AIM OF THE WORK

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

SUBJECTS

The study included 60 patients with liver cirrhosis and refractory ascites admitted to Hepatobiliary Unite, Alexandria University Main Hospital.

The diagnosis of refractory ascites in these patients was done according to the International Ascites Club Definition:

1. Treatment duration: patients must be on intensive diuretic therapy (spironolactone 400 mg by mouth daily and furosemide 160 mg by mouth daily) for at least 1 week and on a sodium restricted diet of less than 90 mmol/L per day or 5.2 g of salt (NaC1) per day.
2. Lack of response: mean weight loss of <0.8 kg over 4 days and urinary sodium output less than the sodium intake.
3. Early ascites recurrence: reappearance of grade 2 or 3 ascites within 4 weeks of initial mobilization.
4. Diuretic - induced complications:
    a) Diuretic - induced hepatic encephalopathy: development of encephalopathy in the absence of any other precipitating factor.
    b) Diuretic - induced renal impairment: increase of serum creatinine by > 100% to a value > 2 mg/dL in patients with ascites responding to diuretics.
    c) Diuretic - induced hyponatremia: decrease of serum sodium by > 10 mmol/L to a serum sodium of < 125 mmol/L.
    d) Diuretic - induced hypo - or hyperkalemia: change in serum potassium to <3 mmol/L or > 6 mmol/L despite appropriate measures.

Patients with refractory ascites will be evaluated for the precipitating factors responsible for refractoriness of ascites.

The study will be conducted in accordance with the ethical guidelines of the 1975 Declaration of Hesinki and an informed written consent will be obtained from all patients before study enrollment.

METHODS

All patients included in the study will be evaluated as regards:

(1) Detailed history taking including:

- Age, sex, history of schistosomiasis, virus hepatitis, drug history.
- Detailed history of salt restriction, diuretics type and dose, other drugs received and daily urine output changes.

(2) Complete clinical examination including:

- General examination, blood pressure, pulse, temperature, body weight, signs of chronic liver diseases (jaundice, previous gastrointestinal bleeding, gynecomastia, spider angioma, palmar erythema, and edema).
- Abdominal examination assessing the liver, spleen and the ascites.

(3) Laboratory investigations including:

a) Complete blood picture (CBC).[8]

b) Serum urea and creatinine.[9]

c) Urinary sodium (Na).[10]

d) Liver profile: Serum aspartate transferase (AST), alanine transferase (ALT), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), serum albumin, prothrombin activity, serum bilirubin (total and direct).[11-14]

e) Anti hepatits C virus antibodies (anti HCV), hepatits B surface antigen (HbsAg),[15,16] indirect hemaglutination for schistosomiasis.[17]

f) Serum alfa fetoprotein (AFP) level.[18]

g) C - reactive protein (CRP) as a marker of inflammation.[19]

h) Ascitic fluid analysis for protein, glucose, LDH and cytology for malignant cells.[20]

i) Serum sodium (Na) and potassium (k).[21]

j) Adenosine deaminase in ascetic fluid will be performed n suspected cases of tuberculous ascites

(4) Severity of liver disease was graded according to the clinico-biochemical classification of Pugh et al as follows:[22,23]

Parameter	Points assigned		
	1	**2**	**3**
Ascites	Absent	Mild-moderate	Severe
Serum bilirrubin mg/dl	≤ 2	2.1-3	>3
Serum albumin g/dl	>3.5	2.8-3.5	<2.8
Prothrombin activity	>70%	40-70%	<40%
Encephalopathy	None	Grade 1-2	Grade 3-4

A total score of 5-6 is considered grade A (well-compensated disease); 7-9 is grade B (significant functional compromise); and 10-15 is grade C (decompensated disease). These grades correlate with one- and two-year patient survival, as follows:

Grade	Points	One-year patient survival (%)	Two-year patient survival (%)
A: well-compensated disease	5-6	100	85
B: significant functional compromise	7-9	80	60
C: decompensated disease	10-15	45	35

(5) Radiological examination including:

- Abdominal ultrasound for assessment of the liver, spleen, ascites, portal vein, hepatic veins, and focal hepatic lesion.[24]
- Tri-phasic CT scan of the abdomen for accurate diagnosis of focal liver lesions if present.[25]
- Doppler ultrasound for portal vein thrombosis.[26]

RESULTS

Demographic data of the studied cases: (n = 60)

Regarding age of the patients, 25 patients (41.7%) aged 51-60 years old; while 20 patients (33%) were above 60 years old and 15 patients (25%) were between 40 and 50 years old. As regarding sex the study was carried on 40 male (66.7%) patients and 20 female (33.3%) patients **(Table l6, Figure3).**

Table 6: Demographic data of the studied cases.

