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**Ascites in patients with non- cirrhotic non- malignant
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view

1 Ascites in patients with non- cirrhotic non- malignant EPVT
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4 **thrombosis**
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1 Ascites in patients with non- cirrhotic non- malignant EPVT
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5 **Abstract**
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10 **Background and Aims.** The clinical significance of ascites in patients with extrahepatic
11 portal vein thrombosis (EPVT) has been poorly defined. The aim of this study was to assess
12 the frequency, natural history and prognostic implication of ascites in patients with EPVT,
13 and to identify risk factors for this complication.
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18 **Methods.** Single-center retrospective study of consecutive patients diagnosed with non-
19 cirrhotic non- malignant EPVT between 1985 and 2009.
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23 **Results.** One hundred and three patients (35% males; median age 43 (range 16– 83) years)
24 were included and followed for a median time of 5.2 (range 0.9 – 32.5) years. Twenty-nine
25 (28%) had ascites at the time of diagnosis. Overall survival was 91% at five years versus 80
26 (28%) had ascites at the time of diagnosis. Overall survival was 91% at five years versus 80
27 % at ten years. Survival in patients presenting with and without ascites was 83% versus 95%
28 at five years and 42% versus 87% at ten years ($p = < 0.01$). There was no correlation
29 between the presence of ascites and extension of the thrombus into the large splanchnic
30 veins, duration of thrombosis or presence of gastrointestinal bleeding.
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38 **Conclusion.** Ascites is present in a quarter of patients presenting with non-cirrhotic non-
39 malignant EPVT. Ascites is a significant and independent prognostic factor and associated
40 with a decreased long-term survival.
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4 **Introduction**

5 Extrahepatic portal vein thrombosis (EPVT) is the second commonest cause of portal
6 hypertension worldwide. In cirrhotic patient EPVT can be encountered in 10-25% of the
7 patients[1]. Main causes of non- cirrhotic non- malignant portal vein thrombosis are
8 myeloproliferative diseases and inherited or acquired thrombophilic disorders[2-6].
9

10 Portal hypertension often develops as a result of EPVT. Ascites is a common complication of
11 portal hypertension in cirrhotic patients[7-9]. Twenty percent of the cirrhotic patients have
12 ascites at the time of diagnosis, while 30% and 50% will develop ascites by 5 and 10 years,
13 respectively [7, 10]. In children with EPVT ascites has been described in association with
14 gastrointestinal hemorrhage and / or surgery and appeared to be transient [11]. In young
15 adult patients with EPVT and a history of gastrointestinal hemorrhage ascites can also
16 develop spontaneously with an annual incidence rate of 20% [12]. In contrast to ascites in
17 cirrhotic patients which is associated with an increased risk for mortality and associated with
18 an expected survival below 50% after 5 years, little is known about the morbidity and
19 mortality of adult patients with non- cirrhotic non- malignant EPVT and ascites [13, 14]. In the
20 current cohort study we investigated the incidence and clinical outcome of ascites in adult
21 patients with non- cirrhotic non- malignant EPVT.
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4 **Patients and methods**

5 Design of the study

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7 From 1985 until 2009 all consecutive patients from our hospital with a non- cirrhotic non-
8 malignant EPVT were enrolled in this study. Date of diagnosis was defined as the first date
9 EPVT was found on radiological imaging either elsewhere or in our tertiary referral center.
10 Patients who were referred to our clinic underwent radiological imaging in our hospital to
11 confirm the diagnosis. In these cases data with regard to the presence of ascites at diagnosis
12 were retrieved from the referring hospital. Follow up started after the diagnosis EPVT was
13 established and lasted until either December 2009 or death, whichever came first. For all
14 patients a standardized clinical record form with data on diagnosis, ascites, treatment and
15 outcome was collected by a systematic review of the medical charts.
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30 Diagnostic assessment

31 Patients with EPVT and previous or concurrent carcinoma, Budd-Chiari syndrome, veno-
32 occlusive disease, liver transplantation or with concurrent heart failure at the time of
33 diagnosis were excluded. Cirrhosis was excluded by liver biopsy and/or a combination of
34 radiological imaging and biochemical tests. EPVT was classified according to international
35 consensus guidelines, namely obstruction of the extra-hepatic portal vein, with or without
36 involvement of the intrahepatic portal veins [11]. The diagnosis of EPVT was based on
37 radiological imaging using Doppler ultrasonography, computed tomography, magnetic
38 resonance imaging or venography. EPVT was defined as chronic, when multiple hepatopetal
39 collaterals, so called portal cavernoma or gastrointestinal varices were present. When these
40 features were absent the presentation of EPVT was considered acute. Ascites was
41 diagnosed by radiological imaging. Examination of the ascitic fluid was performed in case of
42 clinical suspicion of bacterial peritonitis or if other causes of ascites than EPVT were
43 suspected.
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Statistics

