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Carcinoma of gall bladder in Central India – Is there a shifting trend?

Shyamji Rawat¹, V.S. Haritha^{1,*}¹Dept of Radiation Oncology, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India

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ABSTRACT

Aim: To evaluate the demographic and clinicopathological profile of patients with gall bladder cancer.**Materials and Methods:** A total of 464 patients of gall bladder cancer were taken in the study from January 2017 till December 2021. Both demographic and clinicopathological data was obtained retrospectively from the medical record database.**Results:** We found that there is a shift in age group over the period of 5 years with most of the patients previously being in the age group 61–70 years with a recent shift in the last two years to the age group 51–60 years. Majority of the patients were females coming from a rural background. Most of them had a non-vegetarian diet. Addiction in the form of tobacco chewing and smoking was present in 44.8% and 18.7% respectively and alcohol intake was seen in 12.2%. The most common site of disease was found to be involving the body 69.3%. Less commonly the disease was reported at the neck. Almost all patients had adenocarcinoma as the histology with moderate grade of differentiation. 96.7% of patients presented to us in the advanced stage. Stage IVB presentation was seen in 54.3% of patients. Majority of the patients had a direct and lymphatic mode of dissemination. Presence of gall stone was seen in 36.2% of patients. Pain was the most common presenting symptom followed by jaundice and obstruction.**Conclusion:** In our country, incidental GBC is fairly underreported due to no active screening program to detect patients with symptomatic gallstones undergoing routine cholecystectomy. These patients can be easily detected if there is a higher index of suspicion prior to, during as well as after surgery.This is an Open Access (OA) journal, and articles are distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License](https://creativecommons.org/licenses/by-nc-sa/4.0/), which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.For reprints contact: reprint@ipinnovative.com

1. Introduction

Gallbladder cancer (GBC) is a poorly diagnosed and an uncommon malignancy of GI Tract with high mortality rate and without any absolute known cause. The incidence of GBC is found varying, not only in different geographical regions of the world, but also in different locations (e.g., ethnic populations) within a country.¹ It is the 6th most common malignancy of GI Tract, with an incidence of 0.8%– 1.2%, and 80%– 95% malignancy of the biliary tract.² GBC ranked 14th amongst all cancers according to the GLOBOCON 2018 report in India with the number

of new cases being 25,999 and mortality of 19, 676. The incidence of GBC is found considerably high, particularly in North, Central, Eastern and North-Eastern parts of India, lowest being in Southern and Western states. The actual reason for this North-South difference is still not clear.³ The incidence in North India is 10–22/100,000 population and is similar to that of other countries with high incidence such as in South America (Chile, Bolivia, Columbia). East Asia (Korea, Japan, China) and central Europe (Slovakia, Poland, Czech Republic) are regions with moderate incidence.² The adjoining countries in the Indian sub-continent like Pakistan, Nepal, Bangladesh and Bhutan also have reported high incidence of GBC.⁴ However, Sri Lanka, Maldives, Yemen, Afghanistan, Tajikistan, Turkmenistan, Uzbekistan

* Corresponding author.

E-mail address: vsharitha26@gmail.com (V. S. Haritha).

have low incidence of GBC. Certain ethnic groups like Hispanics, American Indians, Mexican Indians, Alaskan natives as well as Asian Indians are at more than normal risk for development of GBC.⁵ The incidence has been steadily rising in India among women as well as men with the average age adjusted rate among women has increased from 6.2/100,000 in 2001–2004 to 10.4/100,000 in 2012–2014.⁶

The major risk factors associated with the occurrence of GBC and GBD were suggested to be a host of environmental pollutants, life style and dietary habits, but a direct cause is yet to be distinctly identified.⁷ Increasing trend in the prevalence and mortality rates of GBC and other cancers of liver and GI tract in India during 1990 to 2016 has also been reported.⁸ As the incidence of this disease is increasing, a systematic trend analysis may help to understand the alterations in incidence with regard to time, place and person distribution, and changing cancer risk.⁹ This study is an attempt to know regarding the demographic profile and incidence of gall bladder cancer among patients attending a tertiary care hospital in Central India.