Age (years)	No.	%
40 – 50	15	25.0
50-60	25	41.7
>60	20	33.3
Min. – Max.	40.0 – 73.0	
Mean ± SD.	56.58 ± 8.04	
Median	57.0	

Sex	No.	%
Male	40	66.7
Female	20	33.3

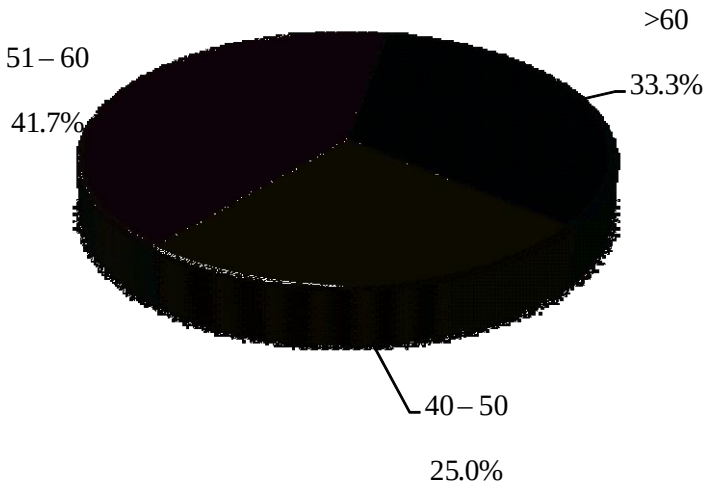

Figure (2): Distribution of the studied cases according to age

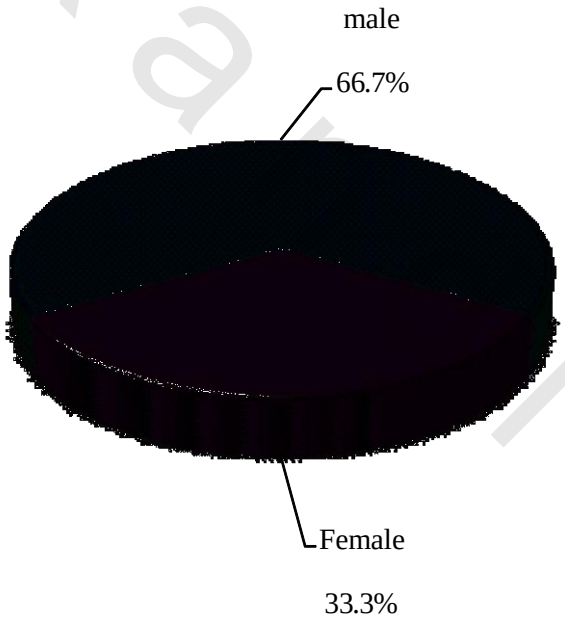

Figure (3): Distribution of the studied cases according to sex

Distribution of the studied cases according to history taking : (Table 7)

The study showed that 26 patients (43.3%) were having history of schistosomiasis; 6 patients (10%) have history of fever; 14 patient (23.3%) have history of weight loss; 52 patient (86.7%) have history of jaundice; 28 patient (46.7%) have history of hematemsis and or melena; 56 patient (93.3%) have history of lower limbs edema; and 43 patient (71.7%) have past history of frequent paracentesis. Maximum dose of diuretics was achieved in 7 patiennts (11.7%) and failed in 53 patients (88.3%). Also all patients undergo salt restriction according to their testimony. **(Table 7, Figure 4)**

Table 7: Distribution of the studied cases according to history taking (n = 60)