1 Ascites in patients with non- cirrhotic non- malignant EPVT

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3 Kaplan Meier method was used to calculate overall survival and the log-rank test was used
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5 for comparing groups. Determinants of survival and the effect of ascites were estimated as a
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7 hazard ration (HR) and corresponding 95% confidence interval (CI) using Cox regression
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9 analysis adjusted for sex and age. Occurrence of ascites during follow-up was analysed as a
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11 time-dependent factor. Proportionality assumption was checked for each determinant and no
12
13 significant division from proportionality was found. A p-value of < 0.05 was considered
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15 statistically significant. All statistical analysis were performed with the Statistical Package for
16
17 Social Sciences for Windows, version 16.0 (SPSS, Chicago, IL).
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23 Results

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25 From a total of 113 patients presenting with non- cirrhotic non- malignant EPVT 103 patients
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27 were included in this study. Ten patients were excluded due to lack of reliable data with
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29 regard to ascites at the time of diagnosis. The median age of those enrolled in the study was
30
31 43 years (range 16 – 83 years). The median duration of follow up was 5.2 years (range 0.9 –
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33 32.5 years). Baseline patient characteristics according to the presence of ascites at baseline
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35 are summarized in table I. The presence of ascites at baseline was demonstrated by ct-scan
36
37 (n=18) and ultrasonography (n=11).Cirrhosis was excluded by liver biopsy in 39 patients.

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39 At baseline and during follow up ascites was diagnosed in a total of 39 patients. Twenty-nine
40
41 patients had ascites at the time of diagnosis and ten patients developed de novo ascites
42
43 during follow up. The overall risk of developing ascites was 36% (95% CI 27-45) at 1-year
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45 and 37% (95% CI 28-46) at 10- years (figure 1A). Diagnostic paracentesis was performed in
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47 fourteen patients. Examination of the ascitic fluid showed a serum-ascites albumin gradient
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49 ≥ 11 gr/ l in all cases. Bacterial peritonitis was diagnosed in three cases during follow up. In
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51 all the other patients the ascitic fluid showed no elevated absolute polymorphonuclear
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53 leukocyte count (< 250 cells/mm³) and bacterial cultures were negative.
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57 In the twenty-nine patients who had ascites at the time EPVT was diagnosed, thrombosis
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59 was seen in the portal vein only (n= 15), in the portal and splenic vein (n= 1), in the portal
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and superior mesenteric vein (n= 3) and in the portal, splenic and superior mesenteric

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3 vein(n= 10). EPVT was acute in six of 28 patients and chronic in 22 of 28 patients. In one
4 patient no description of acute or chronic EPVT was given.
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6
7 Among the total group of 103 EPVT patients 33 (32%) had a myeloproliferative disorder
8 (MPD). JAK2 mutation was tested in 59 patients and was positive in 21 patients. Forty-eight
9 patients underwent a bone marrow biopsy. All patients with a JAK2 mutation who underwent
10 a bone marrow biopsy had overt MPD. There was no significant correlation between the
11 presence of ascites and other important baseline variables such as MPD, duration of
12 thrombosis (acute versus chronic), the extension of thrombosis into any of the splanchnic
13 veins or with concomitant variceal bleeding.
14

15
16 The presence of ascites during follow up was diagnosed by radiological imaging in 95
17 patients and by a laparoscopic procedure in one patient. In the patients a median of three
18 (range 1-11) radiological imaging procedures were performed during follow-up. In 23 patients
19 ascites (re)occurred during follow up. Refractory ascites was seen in six patients. The risk of
20 recurrence of ascites was at the first year 18% (95% CI 4-33) and at five years 77% (95% CI
21 54-100) (figure1B). Ascites which developed during follow up could be related to various
22 causes in thirteen patients, namely (gastrointestinal) blood loss (n=6) surgical intervention
23 (n=1), septic shock with diverticulitis and liver abscesses (n=1) extramedullary
24 haematopoiesis (n=1), protein losing enteropathy (n=1), peripheral stem cell
25 transplantation (n=1), kidney failure (n=1) and shunt occlusion (n=1). In ten patients there
26 was no identifiable cause.
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49 Treatment

