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ORIGINAL RESEARCH

Epidemiological Study of Gallbladder Cancer Patients from North Indian Gangetic Planes—a High-Volume Centre's Experience

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Abstract
Purpose Gallbladder carcinoma (GBC) is characterized by a dismal prognosis owing to the paucity of early signs and symptoms. North India reports high incidence of GBC possibly due to environmental, dietary and reproductive factors. Understanding the epidemiology of gallbladder cancer has and will continue to provide valuable insights into determining causes and risk factors for gallbladder cancer.
Methods Prospective study of gallbladder carcinoma patients, presenting in our department, was undertaken over three year period to evaluate the epidemiological profile of gallbladder carcinoma patients from our region.
Results The peak incidence of GBC was in 31–50 years age group (58 %). Male to female ratio was 1:4.83, with mean age for females (mean 49.1 years) significantly lower than male counterpart (mean 54.9 years) (p value=0.000423). Majority of patients were non-vegetarians (67 %) and 84 % of them consumed mustard oil (home made/loose packed) as predominant cooking medium. Majority of the patients of GBC in our study were from low socioeconomic strata (68 %) (Kuppuswamy classes IV, V (lower class)). GBC was more commonly seen in females with the age of menarche less than 14 years (83 %) and the age of the first child birth less than 20 years (56 %). Females with more than two children had higher incidence (57 %). Majority of the female patients (71 %) were postmenopausal. Gallstones were present in 390 out of 490 patients (80 %). Incidental gallbladder carcinoma was detected in 158 out of 490 patients (32 %). Pain abdomen was the most common presenting complaint (98 %). Significant proportion of the patients with GBC presented with distant metastasis (stage IVB) (52 %). The most common histological subtype was adenocarcinoma (78 %).
Conclusion Current data suggest that the epidemiology of gallbladder cancer is constantly evolving, with much of this change caused by lifestyle, cultural and dietary factors. Balanced diet, prevention of malnutrition/adulteration, tobacco prevention and early intervention for cholelithiasis may help in decreasing the incidence of this dreaded disease. More structured studies need to be carried out to ascertain risk factors for GBC in our population subgroup.

Keywords Gallbladder carcinoma · Cholelithiasis · Epidemiology · Female · Food adulteration

Abbreviations

GBC	Gallbladder carcinoma
FNAC	Fine needle aspiration cytology
CT scan	Computed tomography
IGBC	Incidental gallbladder carcinoma

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Introduction

Gallbladder cancer (*GBC*) is the most common cancer of the hepato-biliary system. It is one of the most commonly occurring malignant gastrointestinal tumours with universally poor prognosis. North Indian Gangetic planes report one of the highest incidence of GBC in the world. The incidence of gallbladder cancer also shows wide geographic and ethnic variations. Its incidence is markedly higher in northern than in southern India (4.5 per 100,000 for males and 10.1 per 100, 000 for females in North India compared to 1.2 per 100,000 for males and 0.9 per 100,000 for females in South India as reported by the population-based cancer registry, Delhi). Marked regional variation in the incidence of GBC in India can be attributable to distinct environmental, dietary and reproductive factors prevalent locally. In addition to regional variations, the incidence of GBC also illustrates prominent age and gender-related differences and is four to seven times higher in patients with gallstones.

Epidemiological data evaluation may present new possibilities for elucidating important and potentially treatable risk factors and lead to focused area of specific primary interventions. This led us to initiate the study to understand the epidemiological aspects of GBC in this part of India, which reports one of the highest incidences of GBC in the world to provide valuable insights into determining causes and preventable risk factors for gallbladder cancer.

Various studies have been undertaken to evaluate the epidemiological risk factors of GBC in northern India, prominent being studies by Gupta et al. (1967–1976, 328 patients), Shukla et al. (1963–1979, 315 patients), Pal et al. (1984–1988, 201 patients), and Kapoor et al. (1989–1994, 297 patients) (Table 1). To the best our knowledge, the present study is the largest one to be reported in the literature to evaluate the epidemiological risk factors of gallbladder cancer, from an area known to be endemic for GBC.