2. Materials and Methods

We studied the demographic characteristics, risk factors and clinical profile of 93 gall bladder cancer patients who attended our hospital from a period of January 2021 till December 2021. The demographic characteristics noted were age; sex and place of residence were noted. Addiction history and dietic habit was noted. Presence of gall stones was taken as a clinical risk factor. The clinical profile included presenting symptoms, presence of jaundice, stage and extent of disease, number and site of metastasis and pathological features.

The data was collected from the medical record section of the hospital in which the demographic characteristics, non-clinical characteristics and dietary habit is mentioned. Documentation of the clinical features in it is done by history, physical examination and imaging studies. The presence of gall stones and the pattern of spread were confirmed by an ultrasound, computed tomography [CT] of abdomen and by PET-CT in few cases.

The inclusion criteria were that of a patient who is histopathologically proven to a case of gall bladder cancer and who is a resident in Central India. The exclusion criteria were that of a cancer diagnosed to be at any other site and who belongs to any region outside Central India.

3. Results

The demographic profile of the patients are presented in table 1. Majority of the patients were of the age group 51-60 years with majority of the patients presenting being more than 40 years (84.9%). Majority of the study patients were females with most of them coming from a rural background. Most of the patients had a non – vegetarian diet. Tobacco

addiction was present in one or the other form in majority of the patients, tobacco chewing being the most common form.

illustrates the clinicopathological profile of patients presenting with gall bladder cancer.

Majority of the patients presented with a locally advanced stage of disease. Pain was the most common symptom present in all patients studied. Jaundice was present in more than half of the patients. 3 patients presented with obstructive features. Gall stones were present in majority. Most common histopathology was that of adenocarcinoma with majority having a moderate grade of differentiation. Among the subsite distribution, majority of patients having a disease involving the body of gall bladder. Majority had a direct and lymphatic pattern of spread. Among the distant site of involvement, liver was the most common site with majority having multiple liver metastasis.

4. Discussion

In this study we evaluated the demographic and clinicopathological profile of 93 patients of gall bladder cancer. Gallbladder carcinoma is relatively infrequent disease, with marked geographic, ethnic, and socioeconomic variation.¹⁰ All our patients included in the study belonged to north central India covering the Mahakoushal region, Vindhya region, Bundelkhand region, Baghelkhand region and Malajkhand region to which our centre caters treatment. In India, the incidence of GBC is 10 times higher in north India compared to the southern Indian states [8.9/100,000 population (Delhi) vs. 0.8/100,000 population (Chennai)]. Amongst patients living in north, eastern and central India the risk for developing GBC is higher than that among patients living in southern India (OR 4.82; 95% CI: 3.87–5.99).¹¹ a major part of north – central India is supplied by the Narmada river with its 41 tributaries. During its flow from west to east it becomes a major source of irrigation thus supporting the agriculturally driven economy of the region. As it flows towards the east the concentration of pollutants as well as bacterial contamination have been found to steadily rise which may account partially for the incidence of gall bladder cancer in this region. Untreated sewage, industrial waste and agricultural effluents unfortunately get added to the water along its course. The fecal coliform count steadily rises as the river flows towards the east. Salmonella typhi (*S. typhi*) and Helicobacter pylori (*H. pylori*) are feco-orally transmitted organisms which have been known to be associated with pathogenesis of GBC and are likely to be increased as the river flows downstream¹¹

The incidence of gall bladder cancer increases with age. In our study the majority of the patients belonged to the age group from 61- 70 years during the years 2017 -19 with a shift in the age group to 51-60 years from 2020 onwards. In the previous studies, the mean age of GBC at diagnosis is

