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Gallbladder Carcinoma: A Review of Literature

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Abstract **Review Article**

Gallbladder cancer (GBC) is the most common cancer of the biliary tract but the sixth most common cancer of the gastrointestinal tract. This tumor has a very high death rate. It is impossible to emphasize how crucial early diagnosis is because GBC grows subtly when it is discovered later. A number of environmental and genetic factors have been linked to the beginning of GBC. Environmental variables such as cholelithiasis, chronic inflammation of the biliary tract, and parasite infections are known to have a substantial impact on the development of gallbladder cancer. Congenital causes include abnormalities in the pancreaticobiliary duct junction and biliary cysts. Over the last ten years, advancements in imaging technology coupled with a more aggressive and drastic surgical approach have enhanced patient outcomes and contributed to longer survival times for GBC patients. This review article focuses on the epidemiology of GBC, its risk factors, and clinical characteristics.

Keywords: Gallbladder carcinoma, Biliary malignancy, Radical Cholecystectomy, Metastasis, Risk factors.

INTRODUCTION

Gallbladder cancer (GBC) is the most common cancer of the biliary tree and arises from the epithelial lining of the gallbladder (GB) and the cystic duct [1]. GBC ranked 22nd in incidence and 20th in mortality worldwide among cancers, according to GLOBOCAN: Global Cancer Statistics 2022. According to this data, there were 122,491 incident GBC cases worldwide for the year 2022. In India, there were 21,780 incident GBC cases with 16,407 deaths in the year 2022 [2]. Thus, India contributes to around 10% of the global GBC burden [3]. Predisposing factors for developing GBC include ethnicity, genetic predisposition, geographic location, female gender, chronic inflammation, and congenital developmental abnormalities. The prognosis for patients with GBC is poor, as diagnosis is late and at untreatable stages of the disease [4].

Vascular, lymphatic, intraperitoneal, neural, and intraductal routes are the routes of spread seen in GBC. Spread to the liver parenchyma and the adjacent internal organs is due to a lack of serosa in the gallbladder wall, proximity, cholecystic veins draining into the liver portal vein, and lymphatics from GB draining into the liver. A direct tumor invasion of the liver should not be regarded as a distant metastasis. Metastases usually occur in the liver, lymph nodes, adjacent organs, and peritoneum [5]. The American Joint Committee on Cancer has developed a TNM staging system determined by the depth of invasion, expansion of GBC into adjacent structures, lymph node involvement, and metastatic spread [6].

Surgical excision is the only curative treatment for gallbladder cancer. Regretfully, the majority of GBC patients have unresectable disease, leaving only 10–30% of patients eligible for surgery at the time of presentation [7]. Over time, there have been changes to the surgical options available for treating GBC, varying from a straightforward cholecystectomy to a radical or extended cholecystectomy, which removes 2 cm of liver tissue from the gallbladder bed along with the gallbladder. More extensive liver resections, such as segment IV and V resections, right hepatectomy, and trisectionectomy, are being done along with regional lymphadenectomy of the pancreatic, periduodenal, and porta hepatis [8].

With a 1-year survival rate ranging from 20% to 50%, metastatic GBC patients had a worse prognosis than their non-metastasizing counterparts. More than half of GBC cases with metastases have the liver as their primary metastasis, according to earlier investigations [9]. The liver was the most common site of metastases, which is in agreement with previous studies, and this may be because tumor cells spread to remote organs through the blood and the liver has the most blood vessels [10]. Furthermore, research has validated hepatic metastasis as a noteworthy risk factor for GBC survival

[9]. Thus, to enhance the prognosis of GBC, clinicians must assess the risk of liver metastasis as soon as feasible and implement preventative therapy alternatives. Few studies have explored the risk factors for liver metastasis in GBC patients. This review article focuses on the epidemiology of GBC, its risk factors, and clinical characteristics.

THE GALLBLADDER ANATOMY

The gallbladder (GB) is a pear-shaped organ situated in the upper right quadrant of the abdomen, typically measuring between 7 and 10 cm in length and 4 cm in width [15]. It is located in front of the undersurface of liver segments IV and V, with a liver surface on top and a peritoneal surface on the bottom. The body of the GB does not have a capsule, although some authors describe Glisson's capsule - an extension of the liver capsule - as covering the exposed surface of the GB. The GB fundus is wide, and it progressively narrows as it leads into the main body. This body then tapers into the infundibulum, which connects to the neck and cystic duct. The GB and cystic duct have spiral valves of Heister at their distal ends, which may assist in GB emptying with neural and hormonal stimulation. Most individuals have a Hartmann's Pouch, which is an inferior outpouching of the GB infundibulum or neck.[16] Consequently, the GB is composed of the following parts: the fundus, the main body, the infundibulum, the neck, the cystic duct, and Hartmann's Pouch.

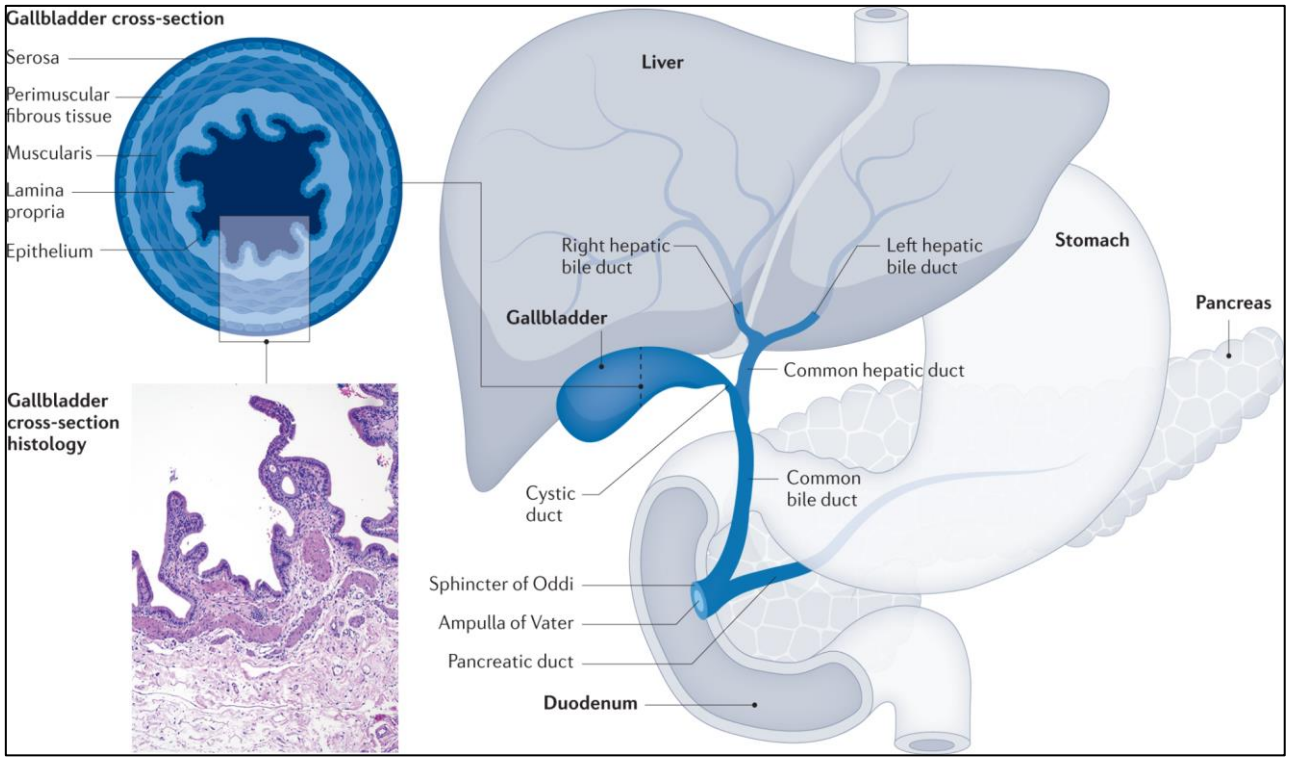

Figure 1: Anatomy and histopathology of gallbladder [1]