Table 1 Various epidemiological studies of GBC patients reported from India

Study zone	Place, zone	Period	No. of patients
Prakash et al.	New Delhi, North	1959–1973	100
Gupta et al.	Varanasi, North	1967–1976	328
Shukla et al.	Varanasi, North	1963–1979	315
Chattopadhyay et al.	New Delhi, North	5 years	143
Pal et al.	Calcutta, East	1984–1988	201
Zargar et al.	Kashmir, North	3 years	98
Kapoor et al.	Lucknow, North	1989–1994	297
Chaudhary et al.	New Delhi, North	1987–1996	196
Nissar Hussain	Calcutta, East	2004–2011	198
Imran Khan	Calcutta, East	18 months	63
Present study	Lucknow, North	2012–2014	490

Methodology

A large, single-centre, prospective study of gallbladder cancer was conducted in King George's Medical University, Lucknow, from August 2012 to July 2014. Case subjects with cytologically/histologically confirmed diagnosis of GBC were accrued in the study. Cancer diagnosis was confirmed by either a curative surgery (radical/simple cholecystectomy) or FNAC/core needle biopsy of gallbladder mass/metastatic foci (in cases of inoperable or metastatic disease) at the time of presentation.

Over 3 years of the study period, 490 patients of GBC were identified, and their history and clinical findings were tabulated and analysed. Patients dietary, reproductive history and socioeconomic status were properly recorded in proforma and analysed and reviewed with the objective to identify putative risk factors contributing to the aetiopathogenesis of the disease. The history of coexistent gallstone disease was recorded along with the stage at presentation, histological subtype and the grade of the tumour.

Results

Age and Gender Incidence

A total of 490 patients (84 males and 406 females) of GBC were included in the present study with their age ranging from 25–78 years (mean age=51.2 years) (Table 2). The peak incidence was in 31–50 years age group (58 %). The male to female ratio was 1:4.83, with the mean age for females (mean − 49.1 years) significantly lower than male counterpart (mean − 54.9 years) (p value=0.000423, significant at 5 %). Compared to male patients, 4 % of female patients (n=16) were below 30 years of age at initial diagnosis, indicating more aggressive and early onset of

Table 2 Age and gender incidence of GBC patients (n=490)

Age-gender distribution				
Age in years	M		F	
	No. of patients	%	No. of patients	%
<30	0	0 %	16	4 %
31 to 50	36	42 %	234	58 %
51 to 70	46	53 %	144	36 %
>70	4	5 %	10	2 %
Total	86 (17.5 %)	100 %	404 (82.5 %)	100 %

disease in female subgroup (Table 2). Most patients were from rural background (73 %).

Clinical Presentations

Abdominal pain was the most common complaint found in almost all patients of GBC (96 %, *n*=470), followed by palpable lump in the right upper quadrant (19 %, *n*=93), jaundice (14 %, *n*=69) and ascites (3 %, *n*=14), respectively, with mean duration of symptoms <3 months in 57 % of patients (*n*=279). Physical examination revealed palpable gallbladder mass in 51 % of patients (*n*=250), scar site metastasis in 5.3 % (*n*=26), palpable supraclavicular node in 1.6 % (*n*=8) and Sister Mary Joseph nodule in 0.45 % (*n*=2) patients respectively (Table 3).

Diet, BSA and Addictions

Majority of patients were non-vegetarians (67 %) and 84 % of them consumed mustard oil (loose/home made) as a main cooking medium (Table 3). Most patients had body surface area (BSA) between 1.2 and 1.4 (59 %) and 1.4 and 1.6 (39 %) respectively. Around 38 % of patients consumed tobacco, 20 % were smokers and 5 % were alcoholic. All addictions were more prevalent in male patients, as compared to female.

Reproductive Factors

GBC was more commonly observed in females with the age of menarche less than 14 years (83 %), age of first childbirth before 20 years (56 %) and with more than two live children (Table 3). The incidence of GBC in postmenopausal female patients was 71 % (menopausal age <45 years and >45 years was 39 % and 32 %, respectively) while 29 % of the patients were premenopausal.