Fig	No.	%
Schistosomiasis		
Negative	34	56.7
Positive	26	43.3
Fever		
Negative	54	90.0
Positive	6	10.0
Weight loss		
Negative	45	76.7
Positive	14	23.3
Jaundice		
Negative	8	13.3
Positive	52	86.7
Hematemsis and/or melena		
Negative	32	53.3
Positive	28	46.7
Edema of lower limb		
Negative	4	6.7
Positive	56	93.3
paracentesis		
Negative	17	28.3
Positive	43	71.7
Maximum dose of diuretics		
Failure to achieve max. dose of diuretic	53	88.3
Achieving max. dose of diuretic	7	11.7
Salt restriction		
Negative	0	0.0
Positive	60	100.0

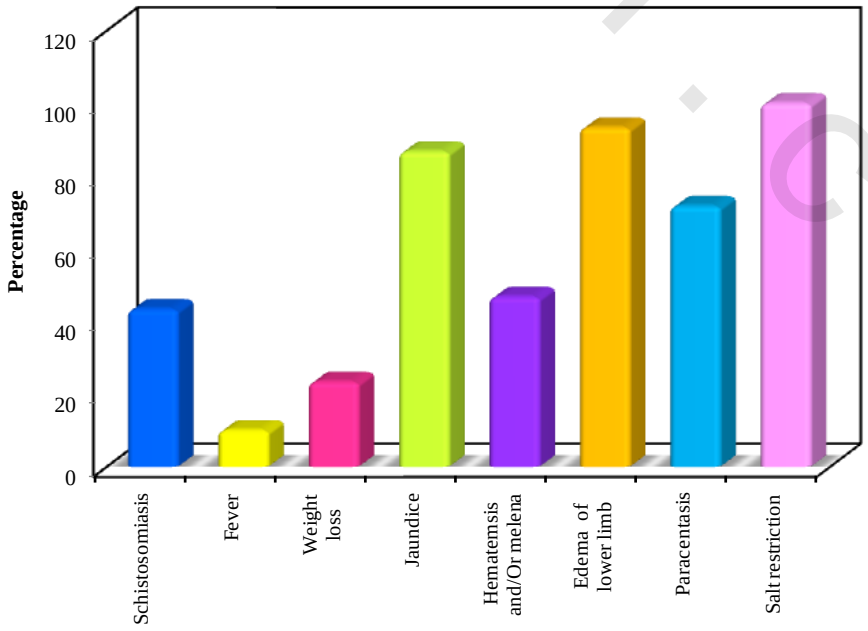

Figure (4): Distribution of the studied cases according to history taking

Distribution of studied cases according to Clinical examination

The study showed that 48 patients (80%) have shrunken liver while 12 patient (20%) have hepatomegaly; 38 patient (63.3%) have splenomegaly; 10 patients (16.7%) suffers from liver tenderness, Also there were 49 patient (81.7%) have tense ascites while only 11 patient (18.3%) have moderate ascites. Hepatic encephalopathy was observed in 37 patients (61.6%); it was mild in 11 patients (18.3%) ; moderate in 20 patients (33.3%) and severe in 6 patients (10%). **(table 8, Figure5)**

Table 8: Distribution of studied cases according to Clinical examination (n = 60)

	No.	%
Liver size		
Shrunken	48	80.0
Hepatomegaly	12	20.0
Liver tenderness		
Negative	50	83.3
Positive	10	16.7
Spleen size		
Normal	12	20.0
Splenomegaly	38	63.3
Splenectomy	10	16.7
Degree of ascites		
Moderate	11	18.3
Tense	49	81.7
Degree of hepatic encephalopathy		
No	23	38.3
Mild	11	18.3
Moderate	20	33.3
Sever	6	10.0