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51 Twenty-five patients were on diuretic treatment. Reasons to start diuretics were presence of
52 ascites (n=20), developing heart failure (n=4) and hypertension (n=1). Only the last patients
53 was already on diuretic treatment before the diagnose EPVT was established.
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57 Two patients underwent porto-systemic shunt surgery for variceal bleeding refractory to
58 endoscopic treatment. Three patients received a trans-jugular intra-hepatic porto-systemic
59 shunt (TIPS) to enable local thrombolysis in the portal vein.
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3 Oral anticoagulation was used in 14 (50%) patients with ascites. We found that patients with
4 ascites, who were not on anticoagulation therapy, had a higher mortality rate ($p= 0.07$).
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10 Survival

11 Among the total group of 103 patients 20 patients died during follow-up. Causes of death
12 were: MPD ($n= 5$), variceal bleeding ($n= 2$), infectious diseases ($n= 3$), cardiovascular
13 diseases ($n= 2$) and various other causes ($n= 5$). In three patients the cause of death was
14 unknown.
15

16 Survival in the total group of 103 patients was 91% (95% CI 85-97) at five years and 80%
17 (95% CI 69-91) at ten years (Figure 2). When we compared patients without ascites at
18 diagnosis and with ascites, we found a five years survival of 95% (95% CI 89-100) versus
19 83% (95% CI 68-99) and a ten years survival of 87% (95% CI 76-97) versus 42% (95% CI 0-
20 83) (Figure 3). In the univariate analysis we found that age (HR = 1.1 $p = <0.001$), MPD (HR
21 = 3.7 $p = 0.004$), chronic portal vein thrombosis (HR 2.89 $p = 0.03$), variceal bleeding (HR
22 3.64 $p 0.01$) and ascites at time of diagnosis (HR = 6.6 $p = 0.001$) were significant predictors
23 of survival (table 2). In the multivariate analysis, after adjustment for age ($p<0.01$) and sex
24 ($p= 0.06$), we found that the presence of ascites at diagnosis (HR 5.1 $p=0.03$) was the only
25 independent significant factors which predicted survival.
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4 **Discussion**

5 In this study we investigated the morbidity and mortality in adult patients with a non-cirrhotic
6 non-malignant EPVT and ascites. We found that in approximately a quarter of the patients
7 ascites was present at the time of diagnosis and that 75% of these patients were at risk for a
8 second episode of ascites. This group of patients had a significant reduced survival
9 compared to patients without ascites.
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12 According to the literature, ascites in patients with an acute EPVT is correlated with
13 mesenterial thrombosis, intestinal ischemia or intestinal infarction [15, 16]. In patients with a
14 chronic EPVT ascites is correlated with gastrointestinal hemorrhage, renal insufficiency,
15 sepsis and / or surgery [11]. Most of the patients with ascites in our study were patients with
16 a chronic EPVT. However in our patients renal function was normal, there was no significant
17 relation between age, gastrointestinal hemorrhage, surgery or infection and the presence of
18 ascites. Other causes that could clarify the presence of ascites, such as liver failure or low
19 osmotic pressure, appeared also unlikely, because all patients lacked histological,
20 biochemical and radiologic evidence of cirrhosis. It is known that the onset of ascites in
21 patients with a history of thrombotic disease should heighten the clinical suspicion of
22 mesenterial venous thrombosis [15]. However, we found no correlation between the
23 extension of the thrombus towards the superior mesenteric vein and the presence of ascites.
24 Mortality in patients with EPVT is often determined by underlying causes [17]. We found
25 however a remarkably high mortality rate in the group of patients with ascites at the time of
26 diagnosis, which was not correlated with the underlying MPD or other etiological factors.
27 Patients with EPVT and an underlying prothrombotic state, who did not use oral
28 anticoagulation, had a significantly higher incidence rate of splanchnic venous obstruction
29 compared to patients who did use oral anticoagulation[18]. We found that in patients with
30 ascites, who were not using oral anticoagulation survival was decreased compared to those
31 who did use oral anticoagulation. This underlines the need of anticoagulation in EPVT even if
32 esophageal varices are present[18-21].
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1 Ascites in patients with non- cirrhotic non- malignant EPVT

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3 Our study suffers from the following limitations. Firstly, not all the patients did have a liver
4 biopsy, therefore we looked in all other possible ways to exclude cirrhosis. Secondly,
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6 decisions about performing a radiological imaging and starting a specific treatment were
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8 made by the treating physician. This led to the fact that not all patients did have a systemic
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10 radiological imaging during follow up and that the time between the radiological imaging
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12 differed among the patients. Ascites could have occurred in some patients and remained
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14 unidentified. There were however clearly no significant signs or symptoms suggesting the
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16 presence of ascites, according to the medical charts.
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20 In conclusion, in our series of patients with non-cirrhotic non- malignant EPVT, ascites is
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22 present in about one quarter of the patients. Ascites at the time of EPVT diagnosis is
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24 independently related to a high mortality rate.
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Ascites in patients with non- cirrhotic non- malignant EPVT

