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Role of Routine Bone Marrow Biopsy Preoperatively in Non Cirrhotic Portal Hypertension

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Authors' contributions

This work was carried out in collaboration among all authors. Author KC conceptualized the study. Author KC collected the data. Authors KC, SS, PR and SC designed the study. Author KC analysed the data. Authors KC and PR contributed to the interpretation of the analyses. Authors KC and SS drafted the article. Author PR approved the final manuscript. Author SC revised for intellectual content. All authors read and approved the final manuscript.

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ABSTRACT

Background: A bone marrow biopsy is routinely done prior to surgical intervention in patients with Extrahepatic portal venous obstruction (EHPVO) and Non-Cirrhotic portal fibrosis (NCPF) to rule out other aetiologies pertaining to pancytopenia. However, there are no guidelines for whether it is indicated or has any value in management protocols.
Methods: 58 patients were retrospectively analyzed who had undergone surgery for established cases of EHPVO or NCPF. The diagnosis was made with imaging studies, either a doppler

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ultrasound or a CT scan. Baseline characteristics were analyzed, and the patients who had undergone a bone marrow biopsy preoperatively were compared to those who hadn't. The impact of the bone marrow study on the line of management was also evaluated.

Results: There was no difference in the outcomes of patients who have undergone bone marrow biopsy and those who didn't in univariate analysis. Also, we have noted that none of the patients had any deviation in the line of treatment.

Conclusions: To our knowledge, this is the first study to evaluate the role of preoperative bone marrow biopsy in non-cirrhotic portal hypertension. A bone marrow biopsy is an invasive procedure, time-consuming, and has its complications. Cytopenia in non-cirrhotic portal hypertension can be attributed to hypersplenism and portal hypertension, and a routine bone marrow biopsy may be avoided.

Keywords: Bone marrow; biopsy; non-cirrhotic portal hypertension; cytopenia; portal venous obstruction; extrahepatic; portal fibrosis.

1. INTRODUCTION

Non cirrhotic portal hypertension (NCPHTN) is an important entity causing portal hypertension in developing countries. Two main presentations include extrahepatic portal venous obstruction (EHPVO) and Non-Cirrhotic portal fibrosis (NCPF). NCPF is referred to as idiopathic portal hypertension in Asian countries [1]. These patients often need surgical therapy to control their symptoms. Most are referred for surgery, either shunt procedures or devascularization after failed endotherapy [2] or symptomatic hypersplenism. Some of these patients have persistent pain in the abdomen and heaviness due to a massively enlarged spleen. A few other indications include portal biliopathy, stunted growth, and acute gastrointestinal bleeding in emergencies [3]. Preoperatively, patients are subjected to a routine bone marrow biopsy (BMB) to rule out other causes of pancytopenia. However, there is no consensus on whether bone marrow biopsy is indicated for these cases of NCPTN, where the majority are chronic patients who are already on follow-up or have undergone repeat endoscopic interventions.

2. MATERIALS AND METHODS

A retrospective analysis of 58 patients that have undergone surgery for EHPVO or NCPF in our institute from 2010 to 2023 was done. Data was analyzed from a prospectively maintained database. Patients' characteristics between EHPVO and NCPF were compared and analyzed. Informed consent was obtained from all patients before undergoing treatment, and most of the patients with EHPVO underwent shunt surgeries. Proximal splenorenal shunt (PSRS) was commonly done as shunt surgery, as many patients presented with massive splenomegaly and symptomatic hypersplenism. In the event of unshuntable veins or unfavourable anatomy, devascularization procedures were done.

Devascularization procedures were the first choice for NCPF. A modification of the Hasaab procedure [4,5] was commonly performed in devascularization surgeries, which included splenectomy, ligation of short gastric vessels, devascularization of the proximal two-thirds of the lesser and greater curvature of the stomach, and devascularization of the lower 10 cm of the stomach. The left gastric vein was not ligated, and a vagotomy was not performed. Some patients underwent a modification of the Sugiura and Futagawa procedure [6, 7], which included splenectomy, devascularization of the proximal two-thirds of the stomach along the lesser and greater curve, along with 10 cm of the lower esophagus, and a transaction of the lower esophagus with an end-to-end anastomosis stapler performed through a single midline abdominal incision. The left gastric vein was ligated along with a truncal vagotomy and pyloroplasty. Intraoperative and post-operative outcomes of the patients who have undergone bone marrow biopsy and who have not been analyzed.