FUNCTIONS OF GALLBLADDER

Most of the bile secreted by the liver is handled by the GB, which also controls the outflow of bile into the intestine. It has been estimated that the GB receives 80% or more of hepatic bile [17]. The liver produces at least 1000 ml of bile per day, with rates varying between 0.5 and 1 ml/min during fasting and between 2 and 3 ml/min after feeding [18]. Whether bile is directed to the gallbladder or duodenum depends on the relative resistance to flow, mainly determined by the contractile state of the gallbladder and sphincter of Oddi [19]. During the inter-digestive period, the pressure gradient favors the entry of bile into the gallbladder, and 90% of hepatic bile is diverted into the gallbladder, where it is stored and concentrated [20]. As a result of phasic contractions of the sphincter of Oddi and increments of intra-gallbladder pressure, 10% of bile flows into the duodenum during late phase II of the migrating myoelectric complex [21]. This helps maintain the enterohepatic circulation of bile acids in the inter-digestive period. Hence, the gallbladder stores the bile produced by the liver, controls how much of it is released into the intestine, and localizes the bile within the GB with the most rapid flow in the neck region and a slower flow in the fundus, allowing the bile to be concentrated in the deeper unstirred layers of the fundus [22].

The gallbladder absorbs fluids that aid in storing and concentrating bile. It secretes fluids to facilitate the emptying of the gallbladder and prevent stagnation of bile salts [23]. Additionally, it secretes bicarbonate and mucins, which serve as protection against injury caused by bile acids. Moreover, it actively transports sodium chloride and passively absorbs water across the mucosa, thereby increasing the solubility of cholesterol and calcium salts to prevent gallstone

formation. Lastly, the gallbladder plays a role in transporting lipids and bile acids.

EPIDEMIOLOGY OF GBC

While the gallbladder is no more than an inch (2 cm) wide, GBC accounted for 89,055 cancer deaths in 2022 [2]. The incidence of GBC worldwide is based on gender, geography, and ethnicity which makes it very different from all other cancers. This suggests that not only genetic factors but also environmental factors play an important role in its pathogenesis. The rate of GBC occurrence is comparatively higher in South American countries such as Chile, Bolivia, and Ecuador and some regions of Asian countries like India, Pakistan, Japan, and South Korea [24]. European countries have observed intermediate rates of incidence. Though the rate of occurrence of GBC is lower in the United States, Native Americans have a higher incidence. Additionally, the risk of GBC in rural regions is higher than that in urban areas [5]. Globally GBC is still rare among cancers and ranks 22nd in terms of incidence and 20th in terms of mortality. As per the Global Cancer Observatory 2022 data, the highest incidence of GBC is in the South American counties of Chile followed by Bolivia. Chile registered 1917 new cases of GBC with 1236 deaths in 2022 making GBC the 7th most common cancer in the country. Bolivia also registered 1,006 new cases of GBC with 831 deaths in 2022 making GBC the 6th most common cancer in the country [2].

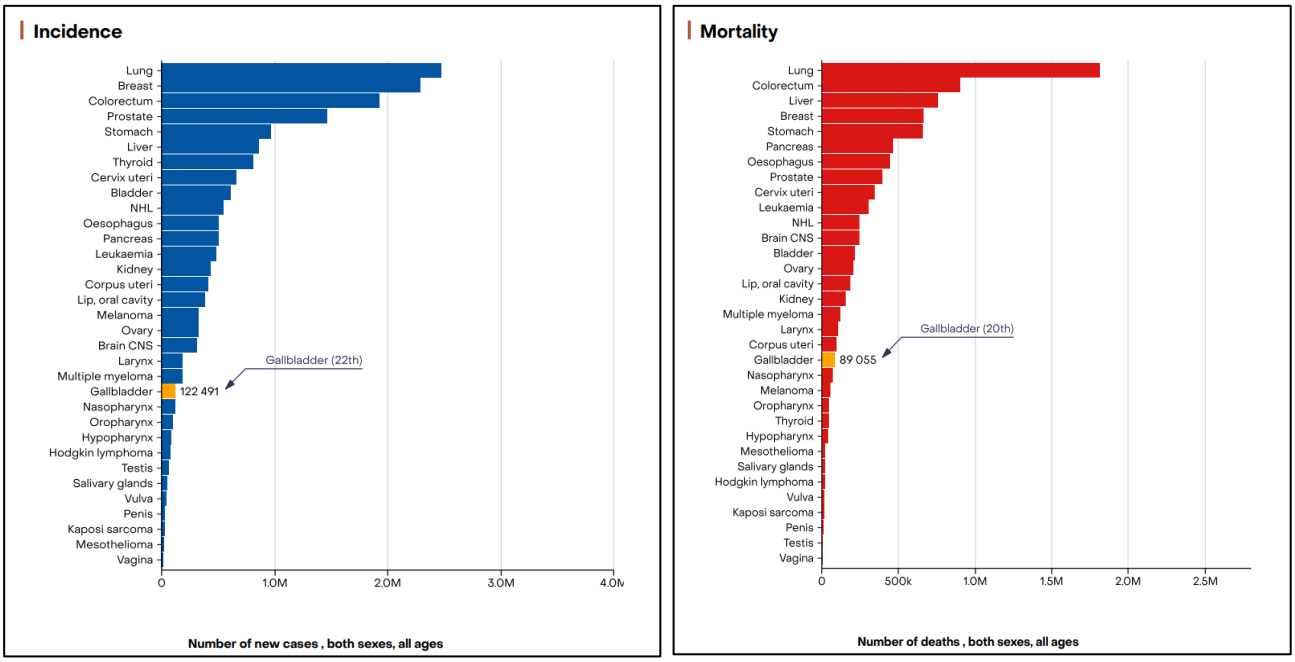

Figure 2: Bar graph showing the ranking of cancers as per world wide incidence and mortality. [2]