Table 1: Demographic profile of patients

Characteristics	2021	2020	2019	2018	2017
Age group [in years]					
21- 30	2	1	1	2	2
31- 40	9	7	9	10	10
41-50	25	17	14	18	17
51- 60	35	24	25	37	29
61- 70	15	10	36	42	41
71- 80	3	2	4	3	3
81- 90	1	0	0	1	1
Gender					
Male	43	28	41	52	50
Female	50	32	47	60	58
Residence					
Urban	25	16	23	30	29
Rural	68	44	65	82	78
Dietic habits					
Vegetarian	5	3	4	6	6
Non – vegetarian	88	57	84	106	102
Addiction					
Tobacco chewing	42	27	40	51	48
Bidi smoking	18	11	17	21	20
Cigarette smoking	0	0	0	0	0
Alcohol	12	7	11	14	13

64–69.4 years.¹² The median age of presentation was 67 years in a Memorial Sloan–Kettering report of 435 GBC patients.¹³ The mean age of presentation of GBC in India is younger than their counterparts in the USA and western European countries. The average age at diagnosis in India was 51±11 years in contrast to 71.2±12.5 years in the West. The mean/ median age is usually 50–55 years.¹⁴

Women are at 2–6 times higher risk for developing GBC.¹⁵ The observed risk is higher among women compared to men (OR 6.04; 95% CI: 4.52–8.07 versus OR 3.17; 95% CI: 2.23–4.50). Among patients with gallstones, women are at 2.4 times higher risk for GBC.¹⁶ The female:male ratio varies from 3:1 to 4.5:1 in various Indian series.¹⁷ Women are exposed to higher levels of estrogen and progesterone during their lifetime more so during pregnancies. Indian women are younger in age at the time of marriage, younger in age at time of 1st pregnancy and have a higher number of pregnancies than their western counterparts in developed countries. The GB mucosa has been found to have estrogen and progesterone receptors which may promote GB stasis, stone formation, and this in turn increases exposure time of the GB mucosa to bacterial and chemical toxins.¹¹ In a recent compilation of data from Asia comprising of 116,048 patients the female:male ratio is 1.2:1 at presentation.¹⁷ Women in India, also are less educated, have less access to economic resources, lesser access to nutrition and poorer access to medical care. Women in India also tend to be undernourished and thus are likely to have suboptimal immune status and micronutrient deficiencies both of which promotes carcinogenesis.¹¹ In

the present study majority of the study population were females thus supporting the literature evidence.

Majority of our patients in the study were from a rural background. Residence in rural areas is associated with increased risk for GBC. It has been assessed in various case control studies from different regions of the country.¹¹ Study by Kumar et al. found that 80% of patients with GBC resided in rural areas compared to 54% patients with gallstones (OR 3.52; 95% CI: 2.48–4.99).¹⁸

In another study in Delhi, residence in rural area was 59% versus 32% among patients with gallstones.¹⁹ Rural residence is associated with lower literacy rates, poorer socio-economic status and poorer access to medical care in India. Low socio-economic status is associated with lower literacy rate, overcrowding, poor access to health care, poorer sanitation and poorer access to clean drinking water than those belonging to upper socioeconomic status.¹¹ It is, hence, associated to higher exposure to feco oral infections like *S. typhi* and *H. pylori*.¹⁸ Though a large proportion of Indians live in rural areas, these studies which compares patients with GBC and GSD, reflects the additional risk conferred by rural residence to our patients with GBC.¹¹

Majority of the patients in our study had a non – vegan diet. The previous results showed that non vegetarians (such as red meat and consumption of carcinogenic impurities in mustard oil) were more prone to GBC rather than vegetarians.¹⁰ In North, North east and eastern India, mustard oil is the staple cooking oil in contrast to coconut oil, sesame or groundnut oil in south and west India. Mustard oil has irritant property on the gut and is often