Table 1. Baseline Characteristics of the 103 Patients

Variable at baseline	Patients with ascites n=29 (%)	Patients without ascites n = 74 (%)
Sex (m/f)	16/ 13	23 / 51
Age (yrs)*	41 ± 16 (27 - 77)	43 ± 17 (16 - 83)
Duration of thrombosis		
- Acute	6 /28(21%)	28/68 (41%)
- Chronic	22/28(79%)	40/68 (59%)
Site of thrombosis		
- Portal vein	15/29 (52%)	43/74 (58%)
- Portal and splenic veins	1/29 (3%)	7/74 (9%)
- Portal and mesenterial veins	3/29 (10%)	10/74 (14%)
- Portal, splenic and mesenterial veins	10/29 (35%)	14/74 (19%)
Underlying causes		
- Inherited thrombophilia	5/23 (22%)	18/61 (30%)
- Acquired disorders	22/29 (76%)	55/74 (74%)
Acquired disorders		
- Myeloproliferative disease	13/29 (45%)	20/73 (27%)
- Infection	5/29 (17%)	16/74 (22%)
- Surgery	3/29 (10%)	24/74 (32%)
Signs and symptoms		
- Abdominal pain	19/29 (66%)	50/72 (69%)
- Splenomegaly	19/25 (76%)	36/67 (54%)
- Ascites	28/28 (100%)	0/74 (0%)
- Hepatomegaly	2/27 (7%)	9/74 (12%)
Varices	17/27 (63%)	33/53 (62%)
- Variceal bleeding (yes / no)	9/27 (33%)	14/59 (22%)
Blood hemoglobin (mmol/ L)*	6.7 ± 1.5 (4.9 – 10.0)	7.7 ± 1.7 (4.3 – 13.8)
Platelet count (x 10E9/ L)*	247 ± 239 (49 –1083)	267 ± 175 (31 – 888)
Bilirubin (µmol/L)*	15 ± 19 (3 – 100)	13 ± 35 (4 – 242)
Aspartate transaminase (U/ L)*	33 ± 15 (7 – 57)	27 ± 41 (3 – 284)

* median ± sd (range)

Ascites in patients with non- cirrhotic non- malignant EPVT

Variable at baseline	Patients with ascites n=29 (%)	Patients without ascites n = 74 (%)
Alanine transaminase (U/ L)*	28 ± 22 (9 – 111)	29 ± 43 (9 – 198)
Serum albumin (g/ L)*	37 ± 8.0 (22- 48)	38 ± 7 (24 – 51)
Serum creatinin (μmol/ L)*	69 ± 26 (44 – 170)	67 ± 56 (35 – 385)
APTT (sec)*	36 ± 17 (25 – 83)	32 ± 13 (3 – 88)
PT (sec)*	15 ± 2.2 (11 – 20)	16 ± 8.8 (10 – 57)
PTINR *	1.3 ± 0.5 (1.0 – 2.8)	1.3 ± 0.9 (1.0 – 4.3)

* median ± sd (range)

Ascites in patients with non- cirrhotic non- malignant EPVT

Table 2. Univariate analysis of variables associated with a poor survival

Variable	HR (CI 95%)	P value
Age (years)	1.08 (1.04- 1.11)	<0.001**
Male gender	1.38 (0.53- 3.59)	0.52
Chronic portal vein thrombosis	3.14 (0.91-10.77)	0.04**
Site of thrombosis		
- Portal vein	1	0.60
- Portal and splenic veins	1.53 (0.33- 7.09)	0.59
- Portal and mesenterial veins	0.34 (0.04- 2.61)	0.30
- Portal, splenic and mesenterial veins	0.94 (0.30- 2.93)	0.92
Ascites at baseline	6.61 (2.21- 19.73)	0.001**
Ascites at baseline and during follow-up*	4.94 (1.73- 14.14)	0.004**
Ascites during follow-up*	1.78 (0.22- 4.66)	0.59
Presence of MPD	3.68 (1.51- 9.00)	0.005**
Presence of varices ¹⁾	1.28 (0.40- 4.11)	0.68
Presence of variceal bleeding ¹⁾	3.54 (1.31- 9.56)	0.02**
Splenomegaly ¹⁾	1.33 (0.46- 3.83)	0.59
Anticoagulation therapy	0.46 (0.17- 1.2)	0.10
Bilirubin ¹⁾	0.03 (1.00- 1.02)	0.03**
Asat ¹⁾	0.03 (1.00-1.02)	0.02**