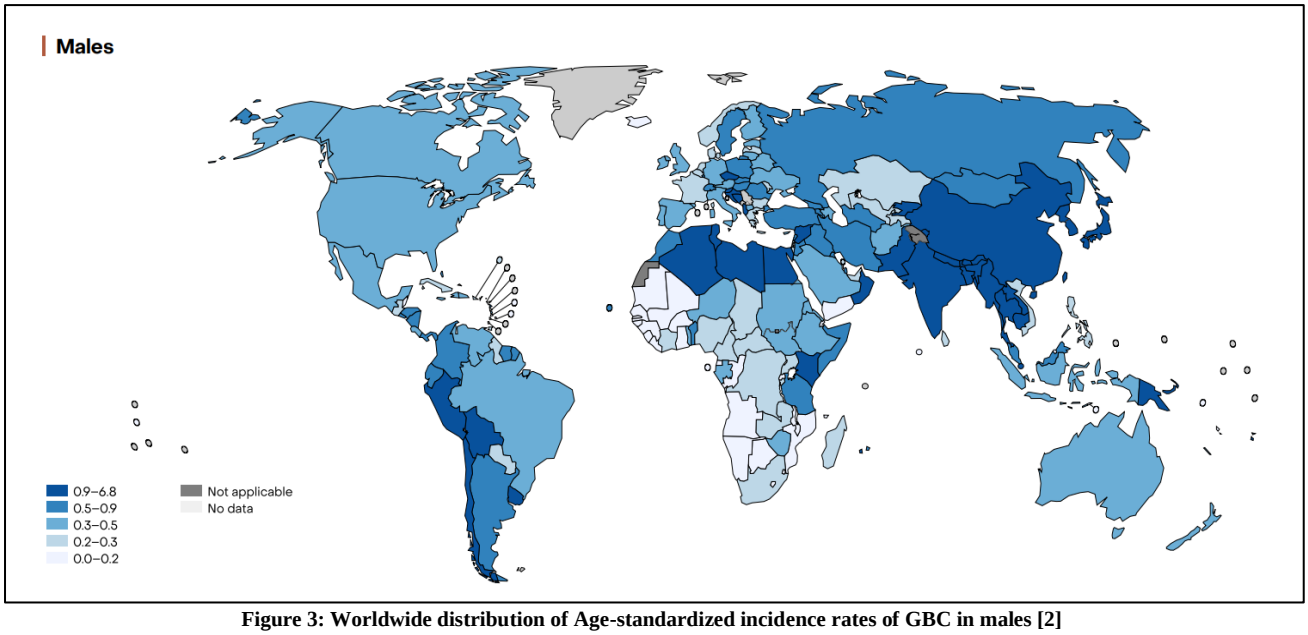

Figure 3: Worldwide distribution of Age-standardized incidence rates of GBC in males [2]

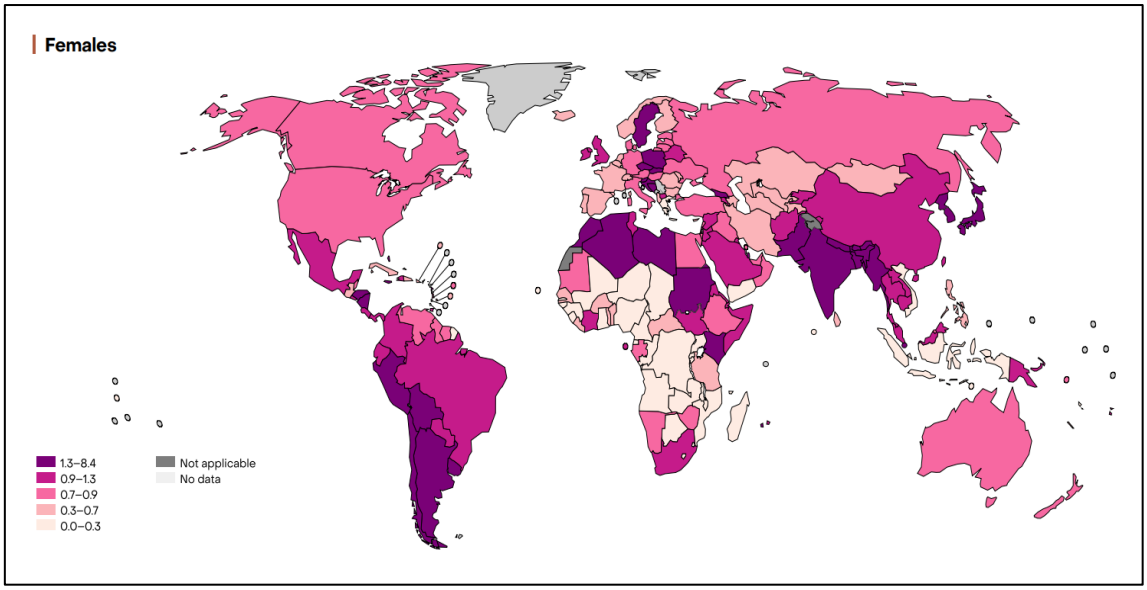

Figure 4: Worldwide distribution of Age-standardized incidence rates of GBC in females [2]

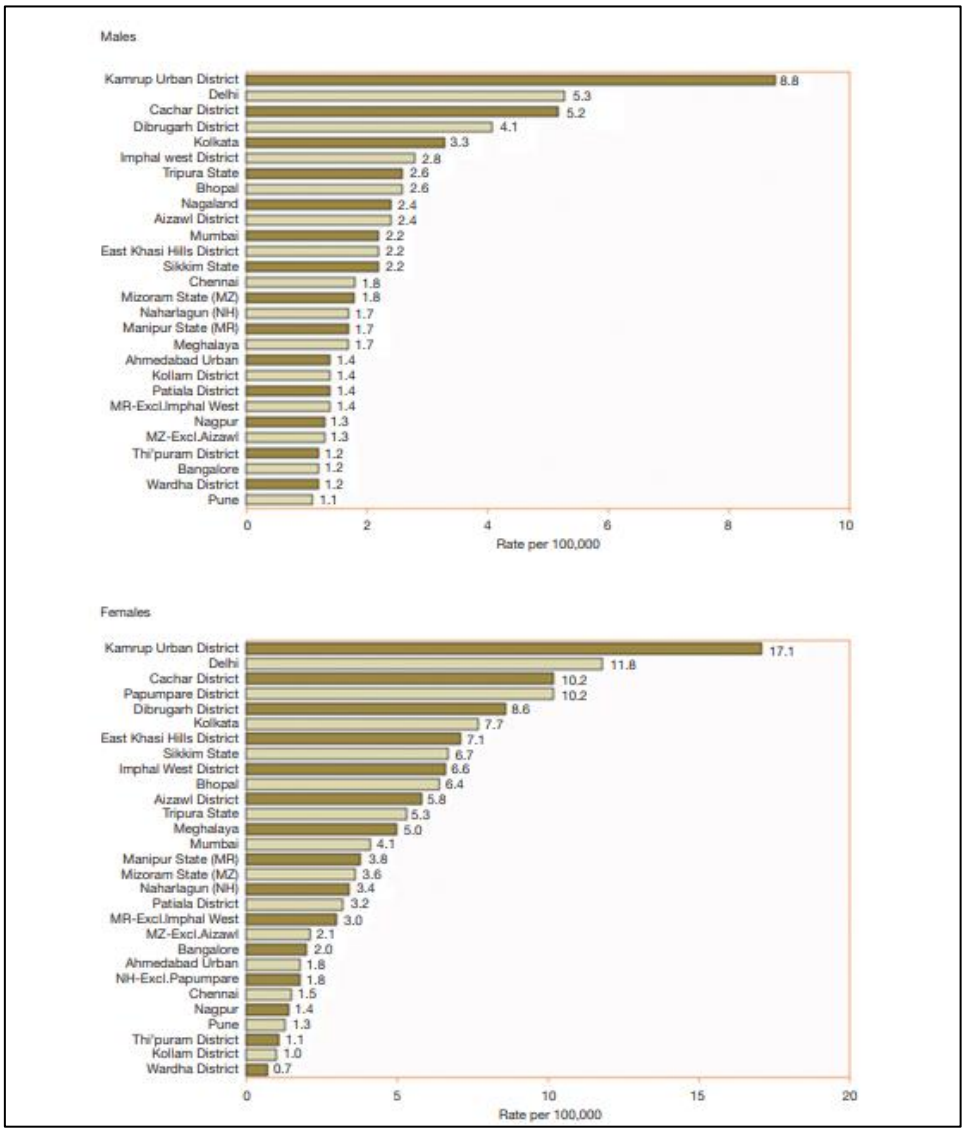

Figure 5. Bar chart showing comparison of age adjusted incidence rates of all population-based cancer registries of gallbladder cancers in males and females of India [26]

In India there were 21 780 new cases of GBC with 16 407 deaths in 2022 making it the 19th most common cancer in India [2]. North and north east India have incident rates comparable to that of Chile and Bolivia. They include states of Jammu and Kashmir, Punjab, Haryana, Himachal Pradesh, Uttarakhand, Uttar Pradesh, Bihar, Bengal, Assam and Manipur. A significant portion of these states comprises of areas that are situated along the country's major rivers, namely the Sutlej, Ganges, Yamuna, and Brahmaputra.

