

Evaluation of Pro-Inflammatory Markers (Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio) and Patient Characteristics in Obstructive Biliary Malignancies Undergoing Palliative Interventional Radiology Management with S.E.M.S (Self Expanding Metallic Stents)

Abhinav Amarnath Mohan¹, Gaurav Sharma², Pankaj Banode³

¹Assistant Professor, D.M.I.M.S. Jawaharlal Nehru Medical College, Department TIFAC CORE Interventional Radiology - AcharyaVinobaBhave Rural Hospital (AVBRH), Sawangi - Meghe, Wardha.

²Associate Professor, D.M.I.M.S. Jawaharlal Nehru Medical College, Department TIFAC CORE Interventional Radiology - AcharyaVinobaBhave Rural Hospital (AVBRH), Sawangi - Meghe, Wardha.

³Professor, D.M.I.M.S. Jawaharlal Nehru Medical College, Department TIFAC CORE Interventional Radiology - AcharyaVinobaBhave Rural Hospital (AVBRH), Sawangi - Meghe, Wardha.

Received: April 2018

Accepted: April 2018

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ABSTRACT

Background: Cholangiocarcinoma and other malignant biliary tract diseases are common causes of obstructive jaundice in elderly patients. Despite advances in imaging these tumors are usually detected at a stage when the resection is no longer possible. In all such cases palliative Interventional Radiology Management with S.E.M.S (Self Expanding Metallic Stents) is one of the best possible palliative treatment options. Utility of pro-inflammatory markers like neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as prognostic markers for predicting various complications in these patients have been studied by very few researchers. We have conducted this study to find out whether raised NLR and PLR values can be used as prognostic factors in patients undergoing SEMS. **Methods:** This was a prospective study conducted in the department of interventional radiology of a medical college situated in a rural area. Patients who have undergone SEMS for palliative management of biliary tract cancers were included in this study on the basis of predefined inclusion and exclusion criteria. NLR and PLR were calculated from complete blood count. The analysis of complication rates (cholangitis, cholecystitis, pancreatitis or any other complication) and sepsis was done in relation to NLR and PLR ratio. Statistical analysis was done with Minitab version 17. **Results:** Out of 76 patients included in this study there were 50 males and 26 females with a M: F ratio of 1:0.52. The most common affected age group was found to be between 41-50 years (26.31%). The most common malignancy encountered was found to be Perihilar cholangiocarcinoma (including its subtypes) (34.21%) followed by distal cholangiocarcinoma (28.94%), intrahepatic cholangiocarcinoma (18.42%), Gall Bladder Carcinoma (13.15%) and Periampullary carcinoma (5.26%). NLR values of more than 3 and PLR values of more than 150 were associated with increased chances of complications and sepsis. **Conclusions:** Raised values of Neutrophil to Lymphocyte ratio (NLR) and Platelet to lymphocyte ratio (PLR) were found to be associated with increased chances of sepsis and other complications. However further randomized controlled trials are needed to validate prognostic ability of these ratios.

Keywords: Obstructive Biliary Malignancies, Pro-Inflammatory Markers, Prognosis, Complications.

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INTRODUCTION

Obstructive biliary malignancies consist of conditions like adenocarcinoma of Gall Bladder, Periampullary adenocarcinoma and cholangiocarcinoma.^[1]

Name & Address of Corresponding Author

Dr Abhinav Amarnath Mohan
Assistant Professor
D.M.I.M.S. Jawaharlal Nehru Medical College, Department
TIFAC CORE Interventional Radiology -

AcharyaVinobaBhave Rural Hospital (AVBRH), Sawangi - Meghe, Wardha.

These are relatively rare tumor usually presenting with obstructive jaundice and have a poor prognosis. The obstructive jaundice caused by these malignancies is referred to as malignant jaundice. Majority of these patients present with abdominal distension, loss of appetite, weight loss and jaundice.^[2] Obstructive jaundice may cause intense itching or pruritis. The prognosis of patients with obstructive biliary malignancy depends upon, size, site and stage of malignant growth. Generally the

prognosis is poor and recurrence after resections is fairly common.^[3] Overall 5 years survival rate is 30-40% but decreases drastically to less than 10% in cases of patients with distant metastasis. The risk factors for occurrence of these malignancies include primary sclerosing cholangitis, recurrent pyogenic cholangitis, choledocholithiasis, caroli's diseases and infections like hepatitis B, hepatitis C and human immunodeficiency virus infection.^[4] Recurrent inflammation of biliary tract and gall bladder is a major predisposing factor for development of these malignancies.

