



## Why Carcinoma Gallbladder is More Common in North India: An Insight Into Etiological and Clinicopathological Trends

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### Abstract

**Background:** *The increasing incidence of carcinoma gall bladder with presentation at advanced stage in North India has been a topic of concern from a long time thus, resulting in many studies.*

**Method:** *In our cross-sectional study, we tried to review the etiological and clinicopathological trends of carcinoma gall bladder in a tertiary care hospital in the city Kanpur. It comprised of study of 108 patients diagnosed with carcinoma gall bladder on the basis on clinical history and examination, radiology and histopathology.*

**Results:** *Maximum number of cases were from rural areas and with low socio-economic status, non-vegetarian and users of locally available mustard oil; age range was 27-80 years, mean age was 53 years, female to male ratio was 2.0:1 with 64% of females having parity>3 and 60% were postmenopausal. Most common symptom was abdominal pain (67%) and lump seen in 14%. Fundus was the most common site and gall stones seen in 83% and polyp in 15% cases. Most common type was adenocarcinoma (98%) and mostly moderately differentiated (41%).*

**Conclusion:** *Female sex, advanced age, multiparity, low socio-economic status, location near river bed, gall stones and polyps are risk factors for carcinoma gall bladder. Most common site is fundus and most common type is adenocarcinoma.*

**Keywords:** *Carcinoma gall bladder, gall stones, Adenocarcinoma.*

### Introduction

Gall bladder cancer was first described by De Stoll in 1777. It is a rare neoplasm with marked ethnic and geographical variations worldwide. It is the most common biliary tract malignancy and the fifth most common malignancy of the gastrointestinal tract. Bolivia and Chile have the highest incidence rates in the world. It is rare in

South Asia but very common in India and Pakistan.

In our country, Delhi has the highest incidence rates. North India has a special predilection for carcinoma gall bladder. In a review of worldwide literature, the female to male ratio is reported to be between 2-3:1. High parity postmenopausal females are at greater risk.

Gall stones are the most common association factor for gall bladder carcinoma and increase the risk by 4-7 times than in those without gall stones. Other associations seen have been with obesity, high fat diet, chronic typhoid infection and environmental carcinogens.

The asymptomatic nature of the disease always remained a problem in the diagnosis and treatment. The symptoms are very non-specific like abdominal pain, abdominal lump, anorexia and weight loss, jaundice and vomiting. Radiological investigations in the form of ultrasonography or computed tomography followed by cytological investigations are therefore needed to diagnose this disease.

With the advent of technology, now surgical management is being given importance and survival benefits being studied. Improved outcomes may occur once the risk factors are clearly identified and accurate initial diagnosis be made.

In our study, we tried to review the etiological and clinical trends of carcinoma gall bladder in a tertiary care hospital in the city Kanpur in North India over a period of one and a half years.

## Methods

A cross-sectional study was carried out in the department of Surgery with the help of Department of Radiology and Department of Pathology in a tertiary care hospital of North India from January 2017 to June 2018. It comprised of study of 108 patients diagnosed with carcinoma gall bladder on the basis on clinical history and examination, radiology and histopathology. Their data was collected and evaluated with respect to etiological and clinicopathological characteristics. Radiological investigations included ultrasound

and/or CT-scan of whole abdomen while histopathological examination comprised of FNAC or USG-guided biopsy. Etiological data analysis included age, sex, residence, closeness to river bed, menopausal status, parity, socio-economic status and dietary factors. Clinical evaluation comprised of chief complaints with history of present illnesses, general and systemic examination for signs such as pallor, icterus, abdominal lump and ascites and, radiological study of site and size of tumour, presence or absence of gall stones, their number and size, presence of polyp or porcelain gall bladder. Histopathological evaluation was done for the type of carcinoma (adenocarcinoma or other rare types) and the differentiation (well, moderately or poorly-differentiated).