The number of cases has been consistently increasing in India, affecting both men and women. Between 2001-2004 and 2012-2014, the rate of occurrence of cervical cancer among women has risen from 6.2 per 100,000 to 10.4 per 100,000 after adjusting for age [25].

There are differences in the frequency of gallbladder carcinoma that are linked to geography, indicating a potential environmental cause that isn't related to race or ethnicity. The exact cause of GBC is still unknown and needs to be established. However, studies have suggested that chronic cholecystitis, gallstones, choledochal cysts, female gender, age, and exposure to carcinogens may all play a role in the development of gallbladder cancer [27].

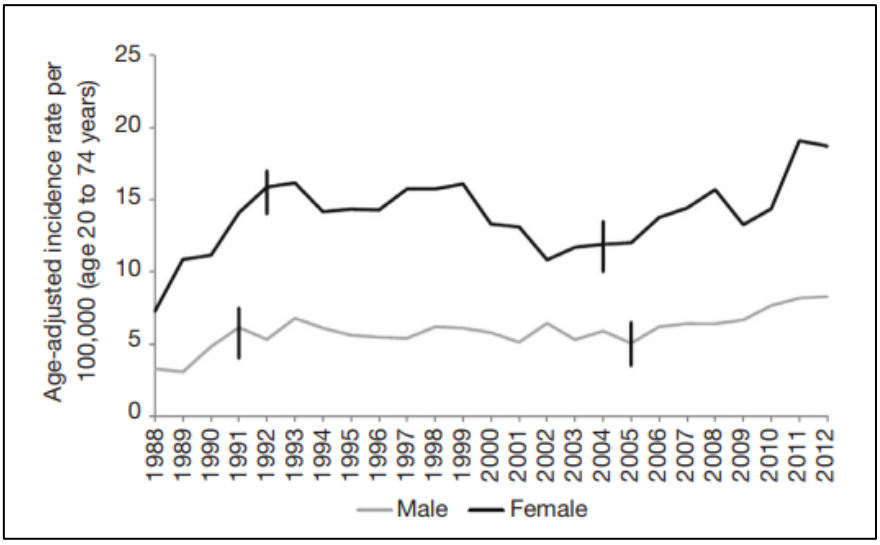

Figure 6. Graph depicting the incidence of gallbladder cancer according to various age groups in both genders [28]

PATHOLOGY OF GALLBLADDER CARCINOMA

Pathologic Stage Classification (pTNM, AJCC 8th Edition)

TNM Descriptors

m (multiple primary tumors)
r (recurrent)
y (posttreatment)

Primary Tumor (pT)

pTX: Primary tumor cannot be assessed
pT0: No evidence of primary tumor
pTis: Carcinoma in situ
pT1: Tumor invades the lamina propria or muscular layer
pT1a: Tumor invades the lamina propria
pT1b: Tumor invades the muscular layer
pT2: Tumor invades perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum) or tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
pT2a: Tumor invades perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum)
pT2b: Tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
pT3: Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
pT4: Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

Regional Lymph Nodes (pN)

pNX: Regional lymph nodes cannot be assessed
pN0: No regional lymph node metastasis
pN1: Metastases to one to three regional lymph nodes
pN2: Metastases to four or more regional lymph nodes
No nodes submitted or found

Distant Metastasis (pM)

pM1: Distant metastasis

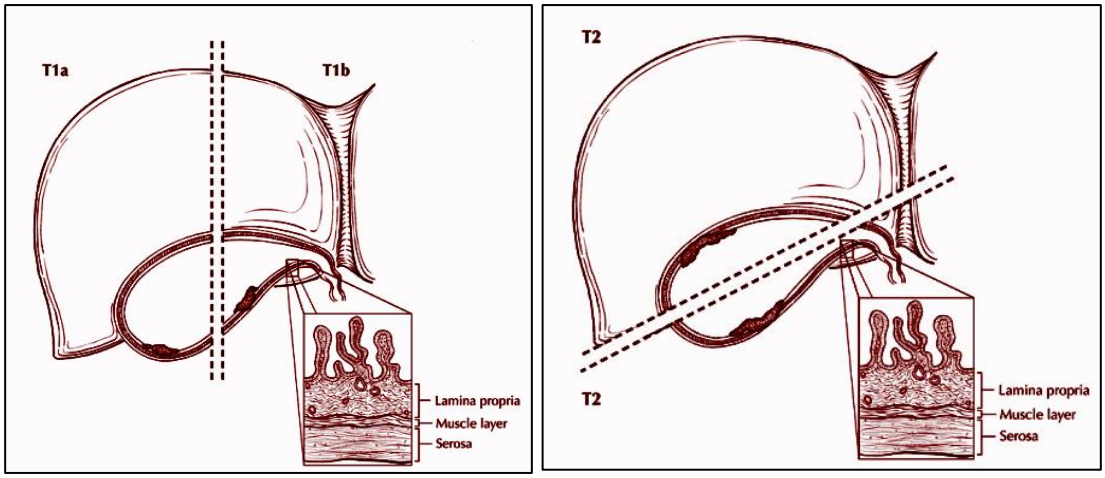

Figure 7: T1a is defined as tumor invading lamina propria; T1b is defined as tumor invading muscle layer. Two views of T2: Tumor invading perimuscular connective tissue (below dotted line) on the peritoneal side without serosal involvement (T2a) and tumor invading the perimuscular connective tissue (above dotted line) on the hepatic side (T2b) without liver involvement. [29]

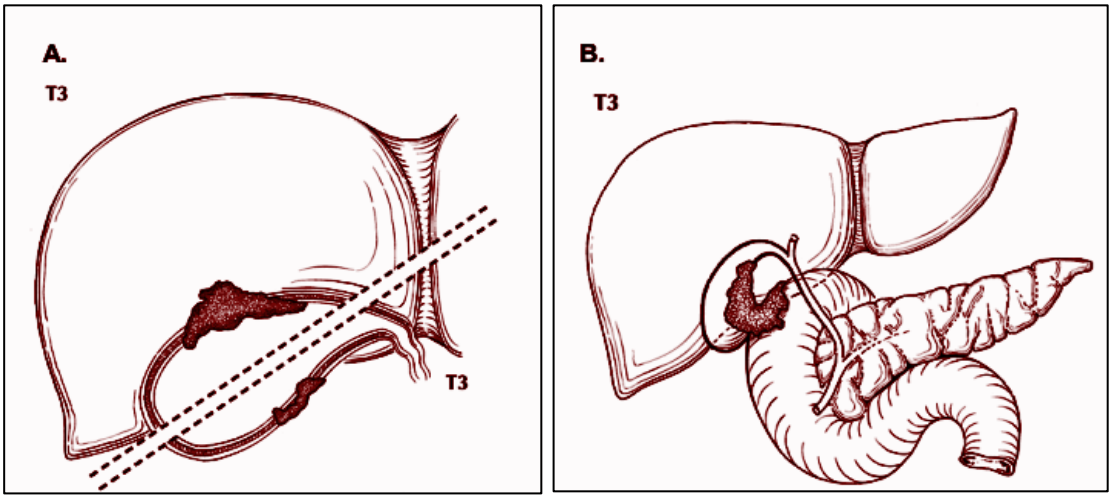

Figure 8. Two views of T3
A. Tumor perforating the serosa (visceral peritoneum) (below dotted line) and/or directly invading the liver (above dotted line).
B. T3 may also be defined as tumor invading one other adjacent organ or structure, such as the duodenum. [29]