Socioeconomic Status

Majority of the patients of GBC in our study were from low socioeconomic strata (68 %) as per Kuppuswamy classification (classes IV and V (lower class)) compared to 27 % in classes II and III (middle class).

Cholelithiasis

Gallstones were present in 390 out of 490 patients (80 %). Incidental gallbladder carcinoma (IGBC) was detected in 158 out of 490 patients (32 %) and most had undergone prior open cholecystectomy (27 %) for treatment of symptomatic gallstone disease. Majority of patients following cholecystectomy presented with symptoms within 3 months of undergoing index surgery (30 %), ranging from 15 days to 60 months. Ultrasonography (USG) was the most common initial imaging modality of choice based on which patients were diagnosed and subjected to cholecystectomy. There was a general trend observed of suspicious sonographic findings (like focal/diffuse wall thickening or GB mass) being overlooked by the index surgeon and not further investigated by computed tomography (CT) scan to rule out the diagnosis of GBC. This may account for exceptionally high incidence of IGBC in our study.

Stage, Histological Type and Grade

Majority (52 %; *n*=256) of the patients with GBC in the present study presented with distant metastasis (stage IVB) and were offered either palliative chemotherapy/supportive care. Patients diagnosed in early stage (stages I–IIIA) were 90 (18 %) while locally advanced disease (IIIB–IVA) was found in 130 (27 %) patients respectively. The most common histological subtype of GBC was adenocarcinoma (78.4 %, *n*=384). Less commonly described histological variants of GBC were mucinous (6 %, *n*=29), papillary (8 %, *n*=39), adenosquamous (3 %, *n*=14), neuroendocrine (1.4 %, *n*=7) and carcinosarcoma (0.2 %, *n*=1). Most of GBCs were well differentiated (38 %, *n*=186) while grade was not commented in 23 % (*n*=113) of the patients (Table 4).

Discussion

Gallbladder carcinoma (GBC) is the most common type of biliary tract cancer and the sixth most common digestive-tract malignancy [1]. It is universally characterized by late diagnosis, unsatisfactory treatment and poor prognosis [2, 3]. It is the most common cause of death from biliary malignancies [4]. GBC shows significant geographical variation in the incidence which correlates closely with the prevalence of gallstones [5]. The highest incidence rates of GBC (up to 7.5 per 100,000 for men and 23 per 100,000 for women) are found amongst populations living in the western parts of the Andes, North American Indians, Mexican Americans and inhabitants of northern India. In Chile, GBC is reported to be the most common malignancy in women and the second most common cancer in men [6]. Chile also reports high death rates due to GBC amongst both women (16.6/100,000) and men (7.8/100,000). North Indian Gangetic planes report one of the highest incidences of GBC in the world. Six cancer registries of the Indian Council of Medical Research (ICMR) (1990–1996) reveal a ten times higher incidence of GBC per 100,000 in North India compared to South India, the age adjusted incidence rates being 4.5 per 100,000 for males and 10.1 per 100,000 for females in North India; 1.2 per 100,000 for males and 0.9 per 100,000 for females in South India as reported by the population-based cancer registry, Delhi [7]. Factors implicated

Table 3 Clinico-epidemiological factors related with GBC patients (n=490)

