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Review

Gallbladder Cancer: An Overview of Epidemiology, Risk Factors, and Novel Approaches in Molecular Screening and Treatment Strategies

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Abstract

Gallbladder cancer (GBC) is an infrequent type of malignant neoplasm and ranks fifth among gastrointestinal malignancies in the world. However, GBC is prevalent in India, and population-based cancer registries' (PBCRs) data revealed its higher incidence rate in North India. Due to the fact that the etiology of this cancer is quite complex, the majority of the cases are diagnosed at a very advanced stage owing to a lack of clinical appearance, which is non-specific. The majority of the cases come to light by coincidence at the time of histopathological examination of cholecystectomy. Several risk factors have been reported that may play an important role in the development and progression of GBC. There is a strong association between gallbladder inflammatory diseases (GIDs), including cholelithiasis (gallstones) and GBC. The presence of gallstones increases the risk of GBC more than threefold and appears to be stronger among ethnic groups that have higher rates of GBC. Surgery is the primary treatment that can cure early-stage gallbladder cancer. Apart from surgery, the use of immunotherapy, molecularly targeted medications, and new developments in radiation and chemotherapy (neoadjuvant-adjuvant gemcitabine, cisplatin, and capecitabine) has made gallbladder cancer treatment more promising in recent years, but there is still insufficient evidence to support their ability to improve patient outcomes, so more research is needed to address these issues; therefore, customized care needs to be used.

1. INTRODUCTION

The gallbladder is a small, pear-shaped organ on the right side of the body, under the right lobe of the liver. It is part of the digestive system and stores about 50 ml of the bile produced by the liver until the body needs it for digestion. The structure measures approximately 7–10 cm in length and about 2.5 cm in width, exhibiting a dark green coloration in humans. Before a meal, the gallbladder contains bile to its maximum; it squeezes all its bile into the small intestine through ducts. The gallbladder itself is not essential for the body, but it helps in fat digestion [1]. The gallbladder includes the fundus, body, and neck; the cystic duct, which in turn links to the common hepatic duct, which eventually becomes a common bile duct; and the tapering neck is connected to the biliary tree. Usually, the gallstones become lodged in the mucosal fold at the

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gallbladder's neck. The tissue layers that make up the gallbladder include serosa, perimuscular, muscular, and mucosal layers. All three organs—gallbladder, liver, and small intestine—are connected by numerous thin tubes called ducts. The common hepatic duct drains the bile from the liver via the left and right hepatic ducts. The cystic duct joins the gallbladder to the common bile duct. The common bile duct is where the hepatic and cystic ducts meet and connect to the small intestine. The gallbladder and bile ducts together are known as the biliary system or biliary tract. The gallbladder stores and concentrates bile; it is a fluid made in the liver. In response to signals, the bile squeezes out of the gallbladder to the intestine through ducts. Bile helps digest fats, but the gallbladder itself is not essential. Gallbladder removal from a healthy person shows no harmful effect, except for a slight chance of malabsorption and diarrhea.

The gallbladder is considered a typical and anatomically "busy" area. This is because of the presence of the adjoining bile duct, portal vein, liver, duodenum, and colon. It is a partially intraperitoneal structure lying attached to the undersurface of the liver on segments IVb and V. The wall of the gallbladder is thin (<3 mm) and composed of a single-layered columnar lining, a thin lamina propria, a thin muscle layer, and serosa. Absence of the serosal layer in the area where the gallbladder is in direct contact with the liver allows early hepatic invasion. Also, some of the cholecystic veins directly drain into the liver bed, facilitating tumor metastasis [2]. This forms the basis behind segment IVb and V resection, even in patients with early GBC. Lymphatic drainage of the gallbladder is extensive and in multiple directions, facilitating early lymphatic spread. According to a study, patients with GBC have a 91% to 94% incidence of lymphatic metastasis, a 65% to 82% incidence of hematogenous spread, and a 60% incidence of peritoneal spread [3].