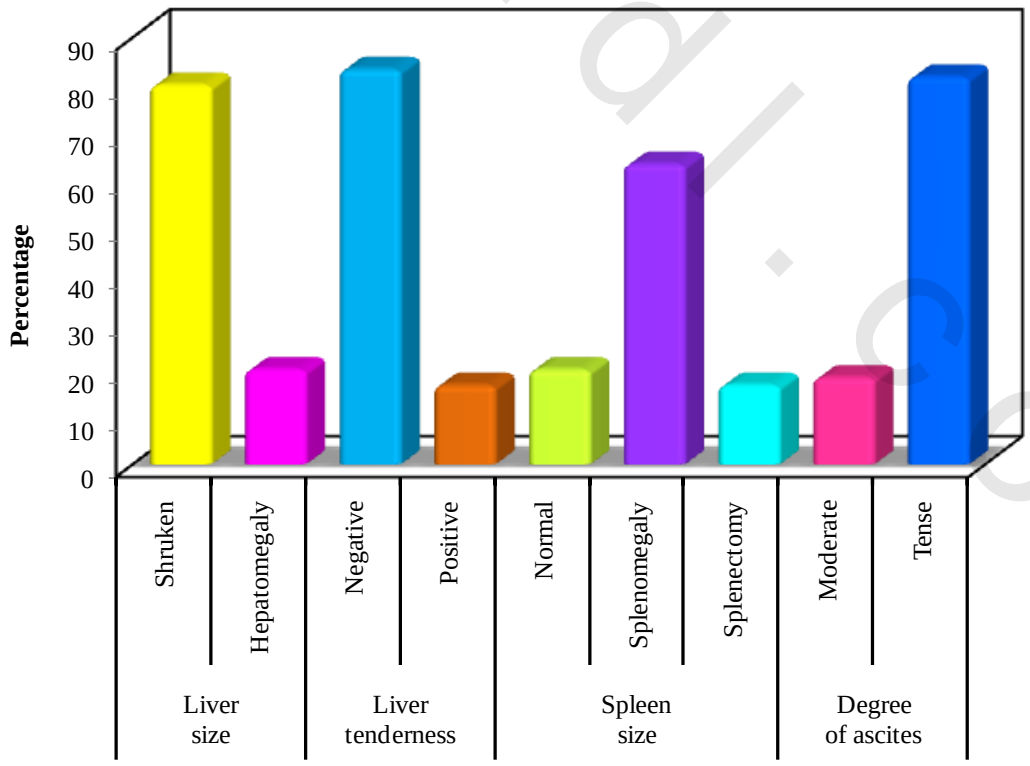

Figure (5): Distribution of the studied cases according to Clinical examination

Distribution of the studied cases according to complete blood picture and renal biochemical profile:

This study showed mild anemia in cirrhotic patients with refractory ascites with median of 10.1 gm/dl .Also evident thrombocytopenia was observed in these patients with a median of 117 10^3/cm. As regarding urine examination there was albuminuria in 23 patients (38.3%) and pus cells in 8 patients (13.3%). No significant abnormalities as regarding renal function tests and serum electrolytes observed in the median of serum urea, creatinine, sodium and potassium. However, we detected renal impairment in the form of albuminuria in 23 patients (38.3%) ; urinary tract infection in 8 patients (13.3%) ; elevated blood urea and serum creatinine in 4 patients (6.6%) ; hyponatremia in 16 patients (26.6%) and hypokalemia in 12 patients (20%). **(table 9)**

Table 9: Distribution of the studied cases according to complete blood picture and renal biochemical profile (n = 60)

		No.	%
Complete blood picture	**Hb** mg/dl		
	Min. – Max.	7.40 – 13.70	
	Mean ± SD.	10.09 ± 1.66	
	Median	10.10	
	Platelet $10^{3/cm}$		
	Min. – Max.	39.0 – 212.0	
	Mean ± SD.	109.17 ± 47.16	
	Median	117.0	
	WBCs $10^{3/cm}$		
	Min. – Max.	2.11 – 15.0	
	Mean ± SD.	7.05 ± 3.37	
	Median	6.48	
Urine examination	**Albumin**		
	Negative	37	61.7
	Positive	23	38.3
	Pus. Cells		
	Negative	52	86.7
	Positive	8	13.3
	Na^+ mEq/L		
	Min. – Max.	8.0 – 28.0	
	Mean ± SD.	15.77 ± 5.56	
	Median	14.0	
Renal function test	**Urea mg/dl**		
	Min. – Max.	21.0 – 156.0	
	Mean ± SD.	61.60 ± 32.05	
	Median	51.0	
	creatinine mg/dl		
	Min. – Max.	0.50 – 2.60	
	Mean ± SD.	1.11 ± 0.52	
	Median	1.0	
Serum electrolytes	**Na^+ mEq/L**		
	Min. – Max.	118.0 – 142.0	
	Mean ± SD.	129.23 ± 5.90	
	Median	130.0	
	K^+ mEq/l		
	Min. – Max.	3.10 – 6.90	
	Mean ± SD.	4.57 ± 0.98	
	Median	4.60	

