on imaging and laboratory studies. Laboratory blood analyses that may be helpful in management of HCC include alpha-fetoprotein serology; however, the validity of alpha-fetoprotein as a prognostic marker is not confirmed. The preferred imaging modality to confirm diagnosis of HCC is computed tomography scanning with a triphasic liver component, which helps to better identify liver lesions. [214]

In our study, HCC was diagnosed by tri-phase computed tomography in 18 patients (30%). All cases with HCC have raised alpha fetoprotein above the cut off value of 200 pg/ml. we suggest that the occurrence of HCC in some of our patients may be a precipitating factor for the refractoriness of ascites in our studied patients.

Ennaifer R et al[200] found HCC in 5 patients (18.5%) of their studied patients with refractory ascites. This is in agreement with our results.

In conclusion, from our study we can suggest the precipitating factors responsible for refractory ascites include liver failure or advancement of liver cirrhosis, infection, electrolyte imbalance, renal impairment, and superadded complications such as portal vein thrombosis and hepatocellular carcinoma.

SUMMARY

Refractory ascites is observed in 5%-10% of advanced cirrhosis cases and has a one-year mortality rate of 20%-50%. Consequently, it is meaningful to investigate predictors of refractory ascites development in cirrhotic patients.

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