SL No.	Parameters	Present study
1	Age	Third to fifth decade (55 %)
2	Sex (M:F)	1:4.83
	Mean age for male (peak incidence in the fifth to seventh decade)	54.9 years
	Mean age for female (peak incidence in the third to fifth decade)	49.1 years
3	Rural:urban	73:27 %
4	Diet	
	Veg	33 %
	Non-veg	67 %
5	Type of cooking oil	
	Consumption of mustard oil (loose packed/home made)	84 %
	Packed mustard oil and other oils (sunflower, groundnut)	16 % (significant p value=0.001)
6	Body surface area	
	1.2–1.4	59 %
	>1.4	41 %
7	Body weight	
	<60 kg	91.1 %
	>60 kg	08.9 %
8	Socioeconomic status	
	Kuppuswamy class I (upper)	05 %
	Kuppuswamy classes II–III (middle)	27 %
	Kuppuswamy classes 1V–V (lower)	68 % (p value=0.001)
9	Tobacco consumption	38 % (n=186)
	Male	69.7 % (n=60/86)
	Female	30.3 % (n=126/404)
1	Smokers	20 % (98/490)
0	Male	93.3 % (81/86)
	Female	4.2 % (17/404)
		(significant p value=0.0001)
11	Alcoholic	15 % (n=73/490)
	Male	70 % (n=60/86)
	Female	3.2 % (n=13/404)
		(significant p value=0.0001)
12	Gallstones (392/490 patients)	80 %
	Multiple	81.8 % (n=319)
	Single	18.2 % (n=73)
13	Incidental gallbladder carcinoma (N=157)	32 %
	Laparoscopic	5 %
	Open	27 %
14	Reproductive factors	
	Age at menarche	
	<14 years	83 %
	>14 years	17 %
	No. of pregnancies	
	<2 children	40 %
	>2 children	60 %
	Age at first child	56 %
	Up to 20 years	44 %
	>20 years	
	Postmenopausal	79 %
	Premenopausal	21 %
15	Clinical presentation	
	Symptoms	
	RUQ pain	96 %
	Lump	19 %
	Nausea	45 %

Table 3 (continued)

SL No.	Parameters	Present study
	Icterus	14 %
	Signs	
	GB lump	51 % (n=250)
	Scar site metastasis	5.3 % (n=26)
	Supraclavicular node	1.6 % (n=8)
	Sister Mary Joseph nodule	0.45 % (n=2)

in the aetiopathogenesis of GBC are still not clearly elucidated; however, various presumptive factors have been described. Gallstones, choledochal cysts, chronic infection of the gallbladder and environmental exposure to specific chemicals such as thoratrast are known predisposing factors. Amongst these, gallstones and chronic inflammation of the gallbladder are the commonest risk factors.

Age and Sex Incidence

The peak incidence of GBC in the present study was observed in 31–50 years age group (58 %). Similar results were seen in other studies from India (Shukla et al., [8]; Pandey et al., [9]; Kapoor et al., [10]; Nissar Hussain et al., [11]; Imran et al., [12]). In stark contrast, studies from west reported the mean age of 67 years (Beltz et al., [13]) and the peak age of incidence in the seventh decade of life (Perpetuo et al., [14]). In our study, the male to female ratio was 1:4.83, with the mean age for females (mean 49.1 years) significantly lower than male counterpart (mean 54.9 years) (p value=0.000423, significant at 5 %). *Thus, females tend to present at younger age at diagnosis compared to the male counterpart.* The above findings were consistent with the results of other studies (Beltz et al., [13]; Shukla et al., [8]; Pandey et al., [9]) where the male to female ratio was reported to be 1:3, 1:3 and 1:2.5 respectively. Based on the review of literature of the worldwide incidence of GBC, the average female to male ratio was reported between 2 and 3 [15] while it was more decisively skewed in favour of the female sex in our study. The skewed sex distribution of GBC in females is more strikingly observed in countries and regions with the highest incidence rates of GBC, such as northern India [6].

Table 4 Clinical stage and histological types of GBC patients (n=490)

AJCC stage	
I–IIIA (node negative)	18 % [n=90]
IIIB IVA (node positive)	27 % [n=130]
IVB (metastatic disease)	52 % [n=256]
No details	03 % [n=14]
Histological type	
Benign	03 % [n=14]
Adenocarcinoma	78.4 % [n=384]
Papillary	08 % [n=39]
Mucinous	06 % [n=29]
Adenosquamous	03 % [n=14]
Neuroendocrine	1.4 % [n=7]
Carcinosarcoma	0.2 % [n=1]
Grade	
Well differentiated	38 % [n=186]
Moderately differentiated	27 % [n=132]
Poorly differentiated	12 % [n=59]
Not commented	18 % [n=89]
Not available	05 % [n=24]