Distribution of the studied cases according to Liver biochemical profile and CRP

This study showed mildly elevated liver enzymes in most cirrhotic patients with refractory ascites. Also mildly elevated serum bilirubin and C-reactive protein. However C-reactive protein was significantly elevated with a cut off value of 12mg/dL in 11patients (16.6%). On the other hand there is significant decrease in serum albumin level with median 2.4 g/dl. **(Table 10)**

Table 10: Distribution of the studied cases according to Liver biochemical profile and CRP (n = 60)

	Min. – Max.	**Mean ± SD.**	**Median**
ALT U/L	20.0 – 106.0	49.75 ± 19.04	46.0
AST U/L	10.0 – 243.0	75.03 ± 43.03	62.0
S. Alb. g/dl	1.30 – 3.40	2.45 ± 0.51	2.40
PA %	28.90 – 100.0	54.75 ± 13.82	56.0
Total Bilirubin mg/dl	0.70 – 16.0	3.48 ± 3.16	2.45
Direct bilirubin mg/dl	0.20 – 12.20	2.32 ± 2.52	1.50
CRP mg/L	3.0 – 260.0	16.05 ± 36.98	13.0

Distribution of the studied cases according to viral markers and Tumor markers

In the study 58 patient were tested positive for HCV infection (96.7%) and only 2 patients (3.3%) were tested positive for HBV infection. Also according to tumor markers there was no significant elevation of serum AFP observed. High value of AFP above 200 Pg/ml was found in 18 patients (30%). (**(Table11, Figure6)**

Table (11): Distribution of the studied cases according to viral markers and Tumor markers (n = 60)

Viral markers		
HCV	58	96.7
HBV	2	3.3
Tumor markers (AFP)		
Min. – Max.	3.0 – 2921.0	
Mean ± SD.	158.83 ± 456.44	
Median	12.0	

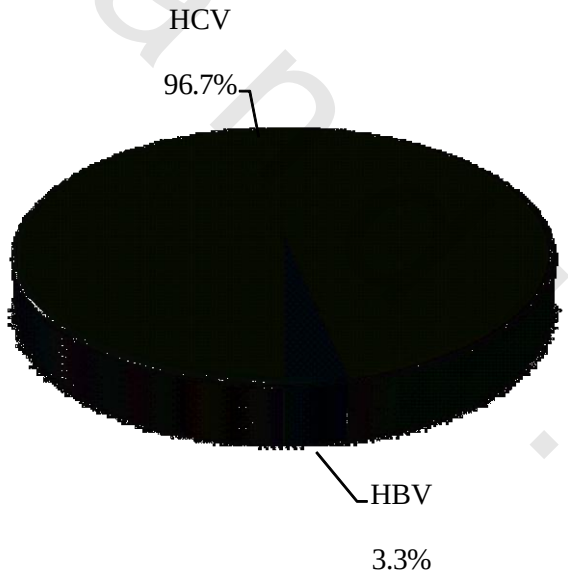

Figure (6): Distribution of the studied cases according to viral markers

Distribution of the studied cases according to Child-Pugh class:

The study showed 42 patient (70%) were Child class C,15 patient (15%) were Child class B and only 3 patients (5%) were child class A . **(Table 12, figure 7)**

Table (12): Distribution of the studied cases according to Child-Pugh class (n = 60)

	No.	%
Child-Pugh class of the studied		
Class A	3	5.0
Class B	15	25.0
Class C	42	70.0