2. EPIDEMIOLOGY

2.1. Geographical Distribution and Incidence of GBC globally

In 2020, out of 19.3 million cancer diagnoses worldwide, 10 million deaths were attributed to the disease [4]. Additionally, GBC is responsible for roughly 1.3% of all cancer cases and 1.7% of all cancer-related deaths globally [5]. GBC is the most common malignant neoplasm of the gastrointestinal tract. The incidence of GBC varies globally; it varies 20-fold based on the geographic region. As per GLOBOCON 2018, 291,420 new cases of GBC were reported worldwide [6]. Many affluent nations, including South Korea, the United States, Canada, the United Kingdom, New Zealand, and Australia, have been looking at the prevalence of GBC [7]. For each country, the age-standardized rate (ASR) of incidence varied from 14.0 (Bolivia) to 0.03 (Guinea), with an incidence of 2.3 per 100,000 people (Fig. 1). Middle Africa (0.35), West Africa (0.37), and Eastern Africa (0.74) had the lowest ASRs, whereas Eastern Asia (3.0), South America (2.8), and Melanesia (2.7) had the highest. This indicates a variation of almost nine times between places. Overall, females had slightly higher incidence rates (2.4) than males (2.2). Countries with Very High (2.5), High (2.4), and Medium (2.0) human development index (HDI) had higher incidences (ASRs) than those with Low (0.55) HDI.

For each nation, the ASR of death was 1.7 per 100,000 people, ranging from 10.6 (Bolivia) to 0.01 (Guinea). The continents of South America (2.0), Melanesia (2.3), and Eastern Asia (2.4) had the greatest ASRs, whereas West Africa (0.28) and Middle Africa (0.29) had the lowest. The variance between the various regions was almost eight times. Like incidence, females had somewhat higher overall death rates (1.8) than males (1.6). Countries with High (1.9), Very High (1.5), and Medium (1.5) HDI had higher mortality rates (ASR) than those with Low (0.45) HDI [8]. Among Chilean women, GBC is the leading cause of cancer death. Other high-risk regions for GBC were Eastern Europe (14/100,000 in Poland), Israel (5/100,000), and Japan (7/100,000). Recently, the incidence of GBC is alarmingly increasing in China; the rate has almost doubled over 20 years compared to the risk of cancer mortality in people who were born in the Indian subcontinent but migrated to England and Wales and found that there was a substantially increased risk of GBC in females of Indian ethnicity compared to other British ethnic migrants [9].

2.2. Incidence of GBC in India

According to the Indian Council of Medical Research, the average age-adjusted the rates of GBC among women of North and Northeast India are 11.8/100,000 and 17.1/100,000 population. Several studies have reported that the incidence of GBC varies within a country; the highest incidence of GBC was found in North India, the Gangetic basin, Uttar Pradesh (65%), and Bihar (51.7%). [10]. Cancer registries of the Indian Council of Medical Research (ICMR 1990-96) show a 10 times lower incidence of GBC in South India as compared with the northern population. However, the latest report of the ICMR population-based registry clearly divides Indian

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regions into high-risk and low-risk areas for GBC [11]. Detailed geographic tracking of 773 GBC patients attending Tata Memorial Hospital in Mumbai between 1990 and 1995 showed that the majority of patients hailed from Uttar Pradesh (41%), Bihar (35.8%), West Bengal (8.1%), and parts of Madhya Pradesh (7.3%) and Assam (7.0%) [12]. In North India, the ASR of GBC is 11.8 per 100,000 people, while in the northeast, it is 17.1 per 100,000 people [13].

The states of Jammu & Kashmir, Punjab, Haryana, Himachal Pradesh, Uttarakhand, Uttar Pradesh, Bihar, Bengal, Assam, and Manipur are among the high-risk areas. Many of these states are situated near the rivers, the Sutlej, Ganges, Yamuna, and Brahmaputra, and get polluted due to human waste and industrial pollutants [14]. Blood and tissue samples from GBC patients are discovered to contain higher content of carcinogenic adulterants in mustard oil, such as diethyl nitrosamine and sanguinarine, than those from cholelithiasis patients [15]. The Ganges is known to contain high concentrations of carcinogenic chemicals, heavy metals, and nitrates. Additionally, biliary concentrations of these pesticides and nitrates are greater in patients with GBC than in those with gallstones without GBC [16].

The reason for the regional difference in the incidence rate of GBC in North and South India is not clear. Furthermore, GBC is more common in the western India population who has migrated from high-risk regions than natural residents of the region. Migration from high-risk region to low-risk region resulted in individuals carrying higher susceptibility even when they moved to lower risk regions (OR 1.36; 95% CI: 1.02–1.82) The risk was maximum amongst those who always lived-in high-risk region compared to those who never lived in high-risk region (OR 5.58; 95% CI: 4.42–7.05). Indians migrating to other countries also carry a high-risk for GBC [17] (**Figure1**).