## Statistical Analysis

The descriptive statistics of patient's data was presented in terms of frequency and percentage (%) for categorical variables and in terms of range (minimum, maximum), mean, median and standard deviation (SD) for the quantitative variables wherever required.

## Results

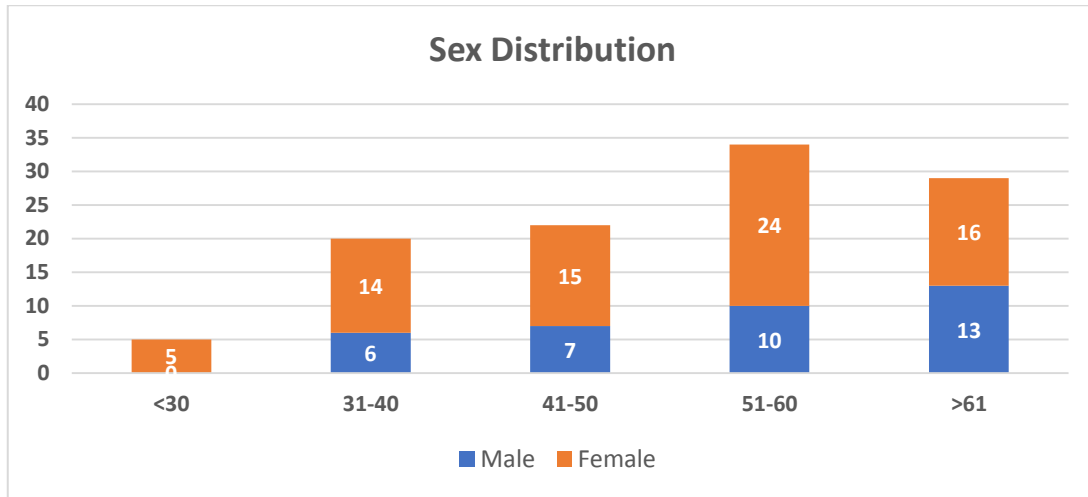
**Residence:** The cases were residents of Kanpur Nagar and surrounding districts namely Kanpur Dehat, Unnao, Fatehpur and Gonda. Maximum number of cases were from Kanpur Dehat (60%) followed by Kanpur Nagar (22%).

**Age Incidence:** In our study, 32% cases were in the sixth decade (51-60 years). The second largest group was from seventh (61-70 years) decade-27%. Mean age was 53 years.

**Male to Female Ratio:** Female to male ratio seen in this study is 2.0:1.

**Table-1** Age and Sex Distribution

Age Group (Yr)	Male	Percentage	Female	Percentage
<30	0	0	5	4.6%
31-40	6	5.6%	14	13%
41-50	7	6.5%	15	13.9%
51-60	10	9.3%	24	22.2%
>61	13	12.0%	16	14.8%
TOTAL	36	33.3%	72	66.7%