All quantitative variables were checked for normal distribution within each category of explanatory variables by using visual inspection of histograms and normality Q-Q plots. Shapiro-wilk test was also conducted to assess normal distribution. The Shapiro Wilk test p value of >0.05 was considered a normal distribution. For normally distributed quantitative parameters, the mean values were compared between study groups using an independent sample t-test (two groups). For non-normally distributed quantitative

parameters, medians and the interquartile range (IQR) were compared between study groups using Mann Whitney U test (two groups). Categorical outcome: The association between explanatory variables and categorical outcomes was assessed by cross-tabulation and comparison of percentages. The chi-square test / Fisher's exact test was used to test statistical significance. Univariate binary logistic regression analysis was performed to test the association between the explanatory variables and outcome variables. Unadjusted Odds ratio along with a 95% CI is presented. Variables with statistical significance in univariate analysis were used to compute multivariate regression analysis. The adjusted odds ratio along with their 95% CI is presented. A P value < 0.05 was considered statistically significant. IBM SPSS version 26 was used for statistical analysis.

3. RESULTS AND DISCUSSION

3.1 Results

The mean age of diagnosis for EHPVO and NCPF was 21.7 years and 33.8 years, respectively (p<0001). The most common presentations included upper-gastrointestinal bleeding and abdominal pain. Around half the patients in both groups presented with massive splenomegaly and hypersplenism. Symptomatic hypersplenism was noted in 12.5% of patients with EHPVO, compared to 38.4% in NCPF. Other presentations of EHPVO included stunted growth and jaundice. The mean of patients presenting and undergoing surgery after diagnosis was seven years and three years for EHPVO and NCPF, respectively (p <0.007). A bone marrow biopsy was done in 28 (48.2%) of the patients (Table 1).

All patients had established evidence of NCPHTN in imaging (either doppler ultrasound or CT scan). The most common indication of surgery was failed endotherapy. Failed endotherapy included patients that had rebleed after two or more endoscopic interventions, or in those cases, bleeding couldn't be controlled with endoscopy. Other common indications included symptomatic hypersplenism or splenomegaly. Four patients had undergone surgery for portal biliopathy and two for growth retardation. Most of the patients with EHPVO underwent PSRS, and those with NCPF underwent splenectomy and devascularization (modified Hasaab procedure). An esophageal transaction was done in eight patients, of whom seven had NCPF. Emergency surgery was done in 12% of the patients for failed endotherapy, out of which esophageal transection was performed in two cases. Post-operative mortality was observed in two cases, of which one was an emergency surgery following a massive gastrointestinal bleed. The second patient died postoperatively due to a massive rebleed. The mean postoperative platelet was 3.8 lakh, compared to 74,151 preoperatively (Table 2).

Comparing patients who have undergone bone marrow biopsy with those without, there was no significant difference in post-operative outcome or complications (Tables 3,4). 28 patients underwent BMB prior to surgical intervention in our study, and none of the patients had any deviation in the line of management (Table 5).

3.2 Discussion

In patients with portal hypertension, peripheral cytopenias are a common occurrence during blood workup [8]. Hypersplenism and portal hypertension attribute to peripheral cytopenia in NCPTHN, while decreased serum erythropoietin levels and decreased hepatic thrombopoietin production result in decreased production of cells from bone marrow in those patients with liver disease [9,10]. Although the presence of hematological abnormalities in the blood of portal hypertension patients can be directly ascribed to the same, bone marrow biopsy is routine practice and ordered according to the decision of the treating doctor. Few studies have evaluated the necessity of bone marrow biopsy in cirrhotic aetiology, but no studies have been done to assess its role in NCPHTN [9,11]. Unwarranted bone marrow studies can prevent complications related to the procedure, such as pain and bleeding [12], and rarely dreadful complications like cardiac tamponade with sternal BMB and gluteal compartment syndrome [13,14]. BMB is an invasive procedure that has to be done in the background of thrombocytopenia, which is time-consuming, and in fact, it has been shown that after splenic artery ligation intraoperatively, the platelet count will increase drastically [15,16]. In this study, all the patients were known cases of NCPHTN that were referred for surgery. The mean duration of referral for a surgical procedure was 7 years and 3 years after diagnosis, which was statistically significant. PSRS was the preferred surgical option for EHPVO, while some of them have undergone devascularization procedures due to unfavourable anatomy. Devascularization procedures were preferred in