Table 2: Clinico- pathological profile of patients

Characteristic	2021	2020	2019	2018	2017
Subsite based					
Body	65	42	62	78	75
Neck	5	3	4	6	5
Fundus	6	4	5	7	7
Body + Fundus	8	5	8	1	9
Body + neck	7	4	6	8	8
Body + Neck + Fundus	2	1	2	2	2
Histopathology					
Adenocarcinoma	92	61	89	113	108
Squamous cell carcinoma	0	0	0	0	0
Adenosquamous	1	0	0	0	0
Grade					
Well differentiated	0	0	0	0	0
Moderately differentiated	86	56	83	104	100
Poorly differentiated	7	4	6	8	8
Stage					
I	0	0	0	0	0
IIA	2	1	1	2	2
IIB	0	0	0	0	0
IIIA	7	4	6	9	8
IIIB	33	21	31	40	38
IVA	0	0	0	0	0
IVB	51	33	48	61	59
Pattern of spread					
Direct	85	55	81	103	98
Lymphatic	85	50	75	100	95
Distant					
• Liver – single	8	5	7	9	9
• Liver – multiple	38	24	36	46	94
• Others	13	8	12	15	15
Gall stones					
Present – single	3	2	3	4	3
Multiple	31	20	29	37	36
Absent	59	38	56	71	68
Clinical presentation					
Pain	93	61	89	113	108
Jaundice – absent	52	34	50	63	60
Present	41	26	39	50	47
Obstruction	3	2	3	4	3
Asymptomatic	0	0	0	0	0

adulterated with butter yellow which is known carcinogen. Higher levels of sanguinarine and diethyl nitrosamine, carcinogenic adulterants in mustard oil, have been found in blood and tissue of GBC patients as compared to patients with cholelithiasis. Diethyl nitrosamine has been reported to induce hepatic carcinogenesis. Mustard oil has proinflammatory properties and induces tumors.²⁰ Individuals belonging to the poorer socioeconomic strata are unable to afford branded safe oils and thus consume loose mustard oils which may be contaminated/adulterated.¹¹

Smoking has been seen to be associated with increased risk of GBC in various studies globally as well as in India.¹¹ Smoking was an independent risk factor for GBC and the

summary RR was 11 (95% CI: 1.7–71) for those who smoked more than 10 cigarettes per day for minimum 5 years compared to non-smokers.¹⁹ In another study from east India, chewing tobacco was associated with increased risk for GBC.¹⁶ In our study majority of our patients [63.5%] were tobacco consumers in one or the other form. Alcohol intake was present in 12.2% of our study population.

The process of carcinogenesis in GBC follows a consequence of metaplasia followed by dysplasia, carcinoma in situ, and invasive cancer.²¹ Gallstones cause local mucosal irritation and chronic inflammation resulting local production of carcinogens, such as secondary

bile acids and eventually may result in carcinogenesis after a long duration.² Incidence of symptomatic gallstones is 20 times higher in north India compared to South India. The nature of stone in north India is of predominantly cholesterol/mixed compared to South India which has pigment stones.²² Various studies in India have documented presence of gall stone in 70–90% of patients with GBC.^{23–25}

In our study 36.2% of the study patients had gallstones present along with GBC.

In the present study majority of the GB disease was seen involving the body with moderately differentiated adenocarcinoma as the histopathology. The prognosis of patients with GBC is dismally poor, as majority of them presents with advanced disease. The presentation at an advanced stage can be attributed to multiple factors including lack of knowledge and education in patients predominantly belonging to lower class, inability to differentiate symptoms of early GBC from those of gallstone disease and poor response to available chemotherapy options.²⁶ In the present study 1.7% had early stage disease whereas 96.7% presented with advanced stage disease. Previous Indian study by Batra et al. has reported slightly lower incidence of early-stage disease (approximately 5%) which is slightly similar to the present study, and the rest 95% patients either locally advanced or metastatic.²³

GBC metastasizes more commonly to liver, lymph nodes, and peritoneum.²⁷ In the present study liver metastasis was seen in 59.4% and lymph node metastasis was seen in 90.9%. Skeletal metastases in carcinoma gallbladder are very rare, with only few case reports of bone metastasis in carcinoma gall bladder at the time of presentation.²⁸

5. Conclusion

Despite a high incidence of GBC in our country, incidental GBC is fairly underreported due to no active screening program to detect incidental GBC among patients with symptomatic gallstones undergoing routine cholecystectomy. These patients can be easily detected if there is a higher index of suspicion prior to, during as well as after surgery.²⁹ Large multicentric studies are needed to identify various risk factors attributing to the disease and for formulating cost effective national strategies for reducing the morbidity and mortality due to gall bladder cancer in the country.