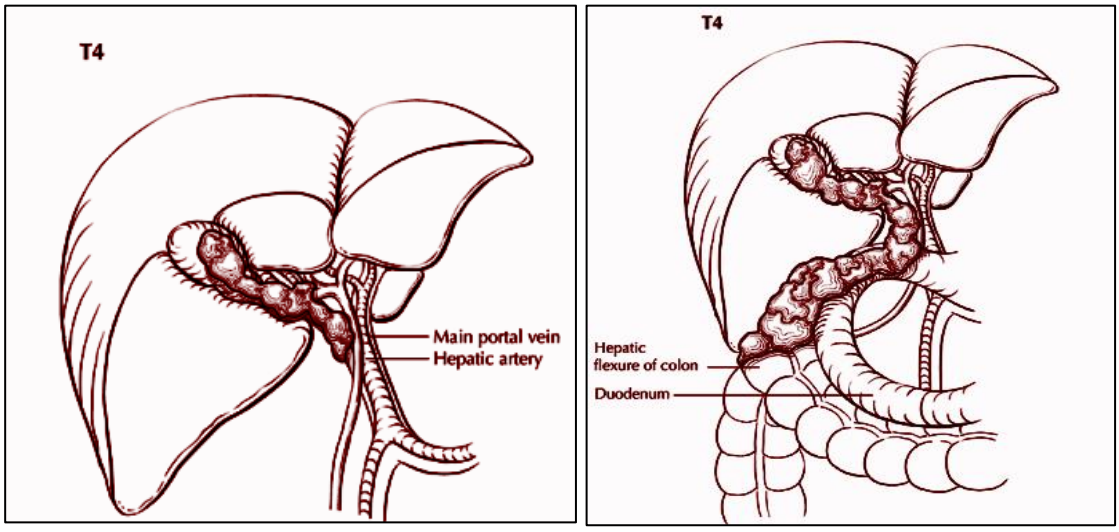

Figure 9: Two views of T4
A. T4 is defined as tumor invading the main portal vein or hepatic artery (illustrated) or invading two or more extrahepatic organs or structures.
B. T4 invading two or more extrahepatic organs or structures (here, invading colon and duodenum). [29]

Protocol for the Examination of Specimens from Patients with Carcinoma of the Gallbladder [30]

Histologic Type:

- For consistency in reporting, the histologic classification proposed by the World Health Organization (WHO) in 2010.
- WHO Classification of Gallbladder Carcinomas
- Adenocarcinoma
- Adenocarcinoma, intestinal type
- Adenocarcinoma, biliary type
- Adenocarcinoma, gastric foveolar type
- Mucinous adenocarcinoma
- Clear cell adenocarcinoma
- Signet-ring cell carcinoma
- Intracystic papillary neoplasm with an associated invasive carcinoma
- Mucinous cystic neoplasm with an associated invasive carcinoma
- Adenosquamous carcinoma
- Squamous cell carcinoma
- Large cell neuroendocrine carcinoma
- Small cell neuroendocrine carcinoma
- Neuroendocrine carcinoma (poorly differentiated)
- Goblet cell carcinoid
- Mixed adenoneuroendocrine carcinoma
- Undifferentiated carcinoma (Tumors with no squamous, glandular or neuroendocrine differentiation have been labeled as undifferentiated carcinomas in the WHO 2010 scheme.)

Histologic Grade:

G1: Well differentiated
G2: Moderately differentiated
G3: Poorly differentiated
GX: Cannot be assessed

Although tumor stage is probably the most important prognostic factor for patient outcome, histologic grade, especially poor differentiation, also has an impact on survival.

Tumor Extension:

- No evidence of primary tumor
- Tumor invades lamina propria
- Tumor invades muscular layer
- Tumor invades perimuscular connective tissue on the peritoneal side without serosal involvement
- Tumor invades perimuscular connective tissue on the hepatic side without liver involvement
- Tumor perforates serosa (visceral peritoneum)
- Tumor directly invades the liver
- Tumor directly invades other adjacent organs or structures

Complete surgical resection with negative margins remains the most effective therapy for gallbladder cancer, with 5-year survival advantages of 30% for patients with negative margins (R0) compared with those with microscopic (R1) or macroscopic (R2) residual disease.

Margins

- Cystic Duct Margin
- Distance of invasive carcinoma from margin (millimeters or centimeters)
- Distance of invasive carcinoma from margin (millimeters or centimeters)
- Liver Parenchymal Margin
- Distance of invasive carcinoma from margin (millimeters or centimeters)
- Lymphovascular Invasion
- Perineural Invasion
- Regional Lymph Nodes

RISK FACTORS OF GBC

Risk factors for GBC include a large variety of clinical conditions, lifestyle behaviours, exposures in environment and lifestyle changes along with other non-modifiable variables.

1) **AGE -** Numerous studies have demonstrated that GBC incidence rises with aging, and advanced age is a known risk factor for the disease. Typically, the age range of 50–55 is the mean/median [31]. Compared to their western counterparts, GBC presenters in India typically present at a decade younger age.
2) **GENDER -** Female are 2-6 times more likely than male to develop GBC. In different Indian series, the women to men ratio ranges from 3:1 to 4.5:1 [32]. Even among women in India, multiparity is linked to a greater risk of GBC. It has been documented that the development of gallstones and subsequent GBC is influenced by estrogen receptors [33].
3) **GALLSTONES -** Gallstone disease is listed as the most prevalent ailment related to GBC. With a history of cholelithiasis reported in 45–60% of gallbladder cancer cases, it represents one of the most consistently associated risk factor for the disease development. Northern India has a twenty-fold greater incidence of symptomatic gallstone disease than South India. In contrast to South India, which has pigment stones, the majority of stones in North India are cholesterol/mixed in nature [34]. Gallstones are thought to cause GBC through an unclear exact mechanism, although chronic mucosal epithelial irritation and damage is frequently suggested as the cause. Gallstone size greater than three cm has been linked to a 9.2 to 10.1 fold higher risk of GBC as opposed to gallstones less than one cm. This is in accordance with several studies that suggest the size of the gallstone is the factor in an important factor contributing to the development of GBC. In addition to size, multiple gallstones, the lengthier duration of their presence, and larger

stone volumes (>6 ml) are all linked to a greater risk of gallbladder cancer [35].