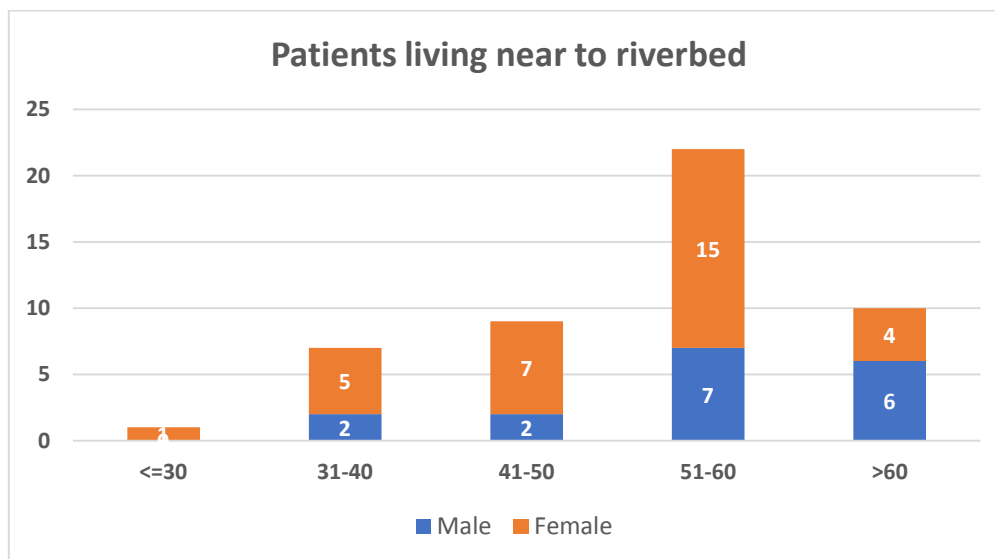


**Relationship to Residence near River Bed:**  
 Around forty-five percent patients resided near a

river bed of which 13.9% were females in the age group 51-60 years.

**Table-2** Age and Sex Distribution of Patients Living Near Riverbed

Age Group (years)	Male	Percentage	Female	Percentage
<=30	0	0	1	0.9%
31-40	2	1.8%	5	4.6%
41-50	2	1.8%	7	6.5%
51-60	7	6.5%	15	13.9%
>60	6	5.6%	4	3.7%
Total	17	15.7%	32	29.6%



**Relationship to Parity:** 64% females had parity 3 or more.

**Relationship to Menopausal Status:** Of total females, around 60% were postmenopausal, only 40% being premenopausal.

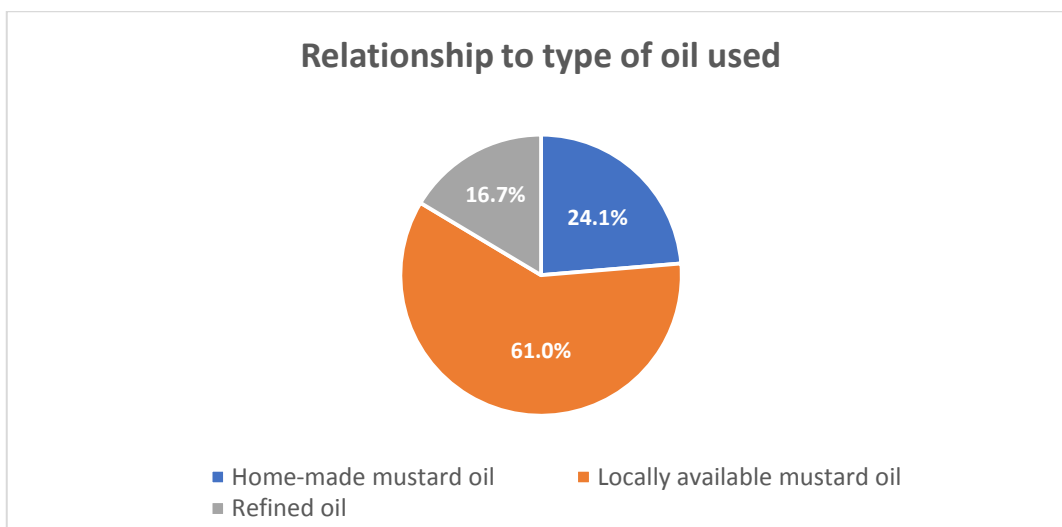
**Socio-Economic Status:** The maximum number of patients belonged to the upper lower and lower class, total comprising about 84%.