6. Source of Funding

None.

7. Conflict of Interest

None.

References

1. Barbhuiya MA, Singh TD, Poojary SS, Gupta S, Kakkar M, Shrivastava BR, et al. Gallbladder cancer incidence in Gwalior district of India: five year trend based on the registry of a regional cancer center. *Indian J Cancer*. 2015;52(3):430–7. doi:10.4103/0019-509X.176736.
2. Hundal R, Shaffer EA. Gallbladder cancer: epidemiology and outcome. *Clin Epidemiol*. 2014;6:99–109. doi:10.2147/CLEP.S37357.
3. Dutta U, Bush N, Kalsi D, Popli P, Kapoor VK. Epidemiology of gallbladder cancer in India. *Chin Clin Oncol*. 2019;8(4):33. doi:10.21037/cco.2019.08.03.
4. Hasan MM, Laila SZ, Mamun MMH. Incidence of Gallbladder Carcinoma in Thick Walled Gallbladder in Comparison with that of Normal Thickness - A Study of 300 Cases. *J Bangladesh Coll Physicians Surg*. 2017;34(4):193–8. doi:10.3329/jbcps.v34i4.32486.
5. Mahdavi N, Mohammadian-Hafshejani A, Ghafari M, Salehiniya H. Incidence and mortality of gallbladder cancer and its relationship with human development index(HDI) in Asia in 2012. *WCRJ*. 2017;4(4):e974. doi:10.32113/wcrj.201712_974.
6. Phadke P, Mhatre S, Budukh A. Trends in gallbladder cancer incidence in the high- and low-risk regions of India. *Indian J Med Paediatr Oncol*. 2019;40:90–3. doi:10.4103/ijmpo.ijmpo_164_18.
7. Malhotra RK, Manoharan N, Shukla NK, Rath G. Gallbladder cancer incidence in Delhi urban: A 25-year trend analysis. *Indian J Cancer*. 2017;54(4):673–7. doi:10.4103/ijc.IJC_393_17.
8. Shah D, Makharia GK, Ghoshal UC, Varma S, Ahuja V, Hutfless S, et al. Hutfless: Burden of gastrointestinal and liver diseases in India. *Indian J Gastroenterol*. 1990;37(5):439–45. doi:10.1007/s12664-018-0892-3.
9. Murthy NS, Rajaram D, Gautham M, Shivraj N, Pruthvish S, George PS, et al. Trends in incidence of gallbladder cancer - Indian scenario. *Gastrointestinal Cancer: Targets Ther*. 2011;1:1–9. doi:10.2147/GICTT.S16578.
10. Dubey AP, Rawat K, Pathi N, Viswanath S, Rathore A, Kapoor R, et al. Carcinoma of gall bladder: Demographic and clinicopathological profile in Indian patients. *Oncol J India*. 2018;2(1):3–6. doi:10.4103/oji.oji_1_18.
11. Dutta U, Bush N, Kalsi D, Popli P, Kapoor VK. Epidemiology of gallbladder cancer in India. *Chin Clin Oncol*. 2019;8(4):33. doi:10.21037/cco.2019.08.03.
12. Cavallaro A, Piccolo G, Vita M, Zanghi A, Cardì F, Mattia PD, et al. Managing the incidentally detected gallbladder cancer: algorithms and controversies. *Int J Surg*. 2014;12(2):108–19. doi:10.1016/j.ijssu.2014.08.367.
13. Duffy A, Capanu M, Abou-Alfa GK, Huitzil D, Jarnagin W, Fong Y, et al. Gallbladder cancer (GBC): 10-year experience at memorial Sloan-Kettering Cancer Centre (MSKCC). *J Surg Oncol*. 2008;98(7):485–9. doi:10.1002/jso.21141.
14. Alvi AR, Siddiqui NA, Zafar H. Risk factors of gallbladder cancer in Karachi—a case-control study. *World J Surg Oncol*. 2011;9:164. doi:10.1186/1477-7819-9-164.
15. Konstantinidis IT, Deshpande V, Genevay M, Berger D, Castillo CF, Tanabe KK, et al. Trends in Presentation and Survival for Gallbladder Cancer During a Period of More Than 4 Decades: A Single-Institution Experience. *Arch Surg*. 2009;144(5):441–7. doi:10.1001/archsurg.2009.46.
16. Jain K, Sreenivas V, Velpandian T. Risk factors for gallbladder cancer: A case-control study. *Int J Cancer*. 2013;132(7):1660–6. doi:10.1002/ijc.27777.
17. Bhagabaty S, Sharma J, Krishnatreya M. A Profiles of gall bladder cancer reported in the hospital cancer registry of a Regional Cancer Center in the North-East India. *Int J Res Med Sci*. 2014;2(4):1683. doi:10.5455/2320-6012.ijrms20141183.
18. Kumar S. Infection as a risk factor for gallbladder cancer. *J Surg Oncol*. 2006;93(8):633–9. doi:10.1002/jso.20530.
19. Dutta U, Garg PK, Kumar R. Typhoid carriers among patients with gallstones are at increased risk for carcinoma of the gallbladder. *Am J Gastroenterol*. 2000;95(3):784–7. doi:10.1111/j.1572-0241.2000.01860.x.

