Demographic Distribution and Staging at Presentation of Patients Presenting with Obstructive Jaundice of Malignant Origin at Tertiary Care Level in Pakistan
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ABSTRACT

Introduction: Obstructive jaundice due to malignancies of the gall-bladder, biliary tree and pancreas accounts for significant admissions to gastroenterology units. These patients represent a specific population subset and their demographic characteristics need to be identified in order to detect modifiable factors.

Aims & Objectives: To see the demographic distribution and staging at presentation of malignant obstructive jaundice.

Place and duration of study: Department of Gastroenterology and Hepatology, Shaikh Zayed Hospital, Lahore, from January 2015 to June 2016.

Material & Methods: Study design: Cross-Sectional Analytical. Sampling technique: Non-probability consecutive sampling. Adult patients aged 18 and above of either sex were included. Demographic data including age, sex, residence, food, type of malignancy and stage at presentation was recorded. Data was analyzed by SPSS version 20. Sample size: 262 patients.

Results: 262 patients were enrolled between January 2015 and June 2016, 141 (53.8%) males and 121 (46.2%) females. Mean age was 57.42± 14.19 years. 97.7% patients were from Punjab with highest number from Lahore district. 93 (35.5%) patients presented within 1 month while the remaining took 2 months or even longer. 80 (30.5%) had cholangiocarcinoma (including that of distal CBD, mid CBD or confluence of hepatic ducts), 70(26.7%) had gallbladder tumors, 61 (23.3%) had pancreatic tumors and 51(19.5%) had ampullary tumors. 32 (12.2%) patients had stage I disease, 32 (12.2%) stage II, 38 (14.5%) stage III and 155 had (59.2%) stage IV disease. Most patients, 217 (82.8%), had incurable metastatic disease at the time of presentation. The highest caste proportion of patients were from the Araeen group. 52.7% patients were main stream city dwellers with 90.8% consuming tap water. Smoking was the commonest addiction, present in 84 (32.1%) patients.

Conclusion: Malignant obstructive jaundice accounts for significant patient load on tertiary care centres. It is vital to recognize such pathologies early for curative treatment before local and distant metastasis occurs. Higher incidence in certain demographic groups needs further investigation.

Key words: Gall bladder tumor, cholangiocarcinoma, ampullary tumor, pancreatic tumor, obstructive jaundice.

INTRODUCTION

Obstructive jaundice is a term used when there is blockage of bile flow to the intestine and it remains in the blood stream. Obstructive jaundice of malignant origin constitutes a fairly large number of patients that present with jaundice to tertiary care units. According to a Chinese study, malignant jaundice accounts for 42.4% of patients. The malignancies which can cause obstructive jaundice include cholangiocarcinoma, gall bladder tumors, pancreatic tumors, peri-ampullary tumors, hepatic malignancies and metastatic disease. Amongst those, pancreatic head carcinoma is the most common malignancy (51.7%). Gracanin AG, in 2013, conducted a study in Croatian population and found malignant cause in 29.8% of patients with pancreatic head carcinoma being the most frequent cause (11.5%). A study conducted by Iqbal J. et al. in 2008 in Pakistani population also showed similar results. The etiology of malignant disease involving the gallbladder, biliary tree or pancreas is dependent on
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Multiple factors. These are related to the environment, lifestyle and genetic factors. Risk factors for pancreatic cancer include hereditary pancreatitis, cystic fibrosis, Peutz-Jeghers syndrome, familial pancreatic cancer, smoking, diabetes mellitus, obesity, certain oral microbiota and chronic pancreatitis. Risk factors for cholangiocarcinoma include parasitic infections, primary sclerosing cholangitis, biliary tract cysts, choledocholithiasis and cholangitis, chronic hepatitis B and C infection and cirrhosis, diabetes, alcohol and smoking. Gall bladder cancer is associated with cholelithiasis, gall bladder polyps, porcelain gall bladder, environmental carcinogens etc.

Due to slow growing nature, non-specific and late symptomatology, these malignancies are often diagnosed in advanced stages with poor prognosis. Accurate characterization and staging of these indolent cancers will determine outcome as majority of the patients are inoperable at the time of presentation. There are multiple modalities available now for diagnosis and staging of disease including biochemical and imaging studies. CA19-9 is the most frequently studied tumor marker but it lacks specificity. Amongst imaging studies, purely diagnostic modalities include abdominal ultrasound, helical CT and MRI/magnetic resonance cholangiopancreatography (MRCP). Endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous trans-hepatic cholangiopancreatography (PTC) can be used both for diagnostic and therapeutic purposes.