**Dietary Factors**

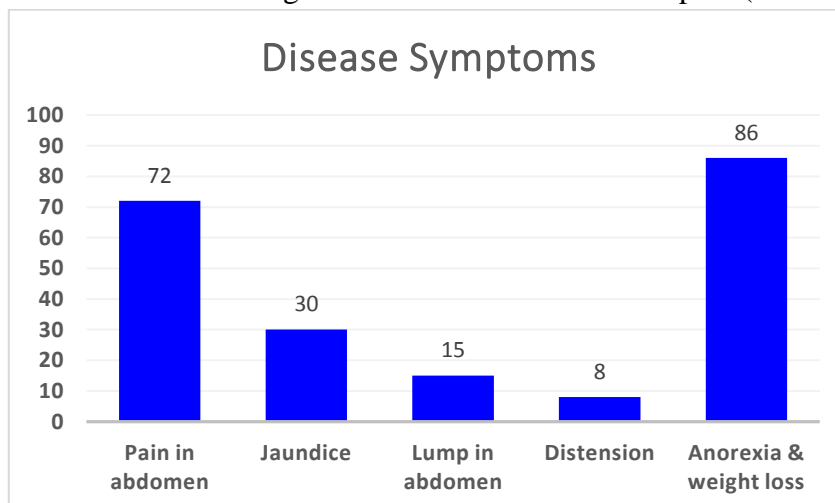
**Type of Diet:** Around fifty-six percentages of the carcinoma gall bladder patients were non-vegetarian by diet and forty-four percent were vegetarian.

**Type of Oil Used:** 61% patients consumed locally available mustard oil.

**Fat-Rich Diet:** Around 62% of our patients used non-fatty food. to take fat-rich diet and 38% patients consumed

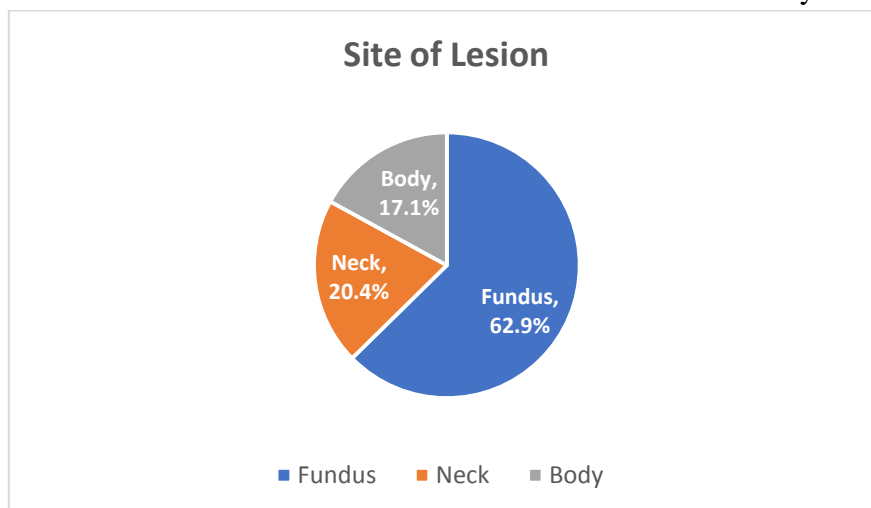


**Clinical Presentation:** The most common non-specific complaints were anorexia and weight loss and most common relatively specific complaint was abdominal pain (66.7%).



About 37% patients had pallor and 36% had icterus.

**Radiological Study- Site:** 63% patients had the site of carcinoma gall bladder as fundus, 20% as neck and in 17% as body.