4) **PORCELAIN GALLBLADDER -** Porcelain GB refers to the development of focal or diffuse GB wall calcification, which is thought to be facilitated by persistent low-grade inflammation. Traditionally, rates of GBC development in the setting of porcelain GB have been described to be as high as 25% but according to a recently published systematic review of 111 papers, the rate and incidence of GBC in these situations is only 6%. Currently, no Indian data available about the function of preventative cholecystectomy in patients with porcelain GB.
5) **POLYPS -** Another condition that is frequently seen in clinical practise is GB polyps. About 5% of adult patients have the low overall incidence. GB polyps can be genuine or pseudo-GB polyps, which can be benign or malignant. An example of a pseudo polyp is a cholesterol polyp. Although polyps are typically asymptomatic, numerous studies have linked the presence of GB polyps to patient symptoms; as a result, the available data is inconsistent [36]. Large polyps (>10 mm), solitary polyps, sessile polyps, gallstones, advanced age, and quickly growing size all point to the polyp's malignant character [37]. There are numerous imaging modalities available for polyp diagnosis, such as contrast-enhanced USG (CEUS), high resolution USG (HRUS), and conventional USG. MRI, CT, and EUS. When determining if GB polyps are benign or malignant, endoscopic ultrasound is useful. One study compared the use of CT scan, endoscopic ultrasound (EUS), and HRUS in the 144 patients, staging of gallbladder polyps and diagnosis, all of whom had a polyp larger than 10 mm. Compared to the other two modalities, HRUS had the highest diagnostic sensitivities for malignancy, and the specificity of both EUS and HRUS was the same [38]. Increased vascularity and a hypoechoic, heterogeneous lesion with a ratio of height to width of 0.8 indicate a higher risk of neoplasia. If the polyps imaging suggestive of malignancy, or there is increased thickness of GB wall (>4mm), or there is a malignancy history in family, associated PSC, or presence of Indian ethnicity, cholecystectomy is the best option. Other polyps require close monitoring for three-six months for assessment of growth of polyp [39].
6) **PSC -** An increased chances of developing carcinoma is linked to Primary Sclerosing Cholangitis (PSC), which is linked to bile duct inflammation, fibrosis, and scarring [40,41]. Patients with PSC are estimated to have a two percent lifetime gallbladder cancer incidence and the significance of prophylactic cholecystectomy remains unclear.
7) **APBDJ -** Anomalies in the biliary tree structure, specifically an anomalous pancreaticobiliary junction, are also related to greater risk of developing GBC. The confluence of the pancreatic & biliary ducts is situated outside of the duodenum in this rare congenital anomaly, and the papillary sphincter muscle of duodenum does not cover the entire length of the fused channel between the pancreatic and bile ducts. Because of the increased pressures in the pancreatic duct, this causes continuous backflow of bile and pancreatic juice. The pancreatic fluid constantly irritates mucosa of bile duct, causing injury to bile duct mucosa and inflammation, which stimulates the mucosa to development of carcinoma [42]. However, the rate and incidence of an abnormal pancreaticobiliary junction is extremely low in India. Only 2.6% of 3,827 ERCPs in our country had APBDU [43]. According to Japanese research, a significant number of GBC patients have APBDU [44].
8) **CHRONIC BACTERIAL INFECTIONS -** Gallbladder irritation and inflammation can also result from long-term bacterial infections, which are typically brought on by Helicobacter or Salmonella typhi species. Every Indian study to date has indicated a distinct but minor possibility that cause for gastric cancer is due to H. Pylori infection [45]. A Japanese study also found that, when compared to patients with other gallbladder disorders, correlation was strong (OR 6.5) between H. bilis and GBC [46]. Salmonella typhi (Typhoid) carriers have twelve times fold increased risk to develop GBC. A number of studies conducted in Chile have shown that having a S. typhi carrier state increases the risk of GBC [47]. A recent published meta-analysis involving seventeen studies revealed that the odds ratio (OR) for studies utilizing serology was 3.5 (95% CI: 2.48–5), while the OR for studies utilizing culture techniques was 4.1 (95% CI: 2.41– 7.12) [48]. Non-typhoid salmonella, which are typically resistant to widely used antibiotics and cause persistent GB inflammation, have also become more prevalent.
9) **OTHER RISK FACTORS -** Since diabetes has been linked to obesity and gallstones, it is challenging to prove a link between the two conditions and gallbladder cancer. Weight gain raises the risk of malignancy of gallbladder, according to a sizable body of research. Being obese (BMI ≥30 kg/m2) was related with a 1.69 (95% CI: 1.54– 1.86) relative risk of gallbladder cancer, suggesting a dose-response curve relationship between obesity and risk of GBC [49]. In fact, there was an inverse correlation

between BMI and GBC in 333 patients with GBC in a case control study in large population from India [50]. Drinking alcohol and smoking tobacco are known risk factors for many cancers. With the exception of gallbladder cancer, smoking was linked to an increased risk of all other types of biliary tract cancer, according to a recent meta-analysis of 26 prospective studies assessing the relationship between alcohol consumption and cigarette smoking and biliary tract cancers. The relationships between alcohol and smoking use and the risk of gallbladder cancer require more investigation. Other environmental risk factors that have been suggested for gallbladder cancer include ochratoxin, arsenic, and fungus aflatoxins. As compared to patients without GB stasis, Pandey et al. also demonstrated that patients with GB stasis had higher levels of toxins and heavy metals in their GB bile [51]. A lower socioeconomic status has long been linked to a higher risk of GBC. According to a different study by Dubey *et al.,* 75% of GBC patients are from lower-middle or lower socioeconomic classes [52].

10) **FAMILY HISTORY AND ROLE OF GENETICS** - An increased risk of five times (summary R.R [4.8]; 95% C.I [2.6–8.9) has been linked to first degree relatives with a history of gallstone disease (GSD) or GBC [53–55]. The pathophysiology of gallbladder carcinoma has also been linked to allele-specific mutations [56]. The KRAS oncogene in gallbladder cancer tissue has been found to contain numerous pathogenic mutations [57–60]. Later stages of the disease have a comparatively higher frequency of TP53 mutations [60–65]. MGMT, Methylation of the genes p73 and DCL1 was found to be significantly correlated with patients' survival from GBC in a small number of studies [66–71].

PATHOGENESIS

Having studied the various risk factors of GBC, when one looks into the actual pathogenesis of GBC, there are still many caveats in our understanding and the exact mechanisms remain poorly understood. Regardless of its lithiasic or non-lithiasic origin, chronic inflammation is a significant cause of GBC, it is still evident. It appears to be a complex process wherein interaction of both host and environmental factors take place and lead to cumulative genetic alternations some of which may ultimately trigger carcinogenesis. Physiologically, GB is a part of the GI tract and secretes bile in a concentrated manner into the gut lumen against gravity. Fundus is the most dependent part of GB in straight posture which might increase its mucosal contact time with various toxins and thereby result in fundus being the commonest site of GBC. Contraction of GB is dependent on an endocrine signaling pathway i.e., by the release of Cholecystokinin by the duodenum, which then acts to cause its emptying Combined with the non-peristaltic nature of GB wall musculature and the bile concentrating ability of the GB which also concentrates the toxins, it definitely confers a disadvantage in terms of the emptying process. The mucosal exposure time is further prolonged by the static nature of a diseased GB. In a study by Mano H et al, bile samples from patients in endemic areas were found to be more mutagenic than those from low incidence areas [72]. Gallstones increase the surface area available for bacterial colonization, and their removal with antibiotic therapy is subsequently challenging. Further mutagenesis is caused by stones' promotion of chronic inflammation and mechanical harm.

CLINICAL PRESENTATION

GBC clinical presentation is often non-specific with vague complaints. In some cases, it may mimic symptoms of chronic cholecystitis or biliary colic owing to the presence of concomitant gall stone disease. Because they benefit from earlier disease detection, these patients typically have better long-term survival [73]. According to a study by Gupta S *et al.*, ascites (3%) and right upper quadrant palpable lump (9%), hyperbilirubinemia (jaundice) (8%), and right upper quadrant pain (98%) were the most common complaints among nearly all GBC patients. Numerous other studies, including those conducted by Gupta *et al.,* [74]; Khan *et al.,* [75], reported consistent results. In addition to the aforementioned, systemic symptoms like anorexia and weight loss may also exist. Pruritis, jaundice, and scleral icterus are among the symptoms that can arise from abnormal elevations in bile and may indicate the progression of the disease [76,77]. Because of their close proximity to the extrahepatic biliary tree, tumors at the neck of the GB have a higher tendency to present with preoperative jaundice, in accordance with their anatomic location [78]. However, the most of gallbladder cancer cases are lately diagnosed, which contributes to the disease's bad prognosis, and most cases of GBC remain asymptomatic even at advanced stages. Additionally, gallbladder cancer is known to metastasize quickly and early.