Table 1. Patient characteristics

	Total (58)	**Extrahepatic portal vein obstruction (32)**	**Non cirrhotic portal fibrosis (26)**	**P-Value**
Mean age	27.16 ± 9.68	21.75 ± 8.23	33.81 ± 6.82	**<0.0001***
Mean presentation from initial diagnosis	5.39 ± 5.13	7.087 ± 5.75	3.31 ± 3.27	**<0.0076***
Clinical presentation				
Upper gastrointestinal bleed	41(70.691%)	23(56.10 %)	18(43.90%)	0.526
Abdominal pain	16(27.59%)	9(56.25%)	7(43.75%)	0.578
Splenomegaly	10(17.24 %)	8(80%)	2(20%)	0.144
Massive spleen	37(63.79%)	20(54.05%)	17(45.95%)	
Hypersplenism	48(82.76%)	27(56.25%)	21(43.75%)	0.718
Symptomatic hypersplenism				
Gum bleed				
Fatigue	4	2(50%)	2(50%)	0.879
Menorrhagia	7	1(16.67%)	6(85.71%)	
Petechia	2	0	2(100%)	
	1	1(100%)	0	
Stunted growth	4(6.90%)	4(100%)	0	0.085
Jaundice	6(10.34%)	5(83.33%)	1(16.67%)	0.152
Preoperative workup				
Mean haemoglobin(gm/dl)	8.18	8.51	7.78	0.3019
Mean total leucocyte count(cells/cmm)	4624.31	4593.43	4662.308	0.9688
Mean Platelet (lakhs/cmm)	74151.72	74615.63	73580.77	0.4963
Previous endotherapy	35(60.34%)	20(62.50%)	15(57.69%)	0.710
Bone marrow biopsy	**28 (48.3%)**	**16 (50%)**	**12 (46.2%)**	**0.771**
Indication for surgery				
Failed endotherapy	19 (32.8%)	11 (34.4%)	8 (30.8%)	0.244
Rebleed	10 (17.2%)	5 (15.6%)	5 (19.2%)	
Symptomatic hypersplenism	8 (13.8%)	3 (9.4%)	5 (19.2%)	
Symptomatic Splenomegaly	10 (17.2%)	5 (15.6%)	5 (19.2%)	
Portal Biliopathy	4 (6.9%)	4 (12.5%)	0	
Acute upper gastrointestinal bleed	1 (1.7%)	1 (3.1%)	0	
Stunted growth	2 (3.4%)	2 (6.3%)	0	

	Total (58)	Extrahepatic portal vein obstruction (32)	Non cirrhotic portal fibrosis (26)	P-Value
Multiple splenic artery aneurysm	2 (3.4%)	0	2 (7.7%)	
Periampullary carcinoma	1 (1.7%)	0	1 (3.8%)	
Operative variables				
Proximal splenorenal shunt	27(46.55%)	20(62.50%)	7(26.92%)	<0.007*
Splenectomy / devascularization	31(53.44%)	12(38.70%)	19(61.29)	
Oesophageal transection	8(13.79%)	3(37.50%)	5(62.50%)	0.242
Emergency	7(12.07%)	3(42.86 %)	4(57.14%)	0.382
Duration of surgery (hours)	5.62	5.79	5.41	0.1821
Blood loss (ml)	634.48	734.37	511.53	0.1636

**Failed endotherapy include patients in whom endoscopic intervention failed to control ongoing bleed.*
*** Rebleed patients include those patients that required repeat endoscopic intervention for UGI bleed. (>two prior endoscopic interventions)*
Some patients had more than one indication for surgery