Relieving obstruction to the flow of bile because of neoplastic growth of biliary tract by endoscopic stent placement has become a common palliative treatment in patients in whom complete surgical resection is no longer possible. Plastic stents can be used in benign strictures of biliary tract whereas self-expandable metallic stent (SEMS) is preferred in malignant diseases because of its larger lumen and less chances of getting blocked.^[5] Metallic stents are usually made up of cobalt-chromium or an alloy, including nickel-titanium. The length and diameters of SEMS may vary depending upon the manufacturer but usual length and diameter is 5-15 cms and between 5-10 mm respectively. The major factor restricting its use in developing countries like that of India is its prohibitive cost.^[6]

Chronic inflammation is well-known forerunner for development of malignant neoplastic diseases. The cytokines like Interleukin 1, interleukin 16 and transforming growth factor- β (TGF- β) are known chemical which can stimulate cancer cell proliferation and invasion.^[7] The carcinogenesis is by cytokine or antitumor immunologic response within the tumor. In context of cholangiocarcinoma it's a well known fact that conditions like chronic cholangitis, biliary tract calculi, clonorchis sinensis infection and primary sclerosing cholangitis are predisposing factors for development of cholangiocarcinoma. All these infectious and inflammatory conditions points towards inflammation as a predisposing factor for development of these malignancies.^[8]

Various prognostic factors include serum albumin, serum carcinoma embryonic antigen levels and grade of tumour.^[9] In developing countries analysis of biomarkers for systemic inflammation is sparingly used because of their prohibitive cost. Relatively cheap and widely available investigations like neutrophil-to-lymphocyte ratio (NLR) and high platelet-to-lymphocyte ratio (PLR) can be used as a prognostic marker in various malignancies. Increased NLR and PLR ratio has been found to be poor prognostic factor in various malignancies.^[10]

We conducted this study to evaluate role of NLR and PLR in biliary tract malignancies as they have been studied in very few studies and hardly any study has been done to evaluate pro-inflammatory markers (NLR and PLR) in obstructive biliary malignancies.

This is particularly important in Indian scenario as it is not feasible or practical to do other complex pro-inflammatory markers in rural setups of India.

MATERIALS & METHODS

The study was conducted in department of interventional radiology of a tertiary care medical college situated in a rural area. Patients of neoplastic diseases of biliary tract presenting with obstructive jaundice and treated with palliative self-expandable metallic stent (SEMS) during study period were included in this study on the basis of predefined inclusion criteria. Patients having any exclusion criteria were excluded from the study. Written informed consent was taken from all the patients included in this study. The patient characteristics like age, gender and history of risk factors was noted in all the patients. Thorough clinical examination and baseline investigations were done in all cases (CBC, Liver functions tests, Renal function tests). All the patients have undergone ultrasound examination & intraprocedure D.S.A Cholangiogram; Computerized tomography and MRI was done in selected cases. NLR and PLR were calculated from complete blood count. The analysis of complication rates (Cholangitis, pancreatitis or any other complication) and sepsis was done in relation to NLR and PLR ratio. Statistical analysis was done with Minitab version 17 running on windows 10. Microsoft word was used for manuscript preparation while excel was used for creation of figures and graphs.

Inclusion Criteria

1. Patients diagnosed with malignancies of biliary tract on the basis of imaging and histopathology.
2. Patients treated with SEMS stenting.
3. Those who consented to be part of this study.
4. Patients on palliative chemotherapy with deranged LFT, for elective SEMS
5. Abandoned ERCP-stenting, referred for percutaneous SEMS under IR
6. Patients with metastatic disease, with good performance status and candidates for palliative chemotherapy.

Exclusion Criteria

1. Patients Who Refused consent.
2. Patients with metastatic disease and poor performance status and moribund patients.
3. Patients with other co-morbid conditions which might affect the outcome like severe or uncorrectable coagulopathy.

RESULTS

Total 76 patients who had undergone SEMS for various malignancies involving biliary tract were included in this study. Out of 76 studied cases there were 50 males and 26 females with a M: F ratio of 1:0.52.

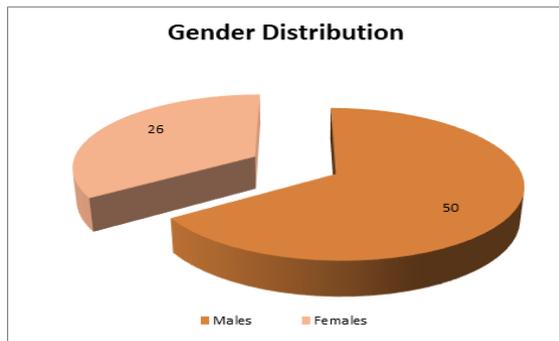


Figure 1: Gender Distribution Of The studied cases.