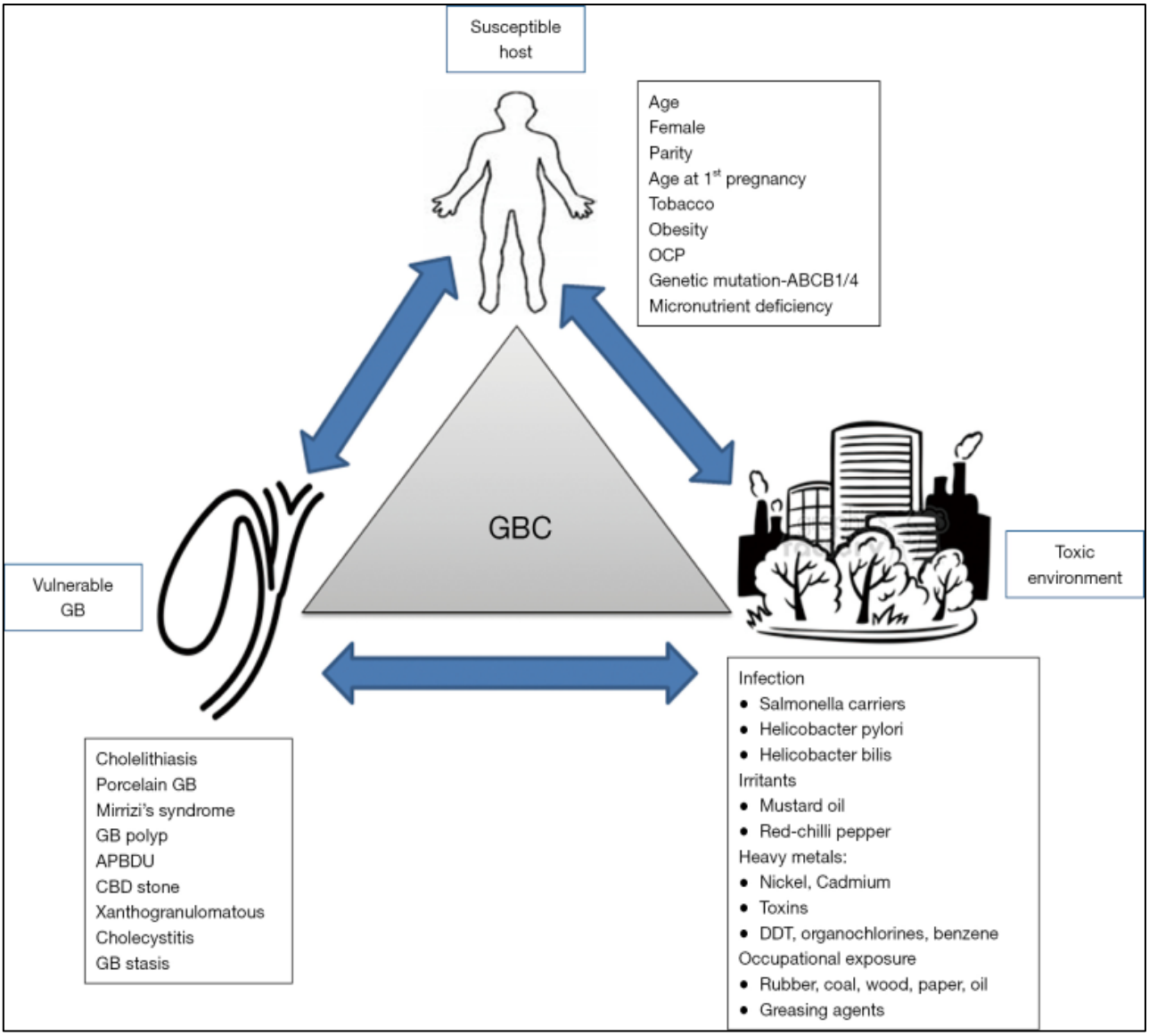

Figure 10: Epidemiological triad depicting risk factors of GBC causation in the Indian setting.

DIAGNOSIS

GBC remains a radiological diagnosis and imaging modalities for evaluation include USG, endoscopic ultrasonography, CT scan and MRI. A mass that entirely fills or replaces the lumen, focal or diffuse asymmetric gallbladder wall thickening, or a polypoid lesion are all possible signs of gallbladder carcinoma using any of these imaging modalities.[79] GBC fills the gall bladder lumen entirely or partially in 40–65% of patients, giving the appearance of a mass. This GBC subgroup usually has simple radiological diagnosis. Focal or diffuse gallbladder wall thickening accounts for 20 to 30% of GBC. GBC is characterized by irregular and asymmetric thickening. But in the early stages of the illness, the thickening of the wall is frequently smooth and indistinguishable from that observed in benign conditions like cholecystitis and adenomyomatosis, as well as systemic conditions like liver or renal failure.[80] Abdominal ultrasonography (US) on healthy adults reveals a 0.3% to 12% prevalence of gallbladder polyps.

A) USG - The first commonest imaging used to assess GB disease is ultrasound. Gallbladder cancer can be diagnosed by USG with 85% sensitivity and an 80% overall accuracy. in cases of locally advanced disease. The sensitivity of USG, however, rapidly declines in the case of tumor which is sessile or flat in its earlier form. The sensitivity of ultrasonography for sessile tumors was 53% in a group of 71 subjects with early-stage GBC [81]. Determining the degree of involvement of the hepatic and biliary arteries or portal veins is another benefit of USG. When compared to conventional ultrasound, high resolution ultrasonography (HRUS) provides more accurate diagnosis because it can see gallbladder wall layered appearance more clearly. This effect results from using a high frequency transducer in addition to the low frequency transducer used in conventional

ultrasonography. Contrast-enhanced ultrasonography (CEUS) is another sophisticated type of ultrasonography that can be used to evaluate gallbladder masses. It enables the gallbladder to be dynamically evaluated, which has demonstrated promising results in separating benign from malignant masses. The detection of increased flow within a lesion and the overall sensitivity of USG as a modality for GBC diagnosis and staging may be enhanced by the use of Doppler USG.

B) ROLE OF EUS - Currently, the gold standard for staging GBC is endoscopic ultrasound (EUS). Gallbladder malignancy could be predicted with similar accuracy using HRUS and endoscopic EUS, according to a study. The corresponding sensitivity values for EUS and HRUS were 86.2% and 86.9%, respectively [82].

C) CROSS-SECTIONAL IMAGING - CT and MR abdominal crosssectional imaging aid in the completion of the staging assessment. When used preoperatively, computerized tomography (CT) can accurately determine whether the gallbladder can be removed, with a 93 percent accuracy rate in identifying any extension to L.N, involvement to liver, or distant metastases. In general, standard MRI is not as useful. With a sensitivity and specificity that are very close to 100%, magnetic resonance imaging (MR) cholangiography and MR angiography can detect bile duct or vascular invasion with remarkable accuracy [83].