3. MOLECULAR PATHOGENESIS INVOLVED IN GBC

GBC is a complex illness with several different genetic alterations. Gallstone-induced chronic inflammation of the gallbladder is frequently the etiology of gallbladder cancer, especially adenocarcinoma. This persistent inflammation causes molecular and genetic alterations that eventually give rise to malignant cells. Dysplasia (abnormal cell growth), metaplasia (change in cell type), and ultimately cancer are common stages of the process. Despite numerous research studies, there is still a requirement for further specific research to fully understand the genetic and molecular alterations in GBC. Delving in depth, it was found that oncogene activation, tumor suppressor gene (TSG) inactivation, microsatellite instability, and epigenetic modifications primarily due to aberrant promoter methylation of gene regions are among the prevalent abnormalities that might be responsible for GBC development [18]. The protein-tyrosine kinases known as the ERBB2/ERBB3 proteins are essential for controlling the cell cycle through the PI3K/AKT/mTOR pathway. When activated, they undergo hyperphosphorylation, which causes the protein complex to become hyperactive. This, in turn, triggers the PI3K/AKT/mTOR pathway, which results in unchecked cell division [19, 20]. A recent study performed whole genome sequencing on genes bearing the most pathogenic and oncogenic relevant mutations and found eight genes (*TP53, SMAD4, ERBB3, KRAS, ARID1A, PIK3CA, RB1, and AXIN1*) showing critical functions in promoting GBC development in the North Indian population [21]. GBC has molecular variations based on ethnicity, just like other gastrointestinal cancers. According to current research, the most genomic alteration was observed in *TP53* (69% and 58%, respectively) and *CDKN2A/B* (26% and 25%, respectively) in 108 Chinese and 107 GBC patients from the USA. Other alterations in the Chinese population included *ERBB2* (19%), *PIK3CA* (17%), and *CCNE1* (13%), while in the US population, *SMAD4* (17%), *ARID1A* (14%), *PIK3CA* (14%), and *ERBB2* (13%) [22]. Javle and colleagues discovered that in nearly 16% of GBC patients, somatic copy number changes could impact *ERBB* family genes and associated pathways [23]. However, a whole-exome sequencing investigation of 157 GBC patients revealed that 7% and 8% of them had *HER2* and HER3 mutations, respectively. This study further validated the prognostic significance of HER/HER3 mutations (median overall survival 8.0 vs. 12.3 months in patients without mutation) [24]. According to a recent study, a significantly higher level of VEGF was observed in serum samples of GBC patients, reducing apoptosis in GBC cells while promoting angiogenesis, cell proliferation, and invasion. Patients with gallbladder cancer (GBC) who have higher serum vascular endothelial growth factor-C (sVEGF-C) levels are at a higher risk of lymph node metastases and have a worse prognosis [25, 26]. Proto-oncogene c-MET, when attached to its receptor hepatocyte growth factor (HGF), activates PI3K/AKT and MAPK/ERK pathways; moreover, HGF induces cell growth, resistance to apoptosis, and invasion. In a study involving 113 GBC patients, the authors discovered that c-MET gene amplification was linked to aggressive clinicopathological