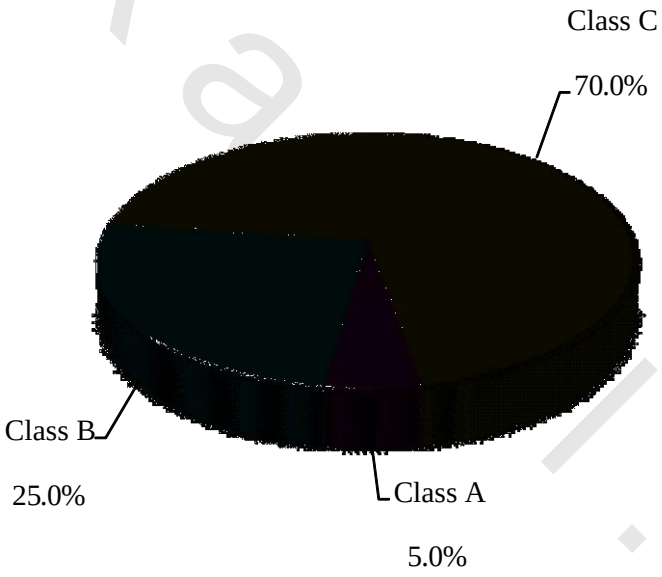

Figure (7): Distribution of the studied cases according to Child-pugh class

Distribution of the studied cases according to ascetic fluid analysis:

In this study we found that the median of SAAG was 1.3 which means that 54 patients were SAAG >1.1 (portal hypertensive ascites) and 6 patients were SAAG <1.1 . Spontaneous bacterial peritonitis (SBP) diagnosed as ascetic fluid neutrophils count above 250/HPF was found in 9 patients (15%). Predominant lymphocytes in the ascetic fluid was observed in 7 patients (11.6%). No suspected cases of tuberculous ascetic so adenosine deamiase was not performed also no malignant cells were detected in the ascetic fluid with patient with HCC . **(Table 13**)

Table (13): Distribution of the studied cases according to ascetic fluid analysis (n = 60)

		Min. – Max.	Mean ± SD.	Median
Protein	g/dl	0.30 – 6.60	1.60 ± 1.31	1.10
Glucose	mm/dl	42.0 – 529.0	139.20 ± 79.37	123.0
LDH	units/ml	26.0 – 1231.0	90.27 ± 154.37	56.0
SAAG		0.50 – 1.50	1.19 ± 0.25	1.30
Neutrophils	cells/HPF	23.0 – 512.0	286.0 ± 63.0	94.0
Lymphocytes	cells/HPF	6.0 – 763.0	178.0 ± 84.0	71.0
R.B.Cs	cells/HPF	4.0 – 12.0	8.0 ± 4.0	5.0

Distribution of the studied cases according to imaging studies:

This table showed that all patients were having liver cirrhosis during ultrasound examination and 38 patients (63.3%) suffering from splenomegaly. Also 12 patient (20%) suffers from portal vein thrombosis during Doppler examination and 18 patient (30%) were found to have HCC during Tri-Phasic CT examination. **(Table 14)**

Table 14: Distribution of the studied cases according to imaging studies. (n= 60)

	No.	%
Ultrasound		
Liver cirrhosis		
Negative	0	0.0
Positive	60	100.0
PV diameter		
Min. – Max.	13.0 – 18.0	
Mean ± SD.	14.33 ± 1.59	
Median	13.50	
Spleen size		
Normal	12	20.0
Splenomegaly	38	63.3
Splenectomy	10	16.7
Doppler examination		
No PV thrombosis	48	80.0
PV thrombosis	12	20.0
Tri-phasic C.T liver enhancing		
No focal lesions	42	70.0
HCC	18	30.0

Distribution of the studied cases according to types of refractory ascites

Diuretic intractable ascites was observed in 52 patients (86.7%). Failure to achieve the maximum dose of diuretics was due to the occurrence of hypotension in 28 patients (46.7%) ; hepatic encephalopathy in 20 patients (33.3%) and the occurrence of renal impairment with elevation of blood urea and serum creatinine in 4 patients (6.1%). Diuretic resistant ascites with failure to achieve response in spite of reaching the maximum dose of diuretics was found in 8 patients (13.3%). **(Table 15, Figure 8)**

Table 15: Distribution of the studied cases according to types of refractory ascites (n=60)

	No.	%
Diuretic intractable ascites	52	86.7
Hypotension	28	46.7
Hepatic encephalopathy	20	33.3
Renal impairment	4	6.7
Diuretic resistant ascites	8	13.3