Treatment options for jaundice secondary to malignancies depend upon the stage of the disease and clinical condition of the patient. Treatment options available are either curative or palliative. Curative treatment involves surgical resection with or without chemotherapy. Liver transplantation may be a curative option in a few patients with cholangiocarcinoma. Palliative treatment options include endoscopic or percutaneous stenting or palliative surgical procedures. The treatment modalities depend on different factors which include age, functional status, co-morbidities and stage of disease.

Patients in good physical condition with early stage disease are referred directly for curative surgery. In other cases endoscopic or percutaneous interventions may be used as a bridge to surgery when treatment of cholangitis or lowering of high bilirubin is required prior to surgery. Patients with advanced disease are referred for palliative care, which may constitute endoscopic or percutaneous drainage procedures or surgical treatment.

It is important to understand the demographic distribution of these patients in order to better target limited health resources towards groups that are identified to have higher incidence of disease. It is also important to see if disease goes unnoticed for long periods or referral to tertiary care centres occurs late. This will allow education of primary care teams who may increase their tumor detection rates for early disease identification and prompt treatment.

**MATERIAL AND METHODS**

After taking approval from TRC, IRB and consideration of ethical issues, this study was conducted at Department of Gastroenterology and Hepatology, Shaikh Zayed Hospital, Lahore, from January 2015 to June 2016. Data regarding patients' gender, age, address, comorbid conditions, caste, eating habits and addiction collected. The disease was staged after admission.

**Study design:** Cross-Sectional Analytical.

**Sampling technique:** A sample size of 262 patients was calculated by 95% confidence level with 6% margin of error and taking expected percentage of gall bladder tumor as 50%. Sampling technique was non-probability consecutive sampling. Inclusion Criteria: All adult patients aged 18 and above of either sex presenting with obstructive jaundice secondary to malignant disease originating from the gallbladder, biliary-tree or pancreas were included in the study. Exclusion criteria: Patients with obstructive jaundice secondary to metastatic disease were excluded from the study.

**Statistical analysis:** Data was analyzed by SPSS version 22. Variables included age, sex, co-morbid conditions, residential city, district and province, caste, type of malignancy, stage of malignancy and time of presentation to tertiary care facility. Nominal data (sex, co-morbid conditions, residential city, district and province, caste, type of malignancy and stage of disease) were analyzed by Chi-square test.
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malignancy) was represented as frequency percentages. Numerical data (age and time of presentation to tertiary care facility) was represented as mean ± standard deviation.

RESULTS

A total of 262 patients were enrolled between January 2015 and June 2016, 141 (53.8%) males and 121 (46.2%) were females (Fig-1, Table-1). The mean age of patients was 57.42 ± 14.19 years (range 22-95) (Table-2). Amongst co-morbid conditions, 65 (24.8%) had diabetes, 45 (17.2%) had hypertension, 20 (7.6%) had ischemic heart disease and 13 patients (5%) had chronic liver disease. Among the other significant co-morbid conditions, 15 (5.7%) patients had Hepatitis C infection and 11 (4.2%) had gall stones (Table-3). Amongst the patients who had gall stones, 8 patients developed gall bladder cancer. Some patients had multiple chronic conditions simultaneously. The overwhelming majority of patients were from Punjab, 256 (97.7%) (Table-4).

The highest number of patients was from Lahore: 55 (21%), followed by Faisalabad: 26 (9.9%), Sialkot: 20 (7.6%), Gujranwala: 19 (7.3%) and Toba Tek Singh 12 (4.6%) (Table-5). 50 patients (19.1%) belonged to Araeen Caste, whereas Jutt and Rajput consisting 27 (10.3%) each. Patients from other castes were less than 10% (Table-6). 124 (47.3%) patients came from rural areas while the remaining 138 (52.7%) were mainstream city dwellers (Fig-2). A high majority of patients, 238 (90.8%), used tap water for consumption while the remaining 24 (9.2%) used canal water or water from wells. The majority of patients: 191 (72.9%) had vegetables as their predominant food while pulses and meat accounted for the predominant diet in 58 (22.1%) and 13 (5%) patients, respectively. All the patients (save one) used metal cooking utensils for preparing food. 50 (9.1%) patients kept pets at home. 148 patients (56.5%) had no history of addiction or smoking, while 84 (32.1%) patients were smokers and 5 (2%) were addicted to other substances such as alcohol, opium etc. (Fig-3)

In terms of time interval between onset of symptoms and referral to a specialized tertiary care facility (In this case, our unit) 93 (35.5%) patients presented within 1 month while the remaining took 2 months or even longer to reach us. This time interval ranged from minimum of 7 days to maximum of 6 months with mean time interval of almost 2 months (Table-2). 80 (30.5%) patients were found to have cholangiocarcinoma (including that of distal CBD, mid CBD or confluence of hepatic ducts), 70 (26.7%) had gallbladder tumor, 61 (23.3%) had pancreatic tumor and 51 (19.5%) had ampullary tumor as the cause of obstructive jaundice (Table-7, Fig-4,5).