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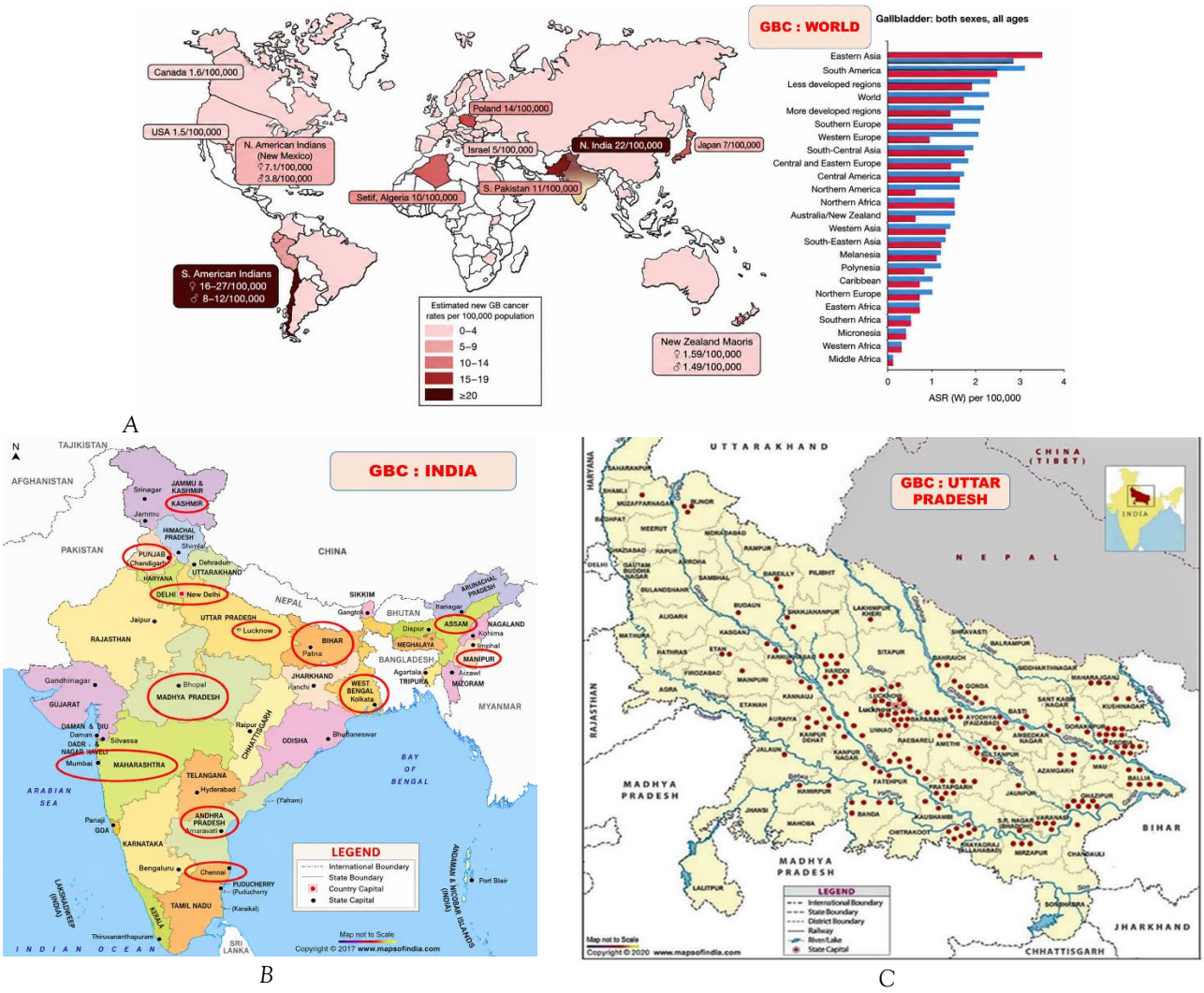

Figure 1. Geographical distribution of gallbladder cancer. [A] World, [B] India, [C] Uttar Pradesh. *References Epidemiology of gallbladder cancer in India. Dutta et al. Chinese Clinical Oncology 2019 and Epidemiological and Geographical Profile of Gall Bladder Cancer Patients from a Hospital-based Registry of Northern Gangetic Plains. Singh et al. Asian Pac Environ Cancer, 2022.*

characteristics and a poor prognosis, while c-MET overexpression was seen in 39.8% of the cases [27]. BRCA1 and BRCA2 mutations were detected in 0.3% and 4% of the 353 GBC cases. Additionally, a correlation between *BRCA* mutations and high microsatellite instability /deficient MMR was noted throughout the entire biliary tract cancer BTC case series, indicating that checkpoint targeting may be beneficial for a subset of BTC patients [28]. In a study of 66 patients with GBC, 54% of patients had IHC-positive results for PD-L1 expression; specifically, tumor cells and peritumoral immune stroma showed 18% and 36% positivity, respectively [29]. Subsequently, PD-L1 expression on cancer cells and tumor-infiltrating lymphocytes (TILs) and PD-1 expression on TILs were examined in a study with 83 GBC patients. Expression levels were discovered to be 15.7%, 13.3%, and 51.8%, respectively [30].