The analysis of the age groups of the studied cases showed that the most common affected age group was between 41-50 years (26.31%) followed by 51-60 years (23.68%) and 61-70 years (21.05%). There were no patients less than 20 years of age.

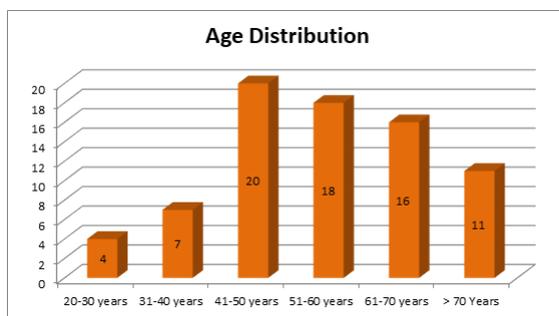


Figure 2: Age distribution of the studied cases.

The most common malignancy encountered was found to be Perihilar cholangiocarcinoma (including its subtypes) (34.21%) followed by distal cholangiocarcinoma (28.94%), intrahepatic cholangiocarcinoma (18.42%), Gall Bladder Carcinoma (13.15%) and Periampullary carcinoma (5.26%). Perihilar Cholangiocarcinoma were subdivided into PCCA 1, PCCA 2, PCCA 3a, PCCA 3b and PCCA 4 on the basis of Bismuth Corlette classification.

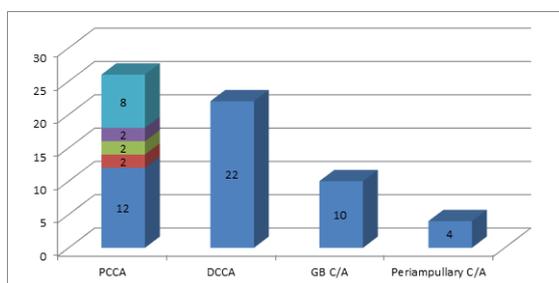


Figure 3: Location of the malignancy in the studied cases.

The serum Bilirubin was done in all the patients. Severity of the jaundice was determined on the basis of total Bilirubin levels. Maximum patients (42.10%) were found to be having total Bilirubin level between 16-20 mg/dl.

Table 1: Bilirubin levels of the studied cases.

Serum Bilirubin Levels	No Of Patients	Percentage
Up to 10 mg/dl	14	18.42 %
11-15 mg/dl	16	21.05%
16-20 mg/dl	32	42.10%
21-25 mg/dl	3	3.94%
26-30 mg/dl	8	10.52%
>30mg/dl	3	3.94%
Total	76	100%

All patients were treated by SEMS stents. Out of 76 patients only 1 stent was required in majority (89.47%) of the patients while 8 (10.52%) patients needed 2 stents

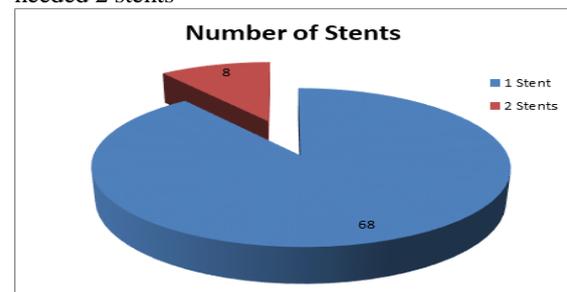


Figure 4: Number of the stents in studied cases.

Neutrophil to Lymphocyte Ratio (NLR) was calculated in all the patients. The value of NLR and PLR and its association with incidence of sepsis and complications was analyzed. The incidence of complications and sepsis was found to be more in patients having NLR more than 3.

Table 2: Neutrophil to Lymphocyte ratio and complications.

Neutrophil to Lymphocyte Ratio	Complications		Total
	Present	Absent	
< 3	9	27	36
> 3	16	24	40
Total	25	51	76
Sepsis			
< 3	14	22	36
> 3	18	22	40
Total	25	51	76

Platelets to Lymphocyte Ratio (PLR) were calculated in all the patients. Value of PLR and its association with incidence of sepsis and complications was analyzed. The value of PLR more than 150 was associated with increased risk of complications and sepsis in the studied cases.

Table 3: Platelets to Lymphocyte ratio and complications.

Platelets to Lymphocyte Ratio	Complications		Total
	Present	Absent	
< 150	14	33	47
> 150	12	17	29
Total	26	50	76
Sepsis			
< 150	21	27	48
> 150	13	15	28

Total	34	42	76
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Overall values of NLR more than 3 and PLR more than 150 were found to be associated with increased risk of complications (cholangitis, cholecystitis, pancreatitis or any other complication) and sepsis.