According to the TNM staging system, 32 (12.2%) patients were found to have stage I disease, 32 (12.2%) had stage II, 38 (14.5%) had stage III and 155 had (59.2%) stage IV disease (Table-8, Fig-6)

| Gender     | Number of patients |
|------------|--------------------|
| Males      | 141 (53.8%)        |
| Females    | 121 (46.2%)        |
| Total      | 262 (100%)         |

Table-1: Gender distribution of patients with malignant obstructive jaundice.

| Minimum | Maximum | Mean     | Std. Deviation |
|---------|---------|---------|---------------|
| Age (years) | 22 | 95 | 57.42 | 14.19 |
| Time interval (months) | 0.25 | 6 | 1.917 | 1.074 |

Table-2: Age distribution and time interval between onset of symptoms and referral to tertiary care level hospital.

| Comorbid condition       | Yes | No | Percentage |
|--------------------------|-----|----|------------|
| Diabetes mellitus        | 65  | 197| 24.8       |
| Hypertension             | 45  | 217| 17.2       |
| Ischemic heart disease   | 20  | 242| 7.6        |
| Chronic liver disease    | 13  | 249| 5.0        |
| HCV infection            | 15  | 247| 5.7        |
| Cholelithiasis           | 11  | 251| 4.2        |

Table-3: Frequency distribution of significant co morbid conditions in patients with malignant obstructive jaundice

| Province                | Number of patients | Percentage |
|-------------------------|--------------------|------------|
| Punjab                  | 256                | 97.7       |
| Khaibarpakhtunkha       | 3                  | 1.1        |
| Balochistan             | 2                  | 0.8        |
| Azaadkashmir            | 1                  | 0.4        |
| Total                   | 262                | 100        |

Table-4: Provincial distribution of patients with malignant obstructive jaundice
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| District       | Number of patients | Percentage |
|----------------|--------------------|------------|
| Lahore         | 55                 | 21         |
| Faisalabad     | 26                 | 9.9        |
| Sialkot        | 20                 | 7.6        |
| Gujranwala     | 19                 | 7.3        |
| Toba Tek singh | 12                 | 4.6        |
| Others         | 130                | 49.6       |
| Total          | 262                | 100        |

**Table-5:** District distribution

| Caste          | Number of patients | Percentage |
|----------------|--------------------|------------|
| Araeen         | 50                 | 19.1       |
| Jutt           | 27                 | 10.3       |
| Rajput         | 27                 | 10.3       |
| Pathan         | 14                 | 5.4        |
| Mughal         | 11                 | 4.2        |
| Others         | 107                | 40.8       |
| Caste not reported | 26           | 9.9        |
| Total          | 262                | 100        |

**Table-6:** Caste distribution

| Cause                     | Males | Females | Total | Percentage |
|---------------------------|-------|---------|-------|------------|
| Cholangiocarcinoma        | 42    | 38      | 80    | 30.5%      |
| Gall bladder tumor        | 32    | 38      | 70    | 26.7%      |
| Pancreatic tumor          | 38    | 23      | 61    | 23.3%      |
| Ampullary tumor           | 29    | 22      | 51    | 19.5%      |
| Total                     | 141   | 121     | 262   | 100%       |

**Table-7:** Causes of malignant obstructive jaundice

| Stage at presentation   | Frequency   |
|-------------------------|-------------|
| Stage I                 | 32 (12.2%)  |
| Stage II                | 32 (12.2%)  |
| Stage III               | 38 (14.5%)  |
| Stage IV                | 155 (59.2%) |
| Not determined          | 5 (1.9%)    |
| Total                   | 262         |

**Table-8:** Stage at presentation in tertiary care center

**Fig-1:** Gender distribution

**Fig-2:** Area distribution

**Fig-3:** History of addiction
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**Fig-4:** Causes of malignant obstructive jaundice

**Fig-5:** Causes of malignant obstructive jaundice

**Fig-6:** Stage at presentation.

Diagnosis

- **Cholangiocarcinoma:** 21, 19%
- **Ampullary Carcinoma:** 88, 31%
- **Gall Bladder Carcinoma:** 70, 23%
- **Pancreatic Carcinoma:** 61, 23%