Table 2. Post-operative variables

	Total (58)	Extrahepatic portal vein obstruction (32)	Non cirrhotic portal fibrosis (26)	P-Value
Post-operative average haemoglobin (gm/dl)	10.49	10.53	10.44	0.8663
Post-operative average Total leucocyte count(cells/cmm)	17642.64	74615.63	9167.82	0.0897
Post-operative mean platelet count ((lakhs/cmm))	3.27	3.22	3.34	0.9570
Complications				
Wound infection	6 (10.3%)	2 (6.3%)	4 (15.4%)	0.460
Ascites	3 (5.2%)	1 (3.1%)	2 (7.7%)	
Thrombocytosis	6 (10.3%)	4 (12.5%)	2 (7.7%)	
Atelectasis	3 (5.2%)	2 (6.3%)	1 (3.8%)	
Abdominal collection	1 (1.7%)	0	1 (3.8%)	
Rebleed	2 (3.4%)	2 (6.3%)	0	
Death	2	2	0	0.198

Table 3. Comparison of various factors with pre-operative bone marrow biopsy (N=58)

	Total (N=58)	With Bone marrow biopsy (N=28)	Without Bone marrow biopsy (N=30)	P value
Age (Mean ± SD)	27.16 ± 9.68	28.32 ± 9.20	26.07 ± 10.15	0.380
Gender				
Male	27 (46.6%)	12 (42.9%)	15 (50%)	
Female	31 (53.4%)	16 (57.1%)	15 (50%)	0.586
Diagnosis				
EHPVO	32 (55.2%)	16 (57.1%)	16 (53.3%)	
NCPF	26 (44.8%)	12 (42.9%)	14 (46.7%)	0.771
Clinical presentation				
Upper gastrointestinal bleed	41 (70.7%)	18 (64.3%)	23 (76.7%)	0.301
Abdominal pain	16 (27.6%)	9 (32.1%)	7 (23.3%)	0.453
Massive Splenomegaly	37 (63.8%)	19 (67.9%)	18 (60%)	0.112
Hypersplenism	48 (82.8%)	23 (82.1%)	25 (83.3%)	0.905
Symptomatic hypersplenism				
Bleeding gums	4 (6.9%)	2 (7.1%)	2 (6.7%)	0.943
Fatigue	7 (12.1%)	2 (7.1%)	5 (16.7%)	0.266
Menorrhagia	2 (3.4%)	1 (3.6%)	1 (3.3%)	1.000
Petechiae	1 (1.7%)	0 (0%)	1 (3.3%)	1.000
Jaundice	6 (10.3%)	4 (14.3%)	2 (6.7%)	0.341
Stunted growth	4 (6.9%)	1 (3.6%)	3 (`10%)	0.334
Patient characteristics				
Haemoglobin (gm/dl)	8.26 ± 2.42	8.56 ± 2.37	7.98 ± 2.47	0.369
Total leukocyte count(cells/cmm)	4567.13 ± 2869.58	4418.33 ± 2525.09	4706 ± 3194.88	0.706
Platelet count (lakhs/cmm)	77582.76 ± 66273.38	87885.71 ± 84475.27	67966.67 ± 42317.75	0.256
Surgery				
Emergency	7 (12.1%)	2 (7.1%)	5 (16.7%)	0.266
PSRS	27 (46.6%)	16 (57.1%)	11 (36.7%)	0.063
Splenectomy	1 (1.7%)	1 (3.6%)	0 (0%)	
Splenectomy, Devascularisation	29 (50%)	10 (35.7%)	19 (63.3%)	
Whipple procedure/ splenectomy	1 (1.7%)	1 (3.6%)	0 (0%)	
Oesophageal transaction	8 (13.8%)	4 (13.3%)	4 (13.3%)	0.916
Blood Loss (ml)	634.48 ± 468.41	676.79 ± 498.61	595 ± 443.22	0.511