DISCUSSION

Obstruction to the flow of bile from liver to duodenum can be caused by various benign or malignant pathological conditions. The benign conditions causing obstructive jaundice include choledocholithiasis, chronic pancreatitis, and postoperative strictures, ascariasis and clonorchis sinensis infections.^[11] In neonatal age group the obstructive jaundice can be caused by neonatal hepatitis, biliary atresia, Dubin Johnson and Rotor syndromes.^[12] Malignant neoplastic diseases of gall bladder and biliary tract are common cause of obstructive jaundice in elderly patients. Cholangiocarcinomas are neoplasms of epithelial origin arising from cholangiocytes and these carcinomas can occur at any level of the biliary tract. In these patients pre-operative biliary drainage is one of the essential components of overall management.^[13] It not only improves liver function but also reduce the postoperative complications. On the other hand despite advances in imaging technique many of the patients with cholangiocarcinoma and other neoplastic diseases of biliary tract present at an advanced stage when tumor excision is either not possible or is associated with unacceptable risk of complications. In all these cases with advance disease stage it is imperative that obstruction to bile flow is alleviated otherwise cholestasis will cause hepatic insufficiency. The commonly used surgical procedures for biliary obstruction in non-resectable tumors include palliative cholangioenteric anastomosis and other surgical interventions, however these surgeries are contraindicated in many patients because of poor general conditions or presence of other risk factors. In all such patients Palliative Interventional Radiology Management with S.E.M.S (Self Expanding Metallic Stents) is an excellent alternative.^[14]

These Self expanding stents have now become a very useful tool in the hands of interventional radiologists to relieve obstruction in patients with benign or malignant biliary tract diseases. In benign obstructive conditions (benign strictures or leaks) plastic stents can be used but in cases of malignant obstructions usually a metallic stent is preferred because of its larger lumen and longer duration for which it is expected to remain patent.^[15] Complications associated with these biliary stents include pancreatitis, perforation, intra-abdominal sepsis and fistulae formation^[16]. One of the unique features of biliary tract cancer is that these

malignancies are closely related to inflammatory process and many patients developing these malignancies have a past history of chronic inflammation like chronic pancreatitis, recurrent cholangitis and cholelithiasis etc. For this reason many researchers and authors have conducted various studies to find out relationship between certain pro inflammatory cytokines and prognosis of patients with biliary tract cancer.^[16] These pro-inflammatory cytokines include interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF α), transforming growth factor beta (TGF β), IL-8 and platelet-derived growth factor (PDGF) B chain. According to researchers these cytokines are responsible for malignant growth of cholangiocytes which possibly explains the pathogenesis of malignancies of biliary tract in patients with a history of cholangitis and cholelithiasis.

Nonetheless the estimation and monitoring of all these cytokines is difficult in resource poor rural areas of developing countries. Neutrophil to lymphocyte ratio (NLR) and platelets to lymphocyte ratio (PLR) are the other tests which can be derived from a simple complete blood count and is reported to be having prognostic value in biliary tract malignancies. Various authors have found increased NLR and PLR to be associated with adverse outcome and increased rate of complications and sepsis.^[18]

Haowen Tang et al in their review of 14 studies comprising of 3217 patients found that an increased pretreatment Neutrophil-lymphocyte ratio was significantly linked with detrimental long-term outcomes and clinic-pathological parameters for patients with biliary tract cancer.^[19] Similarly Zhou LH et al in their meta-analysis of 11 studies comprising of 2392 patients concluded that elevated PLR may be an unfavorable prognostic factor for clinical outcomes in patients with biliary tract cancer.^[20] It must be emphasized here that there are very few studies which have been conducted on prognostic value of NLR and PLR value estimation in patients undergoing palliative Interventional Radiology Management with S.E.M.S (Self Expanding Metallic Stents) and more studies are required for coming to a definite conclusion.

CONCLUSION

Raised values of Neutrophil to Lymphocyte ratio (NLR) and Platelet to lymphocyte ratio (PLR) are associated with increased risk of sepsis and other complication in patients with neoplastic diseases of biliary tract presenting with obstructive jaundice and treated with self-expandable metallic stents (SEMS). However Further studies of pro-inflammatory markers are necessary to better delineate the prognostic ability of these ratios.

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How to cite this article: Mohan AA, Sharma G, Banode P. Evaluation of Pro-Inflammatory Markers (Neutrophil-Leukocyte Ratio and Platelet-Lymphocyte Ratio) and Patient Characteristics in Obstructive Biliary Malignancies Undergoing Palliative Interventional Radiology Management with S.E.M.S (Self Expanding Metallic Stents). *Ann. Int. Med. Den. Res*. 2018; 4(3):RD24-RD28.

Source of Support: Nil, **Conflict of Interest:** None declared