This marked gender bias for GBC—which to some extent reflects a gender bias for cholelithiasis and the distinct geographic and genetic factors involved in pathogenesis—warrants the need for a more detailed evaluation of the role of hormonal (estrogen/progesterone) receptors in the pathogenesis of GBC. Younger age at menarche, early age at first pregnancy, multiple pregnancies, higher number of live births and prolonged fertility/late menopause may potentially increase the risk of GBC because of prolonged levels of estrogen and progesterone. Chao and Greager reported that postmenopausal status as a risk factor with the development of gallbladder carcinoma [16]. La Veechia reported an increased risk of GBC in pregnant women. The use of oral contraceptive is not reported to be associated with higher incidence of GBC [17].

In the present study, amongst female subgroup, GBC was more consistently observed in females with the age of menarche less than 14 years (83 %), age of first child before 20 years (56 %). Also, the trend of increased incidence of GBC was observed with gravida more than two (57 %) as compared to less than two children (43 %). These finding are consistent with the study done by Zatonski et al. who reported that a female with three or more children had a 2.2-fold increased risk compared with those less than two children [18]. The high prevalence of GBC was also seen with early age of menarche (<14 years). The increased duration of exposure of estrogens and progesterone may play a role in gallbladder carcinogenesis, and their role need to be evaluated further to characterize

the markedly skewed incidence of GBC in female patients within reproductive age groups, especially in regions with high incidence rates of GBC as northern India.

Clinical Presentation

GBC is notorious for the paucity of early signs and symptoms, which makes its early diagnosis difficult. The clinical presentations of GBC either remain asymptomatic for a long period or presents with very non-specific symptoms [3]. In majority of cases, symptoms are related to associated gallstones (Shiwani et al.) [19]. In the study by Hussain et al. [11], abdominal pain (88.9 %) followed by abdominal mass (76.3 %) and anorexia (60 %) were the most common presenting features. Consistent results were reported in other studies (Gupta et al., [20]; Khan et al., [4]). Piehler et al. postulated that clinical signs mimic benign gallbladder diseases until the invasion of surrounding structures give clue to correct the diagnosis of GBC [21]. In the present study, the right upper quadrant pain was the commonest complaint found in almost all patients of GBC (98 %), followed by palpable lump in the right upper quadrant (9 %), jaundice (8 %) and ascites (3 %), respectively, with mean duration of symptoms <3 months in 57 % of patients. Physical examination revealed palpable gallbladder mass in 51 % of patients (n=250), scar site metastasis in 4.9 % (n=24), palpable supraclavicular node in 1.6 % (n=8) and Sister Mary Joseph nodule in 0.45 % (n=2) respectively.

Body Weight

There is proposed to be an inverse relationship between the body weight of the individual and risk of gallbladder carcinoma. According to Weiderpass et al., an increase in body weight decreases the risk of gallbladder carcinoma significantly in majority of patients [22]. In the present study, 91.1 % of the patients with GBC had weight less than 60 kg and only 8.9 % patient had weight more than 60 kg (p=0.0001). These results were similar to the study done by Imran et al., where he demonstrated 60.34 and 19.04 % of individuals with GBC weighed between 50 and 55 kg and 55 and 60 kg, respectively (p=0.003) [12]. Low body weight may be attributable to catabolic process associated with GBC as most patient present in advance stage.

Diet and Type of Cooking Oil

In our study, majority of the patients were non-vegetarians (67 %) consuming red meat, fish (added with chilli and spices), eggs etc., compared to vegetarians (33 %). Red meat increases the risk of gallbladder cancer while vegetables and fruits are thought to be protective in nature. In the present study, almost 84 % of patients with GBC consumed home-made/loose-packed mustard oil as primary cooking medium which exposes them to potentially high risk of adulteration and potential carcinogens. In a study by Mishra et al. from North India to assess the carcinogenic potential of argemone oil and butter yellow, the adulterants are encountered in edible oil, in the gallbladder of Swiss albino mice and concluded that these adulterants are responsible for producing GBC in mice along with the stone formation observed in argemone oil-exposed animals [23]. Further, it was observed that female mice were more vulnerable to these adulterants in term of response to inflammatory markers. Similar studies need to be carried out in our subjects to assess the role of food adulterants in the aetiopathogenesis of GBC, and it may be a potentially preventable and modifiable risk factor.