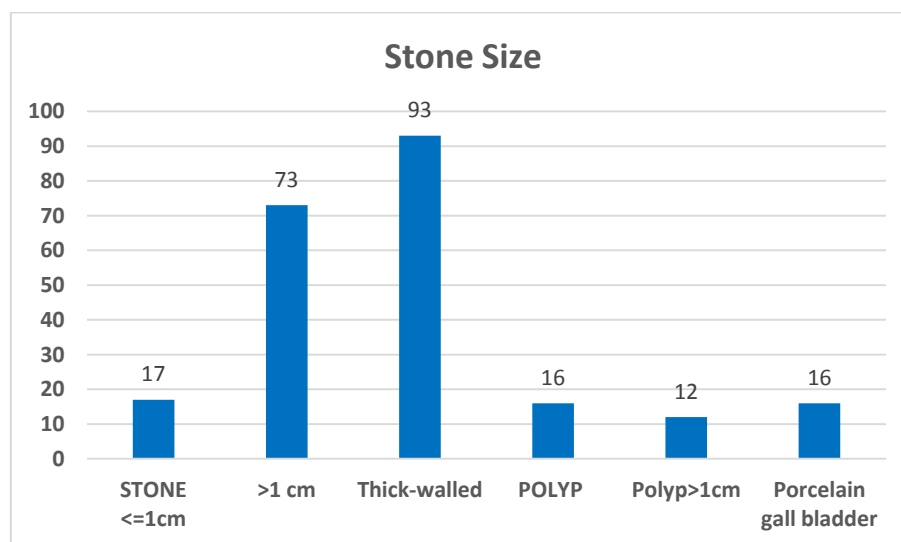
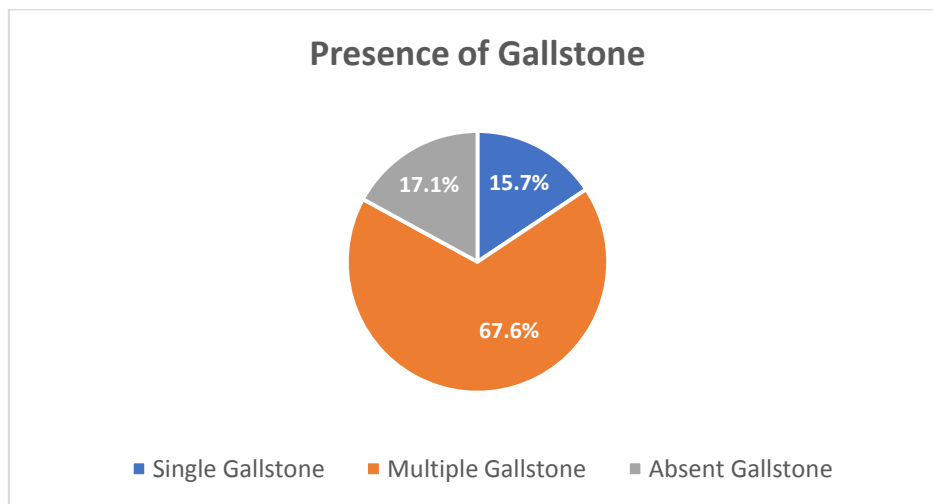
**Presence of Gall Stones:** Gall stones were found radiologically in around 83% of patients. In about 68%, the stone size was more than 1 cm.

Thick-walled gall bladder was a radiological finding in around 86% of cases. Gall bladder

polyp was a finding in around 14.8% cases and in 11%, it was >1 cm. Porcelain gall bladder was found in 14.8% of cases.

**Table-3** Presence of Gallstones and Stone Size

Type	Number of Cases	Percentage
SINGLE GALLSTONE	17	15.7%
MULTIPLE GALLSTONE	73	67.6%
ABSENT GALLSTONE	18	17.1%
STONE <=1cm	17	15.7%
>1 cm	73	67.6%
Thick-walled	93	86.1%
POLYP	16	14.8%
Polyp>1cm	12	11.1%
Porcelain gall bladder	16	14.8%



**Lymph Nodal Group Involved:** Around 68% patients had periportal group of lymph node involvement, 30.6% had peripancreatic and 10.2% had aortic group involved.