¹⁾ variable at baseline

* analysed as a time-dependent factor

** statistical significant

1 Ascites in patients with non- cirrhotic non- malignant EPVT
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4 **Legends**
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8 Figure 1A Occurrence of ascites in patients with EPVT
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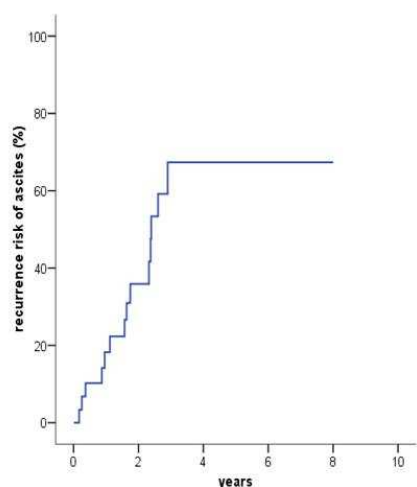
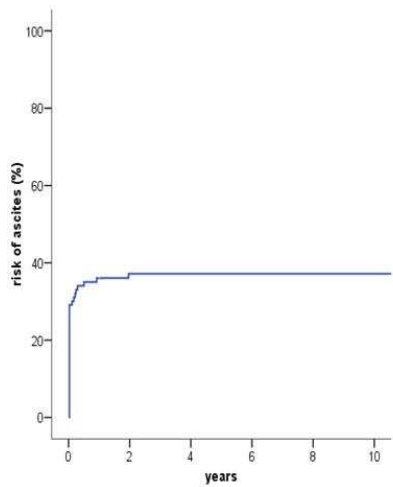
10 Figure 1B Recurrence of ascites in patients with EPVT
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12 Figure 2. Kaplan- Meier curve showing the overall survival of patients with EPVT
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14 Figure 3. Kaplan- Meier curve showing the survival of patients with and without ascites and
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16 EPVT
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For Peer Review

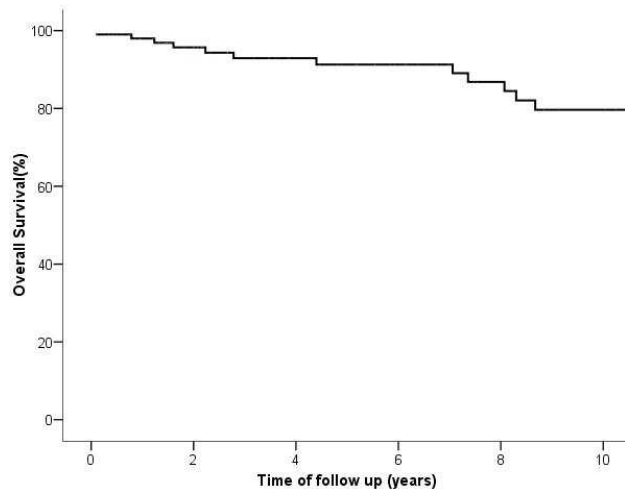
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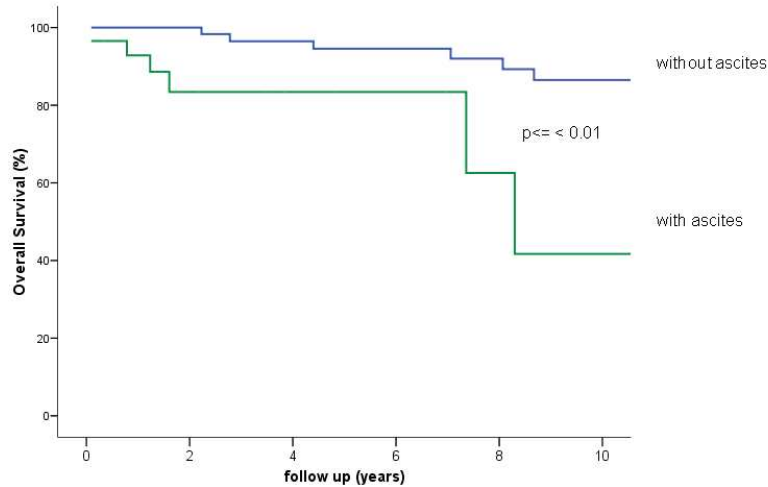
Number of patients

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Review