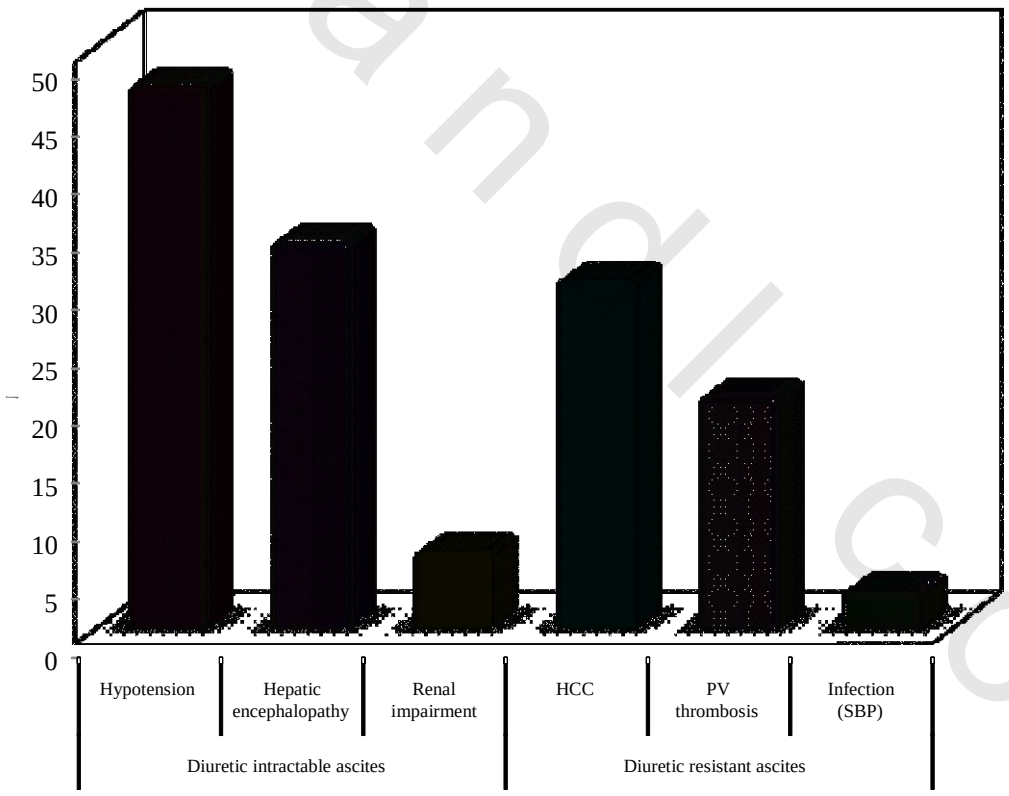

Figure (8): Distribution of the studied cases according to types of refractory ascites.

Suggested precipitating factors for the occurrence of refractory ascites among studied patients:

Advancement of the liver cirrhosis as a precipitating factor for the occurrence of refractory ascites in our patients was observed in 42 patients (70%) whom were in Child class C liver cirrhosis.

Infection was suggested as a precipitating factor with the presence of spontaneous bacterial peritonitis in 9 patients (15%) ; while urinary tract infection was found in 8 patients (13.3%). Obscure infection was also suggested from elevation of the C-reactive protein above a cut off value of 12mg/dl in 11 patients (16.6%).

Portal vein thrombosis was suggested as a precipitating factor for refractory ascites in 12 patients (20%). Hepatocellular carcinoma was also suggested as a precipitating factor in 18 patients (30%).

Renal impairment which may be added to the refractoriness of ascites in our studied patients was observed in the form of proteinuria in 23 patients (38.3%) ; elevated blood urea and serum creatinine in 4 patients (6.6%) ; hyponatremia in 16 patients (26.6%) and hypokalemia in 12 patients (20%). **(Table 16)**

Table 16: **Suggested precipitating factors for the occurrence of refractory ascites in the studied patients:**

Precipitating factors	Number of patients	%
1. Advancement of liver cirrhosis (child class C)	42	70.0
2. Infection		
SBP	9	15.0
UTI	8	13.3
Elevated CRP	11	16.6
3. Portal vein thrombosis	12	20
4. Hepatocellular carcinoma	18	30
5. Renal impairment		
Albuminuria	37	61.7
Urinary Na^+excretion	12	20
Elevated blood urea and serum creatinine	4	6.6
6. Electyrolye imbalance		
Hponatremia	16	26.6
Hypokalemia	12	20

SBP: spontaneous bacterial proteinitis
UTI: urinary tract infection
CRP: c reactive protein
Na+: sodium