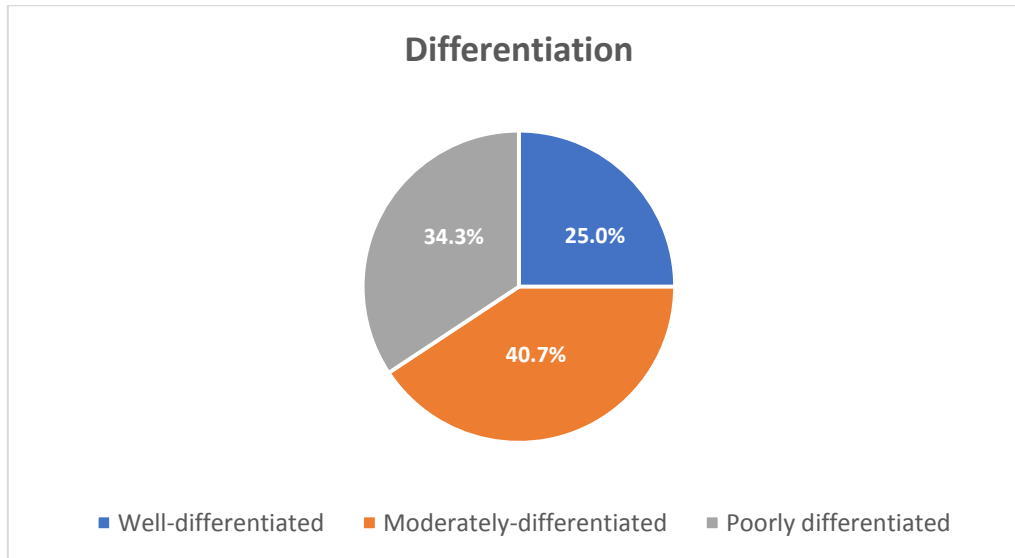
**Other Organ/Structure Involvement:** Around 45.4% of patients had liver involvement and 14.8% had omental involvement. Ascites was seen

in 13% and colon or duodenum involvement was seen in around 11.1% cases.

### Histopathology

In 98.1% of cases, adenocarcinoma was found in histology. In 1.9%, adenosquamous and undifferentiated tumours were seen.

Around 25% patients had a well-differentiated tumour, 40.7% had moderately-differentiated tumour and 34.3% had a poorly-differentiated tumour.



Out of the 45% patients living near the riverbed, the most common type was moderately-differentiated one in females and seen more between the age group of 51-60 years of age.

### Discussion

In the present study, we have investigated some of the etiological, clinical and pathological characteristics of patients with carcinoma gall bladder in Kanpur and surrounding districts who presented to the indoor or outdoor facility of LLR and associated hospitals from January 2017 to June 2018. Why these characteristics should be evaluated in relation to carcinoma gall bladder has its own considerations. Gall bladder cancer is a relatively infrequent neoplasm but shows marked geographic and socio-economic variations. It is a multi-factorial disease.

Our results show that carcinoma gall bladder is predominantly a disease of elderly females above the age of 50 years with a female to male ratio of 2:1. These results are consistent with other studies (Shukla et al.,1985, Pandey et al, 2001, Nandkumar et al.,2001) where the ratios were reported to be between 2:1 to 3:1.

The present study revealed the mean age of the patients to be 53 years, with a range of 27-80 years and sixth decade was the peak age of presentation which is comparable to results obtained from other studies from India (Shukla et al., 1985; Pandey et al., 2001; Kapoor et al.,2003) which show median age around 56 years. In contrast to this, in western countries the mean age of presentation is higher (67 years according to Beltz et al.,1974) and the peak age of incidence is in the seventh decade of life (Perpetuo et al.,1978).

The disease was found to be more common in elderly post-menopausal females and those with parity three or more as compared to pre-menopausal females or, females with parity less than three. Andreotti et al., also showed that high parity led to an increased risk of carcinoma gall bladder in Chinese patients with biliary tract cancer. These observations from various studies suggest a possible role of female hormonal factors in the pathogenesis of gall bladder carcinoma. Another possibility is that there is stasis of bile during pregnancy, which may be toxic to the gall bladder mucosa.