Addictions

Around 38 % of patients consumed tobacco, 36.7 % were smokers, and 20 % consumed alcohol on regular basis. All these addictions were more commonly observed in males. Nearly all male patients were smokers (40/43 male, smokers (p value=.0001); 17/404 females, smokers]. In our study, about 30.3 % of the females consumed tobacco (n=126), while only 4.2 % (n=17) were smokers and 3.2 % (n=13) were alcoholic. In females, tobacco chewing emerged as an important risk factor for GBC. The exact role of smoking, chewing tobacco and alcohol consumption in the aetiopathogenesis of GBC is not well established. Recent data by Tyagi et al. [24] and Shukla et al. [25] reported that smoking, tobacco chewing, and alcohol intake were independent risk factors for GBC. In the study by Imran et al., the risk of GBC was increased significantly in male patients having the history of smoking. In general, lower body weight/body surface area, lower socioeconomic strata, malnutrition, consumption of red meat, and smoking were associated with increased risk GBC [22], and our present study confirms these findings.

Gallstones (Cholelithiasis)

Cholelithiasis is the commonest risk factor implicated in the carcinogenesis of GBC. Gallstones are associated with gallbladder carcinoma in a range of 40–100 %. The relative risk of developing GBC is 2–24 times higher for patients with cholelithiasis compared to those without gallstones. Gallstone disease and GBC have similar risk factors like female gender, reproductive age and obesity. The odds ratio of developing GBC in patients with larger gallstones (diameter 2–2.9 and ≥3 cm) compared with ≤1-cm diameter was 2.4 and 10.1 respectively [13]. According to Nissar Hussain et al. [11], gallstones were present in 86 % of cases of GBC which is comparable to a study from MD Anderson Hospital (Perpetuo et al. [14] in which 51 (88 %) patients had gallstones. Evarts

Graham observed that gallstones were present in 69–100 % of cases of GBC and in turn, GBC was found in 4.5–14 % of patients with gallstones [26]. Other study from India (Pandey et al. [9]) reported the presence of gallstones in 70 % gallbladder cancer patients, whereas (Imran et al. [12]) reported 71.42 % of GBC were associated with stones. In the present study, gallstones were present in 80 % of patients. Majority of the patients had multiple stones (n=319, 81.9 %) compared to single stone (n=71, 18.1 %).

Incidental Gallbladder Cancer

Incidental gallbladder cancer (IGBC) also termed as occult/in apparent/missed GBC is defined as the GBC diagnosed during or after the cholecystectomy done for a benign gallbladder disease. Incidental GBC was referred to a 'histological surprise' of gallbladder carcinoma in a patient treated with simple cholecystectomy for gallstone disease, cholecystitis or gallbladder polyps. It is reported that GBC incidentally detected by histopathological examinations after open or laparoscopic cholecystectomy is encountered in 0.2–2.9 % of patients undergoing cholecystectomy. Incidental gallbladder carcinoma accounts for 27–41 % of all gallbladder carcinomas [27].

In the present study, IGBC accounted for 32 % of cases. Majority of cases occurred after open cholecystectomy (27 %) compared to laparoscopic cholecystectomy (5 %). All patients underwent cholecystectomy for symptomatic cholelithiasis. Based on literature review, Nissar Hussain et al. [11] reported the incidence of IGBC to be 3.5 %; Khoo et al. [28] in a study from Malaysia reported nine cases of incidental GBC. Malick et al. reported 6.15 % of IGBC [29] whereas Shreshtra et al. found the incidence of IGBC to be 1.4 % (8/570 cases) [30]. Exceptionally high incidence of IGBC in our study could be due to overlooking of the preoperative findings suspicious of GBC (focal/diffuse thick-walled GB, GB mass) for inflammatory mass secondary to stones, missed or overlooked by both radiologist and the operating surgeon and subsequently the patient subjected to simple cholecystectomy alone (either laparoscopic/open), only for intraoperative findings and postoperative histopathology to confirm the preoperative suspicion of GBC.