D) ROLE OF FDG-PET - An emerging technique that could be helpful in the clinical detection of patients with gallbladder cancer is FDGPET scanning. PET may be useful in identifying primary lesions that are otherwise unclear, in identifying disease that remains in the gallbladder bed following cholecystectomy for a condition that was thought to be benign, and in identifying distant disease that is not visible with traditional imaging techniques. FDG-PET has 80% sensitivity and 82% specificity in detection of gallbladder carcinoma in sixteen patients whose symptoms, USG, and cross-sectional imaging suggested a probable benign gallbladder disease. In a study of fourteen patients with carcinoma of gallbladder, the majority of whom underwent liver resection or a straightforward cholecystectomy, Anderson et al reported a 50% sensitivity in identifying distant metastases or carcinomatosis and 80% specificity for FDG-PET detecting residual primary disease. FDG-PET scanning's function is still being studied, so each patient's use case should be considered.

E) FNAC- To establish the histopathological diagnosis of GBC, the role of FNAC as an evaluation modality was restricted to unresectable lesions. Nevertheless, a recent published systematic review by Koimtzis GD *et al.*, recommended that FNAC be used to further evaluate any suspicious gallbladder polyps or masses. If the test is positive, the patient ought to be subjected to a cutting-edge HPB facility for additional assessment and care. If not, there is no need for additional testing and the patient can be scheduled for a routine cholecystectomy on an elective basis.

STAGING AND BRIEF MANAGEMENT OF GBC

A variety of staging schemes were used to treat gall bladder cancer. Most widely used system is “The American Joint Committee on Cancer (AJCC) staging system”. The AJCC staging system was released in successive editions as a reflection of our growing knowledge of the prognosis and methods of treating gall bladder cancer. The eighth edition of the AJCC staging system, which was released in late 2016, is the most recent version [84]. The 8th AJCC updates some T and N in comparison to the 7th AJCC. For instance, the side of involvement (hepatic vs. peritoneal) determines the division of the T2 stage into T2a and T2b. This modification was made in response to an international multicenter investigation that demonstrated the side of involvement's prognostic value. Similarly, rather than the positive lymph nodes location, positive lymph nodes number is now used to categorize N stage. A revised definition of certain sub-stages within stages II, III, and IV is also provided by AJCC 8th [85]. An overview of the various stage definitions in accordance with the AJCC 7th and 8th is given in reviewed in the following table.

Comparisons among AJCC 7th and 8th editions

The following updated definitions for certain TNM stages were given by the AJCC 8th edition: On the peritoneal side, Tumour T2a invades the perimuscular connective tissue without affecting the serosa.; On the hepatic side, Tumour T2b invades the perimuscular connective tissue without harming the liver; N staging: switch from a location to a number-based approach; N1, being 1-3 regional lymph nodes; N2 being 4+ regional lymph nodes.

In the present study, the recently revised AJCC 8th staging system for carcinoma of gall bladder was compared with the AJCC 7th staging system. It proved that both staging systems' discriminating performances are equal. Furthermore, the 8th edition's change of a number-based Nodal N category rather than a location-based N category assessment showed no improvement the staging system's overall discriminating performance. Adenocarcinoma, papillary, mucinous adenosquamous, signet ring, neuroendocrine, and undifferentiated carcinoma are among the histological types.

MANAGEMENT

Treatment for patients with advanced GBC is still debatable at this time. For patients with GBC, the

only treatment that can possibly be curative is radical surgical resection. Nevertheless, the most of GBC patients are diagnosed in advanced state, which reduces the possibility of radical resection; even when the disease is moderate, patient have a very poor prognosis with radical resection [86].

When treating a malignant gallbladder tumor, full tumor extirpation with negative histologic margins should always be the aim of resection. Incidental detection of GBC on routine post cholecystectomy specimens is not uncommon. In case of T1a disease in such specimens, cholecystectomy suffices and no further treatment is required. Recurrence rates following a straightforward cholecystectomy are between 85 and 100% provided negative margins are achieved, as nodal metastasis is rare in T1a tumors. When it comes to T1b tumors, a basic cholecystectomy might be all that is needed; however, for patients who are medically fit, it makes sense to try a more drastic procedure first. However, in few cases reoperations are required particularly for T2 tumours and beyond, wherein attempts are made to perform liver resections or nodal clearance. A survival rate of 5-year disease free of 51% was linked to surgical resection in a study by Bartlett et al. on the same subject, with a median follow-up period of 48 months [87]. Research indicates that aggressive surgery is useful for T2 tumours; 5-year survival rates after simple cholecystectomy are 20–40% lower than those after en bloc hepatic resection, which are up to 80% higher [88, 89]. A simple cholecystectomy does not treat T3 tumors.

T3 lesions necessitate, at the very least, regional lymphadenectomy and hepatic resection, similar to many T2 tumors. In cases where the cancer spreads extensively into the liver or involves significant vascular structures, a segmental hepatectomy may also be required. Resection and restoration of the bile duct continuity may also be required if the cancer encroaches on the biliary tree. After obtaining total excision, patients with T3 tumors can have 5-year survival rates of between 30 and 50%. An essential part of major surgery for GBC is lymphadenectomy. T stage and frozen section evaluation of significant nodes are used to determine the degree of locoregional resection and dissection of lymph nodes. During a frozen section during a laparotomy, a positive interaortocaval node implies metastatic and incurable GBC. In a "standard" dissection of lymph nodes, the lymph nodes of the peri-choledochal (12b), cystic (12c), hilar (12h), proper hepatic artery (12a), postero-superior pancreaticoduodenal (13a), peri-portal (12p) and common hepatic artery are removed, and the portal vein, hepatic artery and bile duct are skeletonized [90, 91].

In a study done by Shimuzu *et al.*, curative resection was feasible in 75% of patients without infiltration of bile duct and in <30% of cases with bile duct invasion [92]. Thus, there is no additional survival benefit from standard bile duct resection. When there are tumors in the cystic duct or gallbladder neck, CBD resection is advised.

When a patient has involvement in the duodenum, antro-pyloric region of the stomach, or neighboring colon, distal gastrectomy, segmental colectomy, or sleeve resection of the initial part of the duodenum may be added as needed to achieve full resection [93].

There is currently conflicting data regarding the survival rates of these lengthy multiorgan resections, and more research is required in the Indian setting to customize care for each patient.

Although extended multiorgan resections are being performed for advanced GBC, still, most clinicians prefer palliative chemotherapy for the same. The gemcitabine/cisplatin combination is presently the standard treatment for advanced GBC patients; however, there has not been direct correlations to other combinations of gemcitabine (e.g., with leucovorin-modulated 5-FU, capecitabine or oxaliplatin) or capecitabine plus oxaliplatin in a randomized trial. Although there isn't currently a recognized indication for second line therapy for patients with advanced gallbladder carcinoma, clinical trials are being carried out to compare the FOLFOX regimen with best supportive treatment alone [94].

In cases with carcinoma gallbladder (GBC), percutaneous transhepatic biliary drainage (PTBD) is most often done for palliation purposes or for optimization of the patient before surgery or chemotherapy. Nonetheless, complications like bleeding, inadvertent biliary or vascular radicle injury, tube blockade (leading to cholangitis), catheter dislodgment may occur which further decrease the quality of life in such patients [95].

Pain control forms another pillar of palliative care for which the patient might require high level of opioids-based medications. Pruritus due to obstructive jaundice is another debilitating problem which may be decreased following biliary diversion procedures along with other conservative measures like use of antihistaminic medication, calamine lotion and Ursodeoxycholic acid.

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