The females residing near riverbed in North India had a higher incidence of disease as compared to males residing in the same area. The water of rivers becomes highly polluted with not only agricultural effluents but also domestic sewage and industrial wastes which are being disposed of routinely in the rivers resulting in increased concentration of pollutants like pesticides, heavy metals like chromium, lead and cadmium and industrial wastes like aromatic hydrocarbons, nitrosamines, nitrates and nitrites. Also females are more home-bound than males who are mobile and have less exposure.

In our study, 69.4% of patients belonged to rural areas which included Kanpur Dehat, Unnao, Gonda, and Fatehpur districts. Around 84% of our patients belong to lower and upper-lower socio-economic class according to the modified Kuppaswami SES classification. The reason behind it might be the lack of knowledge in person with lower socio-economic status, use of locally available adulterated mustard oil, more exposure to infections and hormonal imbalance due to high parity.

The role of dietary factors in carcinoma gall bladder is now well defined. Our results showed that the disease was more common in patients who consumed non-vegetarian diet (56%), food rich in fats (62%), and in those who used locally available mustard oil (61%). This fact was supported by the study of Pandey et al, 2002 who had shown the protective effect of vegetables on gall bladder carcinogenesis while meat consumption was associated with an increased risk. The study of Misra et al, 2003 also showed that the consumption of carcinogenic impurities in mustard oil led to carcinoma gall bladder. Edible mustard oil is often adulterated with argemone oil. Sanguinarine and diethylnitrosamine are present in argemone and are known to be carcinogenic and responsible for DNA damage (Dixit et al, 2013, Ghosh et al, 2015).

Our study showed that around 76% of patients had duration of symptoms between 1-3 months and only about 14% had symptom duration more than

3 months. This shows the grave nature of carcinoma gall bladder unlike other carcinomas which have a longer duration of history due to their relatively slow growth.

The most common non-specific symptom associated was found to be anorexia and weight loss (79.6%) and most common specific symptom was pain in abdomen which was seen in around 67% of patients followed by jaundice, seen in around 28% and then lump in abdomen in 14% of patients. This is consistent with previous studies (Khan et al.,2010, Hamdani et al.,2012).

Among clinical examination, most common signs found were pallor (37%), icterus (36%) and abdominal lump was present in around 14% of patients, while ascites was clinically seen in 8% of patients.

Among radiological factors, most common site of tumour was the fundus of gall bladder (63%) then, neck (20%) and the least common was the body (17%) which has been proved in earlier studies also. The size of lesion was three centimetres or more in around 48% of cases.

Gall stones have the strongest association with carcinoma gall bladder and are present in about 65-90% of cases (Misra et al., 1995, Pandey et al.,2001, Hamdani et al.,2012). Stones >3cm confer an increased risk. Chronic trauma because of the gall stones and inflammation can induce dysplasia followed by carcinoma in situ later leading to invasive cancer. In our study, about 83% patients had radiologically evident gall stones associated with carcinoma gall bladder. In about 68% of cases, the stone size was >1cm.

Thick-walled gall bladder was a radiological finding in around 86% of cases which is a radiological pointer of gall bladder malignancy. Gall bladder polyp which is also considered a premalignant lesion was seen in 6.5% of cases and in 5.6%, it was >1cm. Porcelain gall bladder was found in 14.8% of cases. According to some studies (Stephen et al.,2001), it is associated with 12-62% of cases of carcinoma gall bladder while recent studies show little or no association (Towfigh et al.,2001, Schnelldorfer et al.,2013).



Among lymph nodal groups, periportal involvement was seen in 63% cases, peripancreatic in 31% and aortic group in 10% cases. Liver was involved in 45% cases, omentum in 15% cases and ascites was seen in 13% of cases.

The most common histological type found was adenocarcinoma which was present in 98.1% of cases and only 1.9% had either adenosquamous or undifferentiated tumours (Beltz et al., 1974, Hamdani et al., 2012). Only 25% of all cases had well-differentiated tumours and the rest had moderately (41%) or poorly differentiated tumours (34%). Out of the total 49 patients living near the riverbed, the most common gallbladder tumour was moderately-differentiated lesion in women in females and more between the age group of 51-60 years of age.