20. Shukla Y, Arora A. Enhancing effects of mustard oil on preneoplastic hepatic foci development in Wistar rats. *Hum Exp Toxicol*. 2003;22(2):51–5. doi:10.1191/0960327103ht338oa.
21. Lau CS, Zywt A, Mahendraraj K, Chamberlain RS. Gallbladder carcinoma in the United States: A Population based clinical outcomes study involving 22,343 patients from the surveillance, epidemiology, and end result database (1973-2013). *HPB Surg*. 2017;p. 1532835. doi:10.1155/2017/1532835.
22. Jayanthi V, Sarika S, Varghese J, Sharma M, Reddy MS, Srinivasan V, et al. Composition of gallbladder bile in healthy individuals and patients with gallstone disease from north and South India. *Indian J Gastroenterol*. 2016;35(5):347–53. doi:10.1007/s12664-016-0685-5.
23. Batra Y, Pal S, Dutta U. Gallbladder cancer in India: A dismal picture. *J Gastroenterol Hepatol*. 2005;20(2):309–14. doi:10.1111/j.1440-1746.2005.03576.x.
24. Shukla VK, Khandelwal C, Roy SK. Primary carcinoma of the gall bladder: A review of a 16-year period at the university hospital. *J Surg Oncol*. 1985;28(1):32–5. doi:10.1002/jso.2930280109.
25. Dutta U, Nagi B, Garg PK, Sinha SK, Singh K, Tandon RK, et al. Patients with gallstones develop gallbladder cancer at an earlier age. *Eur J Cancer Prev*. 2005;14(4):381–5. doi:10.1097/00008469-200508000-00011.
26. Kapoor VK, Pradeep R, Haribhakti SP, Sikora SS, Kaushik SP. Early carcinoma of the gallbladder: An elusive disease. *J Surg Oncol*. 1996;62(4):284–7. doi:10.1002/(SICI)1096-9098(199608)62:4<284::AID-JSO12>3.0.CO;2-5.
27. Dwivedi AN, Jain S, Dixit R. Gall bladder carcinoma: Aggressive malignancy with protean loco-regional and distant spread. *World J Clin Cases*. 2015;3(3):231–44. doi:10.12998/wjcc.v3.i3.231.
28. Gupta N, Goswami B, Mahajan N, Dey S. Vertebral metastasis in gallbladder carcinoma - An unusual site. *Int J Case Rep Med*. 2012;.
29. Jha V, Sharma P, Mandal KA. Incidental gallbladder carcinoma: Utility of histopathological evaluation of routine cholecystectomy specimens. *South Asian J Cancer*. 2018;7(1):21–3. doi:10.4103/2278-330X.226802.

Author biography

Shyamji Rawat, Professor

V.S. Haritha, Senior Resident

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