	Total (N=58)	With Bone marrow biopsy (N=28)	Without Bone marrow biopsy (N=30)	P value
Duration (Min)	326.84 ±89.59	331.11 ± 113.93	323 ± 61.88	0.736
Post-operative variables				
Haemoglobin (gm/dl)	10.49 ± 1.29	10.36 ± 1.31	10.62 ± 1.28	0.453
Total leukocyte count(cells/cmm)	10485 ± 4469.42	10631.85 ± 4122.58	10348.28 ± 4839.02	0.815
Platelet count(lakhs/cmm)	3.32 ± 1.69	3.12 ± 1.50	3.50 ± 1.87	0.400
Post-operative complication				
Ascites	3 (5.2%)	3 (10.7%)	0 (0%)	0.117
Atelectasis	3 (5.2%)	1 (3.6%)	2 (6.7%)	
Abdominal collection	1 (1.7%)	1 (3.6%)	0 (0%)	
Rebleed- from branch of Right hepatic artery, embolization done	1 (1.7%)	1 (3.6%)	0 (0%)	
Rebleed, Reoperation	1 (1.7%)	1 (3.6%)	0 (0%)	
Thrombocytosis	6 (10.3%)	1 (3.6%)	5 (16.7%)	
Wound infection	6 (10.3%)	4 (14.3%)	2 (6.7%)	
Death	2 (3.4%)	0 (0%)	2 (6.7%)	0.164

Table 4. Factors associated with preoperative Bone marrow biopsy in study population univariate analysis

	Odds ratio	95% CI	P value
Age (Mean ± SD)	1.025	0.971 – 1.082	0.374
Gender	1.333	0.473 – 3.756	0.586
Presentation after initial diagnosis (Median)	1.076	0.967 – 1.198	0.179
Upper gastrointestinal Bleed	0.548	0.174 – 1.723	0.303
Abdominal pain	1.556	0.488 – 4.963	0.455
Hypersplenism	0.920	0.235 – 3.595	0.905
Symptomatic hypersplenism			
Bleeding gums	1.077	0.141 – 8.211	0.943
Fatigue	0.385	0.068 – 2.168	0.279
Menorrhagia	1.074	0.064 – 18.036	0.960
Jaundice	2.333	0.392 – 13.875	0.352
Stunted growth	0.333	0.033 – 3.410	0.354
Pre-operative haemoglobin	1.108	0.888 – 1.383	0.364
Pre-operative total leucocyte count	1.000	1.000 – 1.000	0.701
Pre-operative platelet count	1.000	1.000 – 1.000	0.262
Oesophageal transaction	1.083	0.243 – 4.820	0.916
Devascularization	0.312	0.098 – 0.987	0.048
Blood Loss (ml)	1.000	0.999 – 1.002	0.507
Duration (Min)	1.001	0.995 – 1.007	0.731
Post-operative haemoglobin	0.852	0.565 – 1.286	0.446
Post-operative total leukocyte count(cells/cmm)	1.000	1.000 – 1.000	0.811
Post-operative platelet count(lakhs/cmm)	0.872	0.637 – 1.194	0.393
Duration of Surgery (median)	0.974	0.932 – 1.018	0.236
Duration of hospital stay (median)	0.989	0.962 – 1.016	0.409

Table 5. Results of bone marrow biopsy

Results of bone marrow biopsy	N = 28
Normocellular	16
Erythroid hyperplasia	12
Change in management protocol after bone marrow biopsy	0

NCPF patients in view of the higher morbidity associated with shunt procedures, as described in the literature [17–19]. Whether to perform a preoperative bone marrow biopsy or not is now according to institutional preference, and there are no available studies on its role. There was no significant difference in the outcomes of patients who underwent BMB compared to those who didn't in univariate analysis. None of the patients who underwent BMB prior to surgical intervention had any deviation in the line of management. All the patients either had a normal study or had erythroid hyperplasia. Those with bone marrow hyperplasia had erythrocytosis and megakaryocytosis in most cases. The hematological abnormalities resolved in the post-operative period, and in addition, some patients required thromboprophylaxis for elevated platelet counts. Low-dose Aspirin was prescribed for thrombocytosis, and patients were put on surveillance. This suggests that the cytopenia may be attributed to the increased portal pressure and is not indicative of any underlying bone disease or hematological problems. However, the number of participants is low, and this is a retrospective analysis. Also, a bone marrow biopsy was ordered according to the discretion of the treating doctor.

4. CONCLUSION

To our knowledge, this is the first study evaluating the role of BMB in a patient who had an established diagnosis of NCPHTN pre-operatively. BMB did not have any impact on the outcomes of those patients who underwent BMB. All the patients in the study were established cases of NCPHTN referred for surgical

management. We hereby suggest that blood cytopenias in NCPTN are most likely related to portal hypertension, and routine bone marrow biopsy may be avoided.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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