Socioeconomic Status

The assessment of socioeconomic status (SES) is an inherent part of various epidemiological studies, which guide us to study the effect of SES on different diseases. Various indices such as Kuppuswamy and Pareek have been proposed to stratify the study population based on socioeconomic status. The level of education, type of occupation and family income are the key components of Kuppuswamy index [19]. Majority of the patients of GBC in our study were from low socioeconomic strata (68 %) as per Kuppuswamy classification (classes IV and V (lower class)) compared to 27 % in classes II and III (middle class). These findings were consistent with the study done by Imran et al., where he reported that 69.84 % of the patients with GBC belonged to lower socioeconomic status as per the Kuppuswamy index [12]. Delay in seeking treatment for gallstones and subsequent prolonged inflammation induced by gallstones in lower socioeconomic strata may be contributory factors for high incidence of GBC. The lack of access to safe drinking water may also expose them to various carcinogens. Many studies, especially from Southeast Asia, have proposed a link between chronic typhoid carrier state and gallbladder cancer based either on culture isolation or serological methods [31, 32]. Patients with benign gallbladder diseases were also shown to have significantly higher positivity for Salmonella typhi as compared to healthy controls in a study from North India [33]. While serological testing of anti-Vi antibody titres in serum and the culture isolation rate of S. typhi from the gallbladder specimens has its limitations, a highly sensitive and specific nested PCR amplification of the S. typhi flagellin gene in hepatobiliary specimens capable of detecting the L forms and other non-culturable forms may be more sensitive for the detection of S. typhi carriage state [33]. Various bacterial carcinogens produced by S. typhi may contribute to the carcinogenesis process viz bacterial glucoronidase, bacterial degradation of primary bile acids and producing carcinogenic secondary bile acids, production of nitroso compounds from nitrates by the action of bacterial enzymes and chronic bacterial infection leading to obstruction, and persistent mechanical injuries [34–36].

Stage, Histology and Grade

In our study, majority of the patients of GBC (52 %; n=256) presented with distant metastasis (stage IVB). Patients diagnosed in early stage (stage I–IIIA) were 90 (18 %) and locally advanced stage (IIIB–IVA) were 130 (27 %) patients respectively. According to Roa et al. [37], the most common histological type of GBC is adenocarcinoma representing approximately 90–95 % of all cases. The less commonly described histological variants of GBC are mucinous, papillary, adenosquamous and carcinosarcoma. As per the study by Nissar Hussain et al. [11], adenocarcinoma accounted for 87.7 % of cases followed by papillary (6.9 %) and mucinous (3.8 %) adenocarcinoma. In the present study, the most common histological type of GBC is adenocarcinoma (78 %). The less commonly described histological variants of GBC are mucinous (6 %), papillary (8 %), adenosquamous (3 %), neuroendocrine (2 %) and carcinosarcoma (0.6 %); histopathology analysis revealed comparable findings in other studies reported in the literature (Beltz et al. [13]; Liang et al. [38]).

Conclusion

This data re-emphasizes the high prevalence of gallbladder carcinoma in northern India and potential acronym of '*Gallbladder cancer capital of the world*'. Gallbladder carcinoma portends aggressive behaviour and poor prognosis. Current data suggest that the epidemiology of gallbladder cancer is constantly evolving, with much of this change caused by lifestyle, cultural, mixing of different ethnicities and dietary factors. Balanced diet, prevention of malnutrition/adulteration, tobacco prevention, early intervention for cholelithiasis and referral to specialist centre in case of suspicious radiological findings may help in decreasing the incidence of this dreaded disease and ensure timely intervention. Both the radiologists and surgeons should have a high index of suspicion for GBC in high-incidence areas (northern India) especially with atypical clinical and ultrasound findings. More structured studies need to be carried out to ascertain the risk factors for GBC in our population subgroup.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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