**CAUSES OF MALIGNANT OBSTRUCTIVE JAUNDICE**

|               | MALE | FEMALE |
|---------------|------|--------|
| Cholangiocarcinoma | 42   | 38     |
| Gall Bladder Cancer | 32   | 38     |
| Pancreatic Cancer | 38   | 23     |
| Ampullary Cancer  | 29   | 22     |

**STAGE AT PRESENTATION**

| Stage | MALE | FEMALE |
|-------|------|--------|
| Stage I | 32   | 32     |
| Stage II | 32   | 32     |
| Stage III | 38   | 38     |
| Stage IV | 155  | 155    |
DISCUSSION

It was observed that, overall, males were more affected than females as regards malignancies of the gall-bladder, biliary tree and pancreas. A study done by S Verma also shows that male patients are more affected\textsuperscript{22}. However, in case of gall bladder tumors, females were more affected than males, which is consistent with studies done at other centers\textsuperscript{11,23,24}. The reason being certain hormonal changes in women and high prevalence of cholelithiasis\textsuperscript{11}. The mean age of patients in our study was 57.42 ± 14.19 years (range 22-95) which shows that the patients presented to our center were younger than in other studies. A study conducted by Gupta et al. showed the mean age of patients presented with obstructive jaundice of malignant origin was 68.5 years\textsuperscript{25}.

Amongst 262 patients, a major number of patients had co morbid conditions like diabetes mellitus, hypertension, ischemic heart disease, chronic liver disease, cholelithiasis and HCV infection (24.8%, 17.2%, 7.6%, 5%, 4.2% and 5.7% respectively). This shows a high prevalence of these conditions amongst the patients with malignant obstructive jaundice and can affect the management decision due to severity of these diseases, which affects patient fitness for therapeutic procedures. Diabetes mellitus, HCV infection and gall stones have significant role in these cancers’ etiology\textsuperscript{5-11}. In our study, amongst the 70 patients who had gall bladder tumor, 8 patients (11%) had history of gall stones, which is a known risk factor for gall bladder tumors\textsuperscript{11}. In our study, 84 (32.1%) patients were chronic smokers and 5 (2%) were addicted to other substances e.g. alcohol and opium. Smoking and alcohol are known risk factors for many malignancies including pancreatic and cholangiocarcinoma\textsuperscript{5,6,26}.

The majority of patients came to our center were from Punjab and especially from the district of Lahore, Faisalabad, Sialkot, Gujranwala and other districts in the premises of Lahore which means more than half of the patients coming from these areas. The majority of patients were from Aaraeen caste. This distribution of patients may be attributed to high prevalence of that caste in these areas. This is an area requiring further investigation. 124 (47.3%) patients came from rural areas while the remaining 138 (52.7%) were mainstream city dwellers. This shows slightly increased frequency of patients from urban areas which can be due to environmental factors, lifestyle changes and better accessibility to health care facilities in cities.

We found cholangiocarcinoma as the most common cause of malignant obstructive jaundice (30.5%), which was further divided into Hilar cholangiocarcinoma, proximal CBD, distal CBD and intrahepatic cholangiocarcinoma. It was followed by gall bladder tumor (26.7%), pancreatic cancer (23.3%) and ampullary cancer (19.5%) respectively. These findings contrast with other studies done in different centers which show pancreatic cancer and gall bladder cancer as the most common cause of malignant obstructive jaundice\textsuperscript{2,4,27}. A study done by Siddique et al. shows pancreatic cancer as the most common cause of malignant obstructive jaundice\textsuperscript{2}. Vijay S found gall bladder tumor as the most common cause in 50% of cases of malignant extra hepatic biliary obstruction\textsuperscript{27}.

In terms of time interval between onset of symptoms and referral to a specialized tertiary care facility (In this case, our unit) 93 (35.5%) patients presented within 1 month while the remaining took 2 months or even longer to reach us. The mean time interval was almost 2 months. And when this is combined with the stage at which patients presented to us (59.2% cases in stage IV disease), this can easily show that a high number of patients presented to us at late stages of their disease where only palliative care could be offered to them and thus were ineligible for curative treatment options. These findings are comparable with findings of Vijay S which shows most of the patients presented in late stages (Stage III and IV)\textsuperscript{27}. This can be due to delayed referrals, lack of awareness from patients and general practitioners and poor socioeconomic statuses of patients.

CONCLUSION

Obstructive jaundice secondary to malignancies that originate from the gall bladder, the bile ducts and pancreatic tissue account for a significant number of admissions to gastroenterology units. It is vital to educate the primary care physicians to recognize such pathologies so that they can undergo timely curative treatment before local and distant metastasis occurs. It is also recommended to conduct further studies in order to better understand
incidence of malignancies amongst different ethnic groups in our country.

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