The information about other etiological factors like family history of gallstone, life style information, and fertility were either insufficient or incomplete for statistical analysis. Thus, here we are only presenting the percentage value of our selected parameters, but the given data might be helpful in raising a new hypothesis and in understanding of new parameters related with the development of gall bladder cancer.

### Conclusion

Gallbladder cancer is an uncommon cancer worldwide but common in North India with female predilection and advanced stage at presentation. Risk factors for this may include advanced age, female gender, low socio-economic status resulting in high parity, consumption of adulterated mustard oil, lack of knowledge regarding health and risk factors, chronic exposure to infections, lack of early treatment of cholelithiasis and the proximity to river bed which again has a high concentration of carcinogenic pollutants being daily added to it by domestic and industrial wastes. Most gallbladder cancers presented as advanced stage disease and fundus was the most common site. Adenocarcinoma accounted for the majority of gallbladder cancers.

The status of gallbladder cancer over the last century has not shown any definitive improvement in overall survival and continues to be plagued by the presence of advanced disease at diagnosis. This is directly related to the continued lack of sensitive screening modalities for the detection of early disease. The future, therefore, for improved success in the management of this disease may have to be directed towards the development of sensitive and specific screening strategies with relevant improved understanding of the pathogenesis and risk factors of this disease.

### Declarations

**Funding:** None

**Conflicts of interest:** None declared.

**Ethical approval:** The work has been approved by the Institutional Ethics Committee, GSVM Medical College, Kanpur, UP, India.

### Acknowledgements

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### References

1. S. Misra, A. Chaturvedi, N. C. Misra, and I. D. Sharma, "Carcinoma of the gallbladder," *The Lancet Oncology*, vol. 4, no.3, pp. 167–176, 2003.
2. Pandey M, Shukla VK. (2003) Lifestyle, parity, menstrual and reproductive factors and risk of gallbladder cancer. *Eur J Cancer Prev* 12:269–272.
3. Nandakumar A, Gupta PC, Gangadharan P, Visweswara RN, Parkin DM. (2005) Geographic pathology revisited: development of an atlas of cancer in India. *Int J Cancer* 116:740–754.
4. S. Unisa, P. Jagannath, V. Dhir, C. Khandelwal, L. Sarangi & T. K. Roy (2011) Population-based study to estimate prevalence and determine risk factors of gallbladder diseases in the rural Gangetic



- basin of North India. JHPB 2011; 13: 117–125
5. S. Basu, M. K. Singh, T. B. Singh, S. K. Bhartiya, S. P. Singh, and V. K. Shukla, “Heavy and trace metals in carcinoma of the gallbladder,” *World Journal of Surgery* 2013;37 (11): 2641–2646.
  6. R. Yadav, D. Jain, S. R. Mathur, A. Sharma, and V. K. Iyer, “Gallbladder carcinoma: an attempt of WHO histological classification on fine needle aspiration material,” *Cyto Journal*, vol.10, article 12,2013.
  7. Gall Bladder Cancer and some epidemiological factors: A cross sectional study. Shipra Dwivedi<sup>1</sup>, Amit Madeshiya<sup>1</sup>, Devendra Singh<sup>2</sup>, Shraddha Singh<sup>1</sup>, Akhilesh Krishna<sup>1</sup>. *Journal of Biomedical Research* 2013; 24 (1):83-87.
  8. R. Kanthan, J.L. Senger, S. Ahmed, S. C. Kanthan (2015) “Gallbladder Cancer in the 21st Century”. *Journal of Oncology*, Volume 2015, Article 967472, 26 pages.
  9. Lal M, Raheja S, Bhowmik KT (2018) “Carcinoma Gallbladder-Epidemiological Trends in a Tertiary Hospital in North India”. *Arch Surg Oncol* 4: 131. doi: 10.4172/2471-2671.1000131.