In gallbladder cancer tissue, several harmful mutations in the *KRAS* oncogene have been documented [31]. In GBC, *KRAS* gene mutations primarily impact codons 12, 13, and 61. *KRAS* codon 13 mutations are more prevalent (about one-third) in North India than codons 12 and 61

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[32]. However, no mutations in this gene have been found in numerous additional studies. The majority of TP53 mutations linked to GBC are missense mutations, which result in a protein with a longer half-life that is not functional. According to the research currently in publication, between roughly 27% and 70% of gallbladder carcinomas include TP53 gene alterations [33]. Disease-causing mutations in this gene impact a large number of TP53 codons. Functional molecular research has found that the TP53 gene is deregulated when mutations occur in exons 5 and 8. Transgenic mice used in animal model research have demonstrated that GBC developed in all (100%) of the mice as a result of erbB2 overexpression in the basal layer of the biliary tract epithelium. Additionally, 28% of GBCs had positive HER2/neu expression, which was directly associated with an advanced stage of the malignancy [34]. Moreover, it is speculated that the progression of gallbladder cancer is linked to certain oncogenes. A previous study found that therapeutic targeting of the *EGFR/HER2* pathways increases gemcitabine's anti-proliferative activity in gastrointestinal cancer, including GBC [35]. Recurrent mutations in the ErbB pathway were discovered in one of the first investigations by a Chinese population that was published in Nature Genetics utilizing a high-throughput technique [36]. Multivariate analysis revealed that the MGMT gene was an independent predictor of survival, highlighting the critical role that the epigenetic process plays in the development of GBC [37]. Gallbladder carcinogenesis is significantly influenced by promoter methylation of certain genes, such as *CDH1, CDKN2A-p16, REPRIMO* (cancer suppressor genes), and *UCHL1* (also known as PGP9.5) [38]. Furthermore, very high frequencies of 3p (100%), 8p (100%), 9q (88%), and 22q (92%) sites in gallbladder cancer were examined with the aid of cutting-edge technologies such as high-resolution allele stratification (allelotyping analysis), which resulted in the positional identification of tumor suppressor genes linked to GBC malignancies and pathogenesis. Additionally, certain popular tumor suppressor genes found in chromosomes such as 3p, 5q, 8p, 13q, and 18q can also affect the development of gallbladder cancer [39]. Gallbladder contractility, steroidogenesis, lipid transport, bile acid production, bile canalicular transport, cell cycle, DNA repair, and the inflammatory pathway are among the classical rate-limiting enzymes and proteins for which the majority of candidate genes have been found so far. There are currently very few independently replicated studies in GBC, such as those on *OGG1rs1052133, TP53rs1042522, GSTM1* null polymorphism, and CYP1A1rs1048943 polymorphism, which have been reported [40]. A single genome-wide association research identified that the SNP (rs7504990) in the DCC gene is found to have a six-fold increased risk of GBC in Japan [41]. A haplotype analysis of the DCC gene revealed the cumulative effect of the Grs2229080-Ars4078288-Crs7504990-Ars714 haplotypes in the predisposition to gallbladder cancer, but the study did not show any association between DCCrs7504990 and GBC [42]. A recent review states that miRNAs (miRs) influence molecular pathways that may be therapeutically addressed for gallbladder cancer (GBC) and highlights the necessity of precision medicine to target powerful pathways, using not simply blocking receptors or antibodies but also looking into miRs as a possible therapeutic approach [44]. Furthermore, miR sequencing to identify miR-modulated pathways that may be the focus of GBC treatment has been studied [45]. However, the genetic factors responsible for GBC are still under investigation.

4. HISTOPATHOLOGY AND STAGING OF GBC

Some research indicates that over the course of around 10 to 15 years, the dysplasia-carcinoma pathway in GBC may go from dysplasia to carcinoma in situ and finally to invasive carcinoma. Severe dysplasia and carcinoma in situ have been found in more than 90% of gallbladders that contain GBC. Further, adenoma in the gallbladder also has been previously reported to be a precancerous lesion, but molecular analysis does not show the genetic changes in adenoma associated with GBC [45]. More than 80% of GBC are adenocarcinomas; they can be categorized into papillary, tubular, mucinous, and signet cell types. Less common types are undifferentiated or anaplastic carcinoma, squamous cell carcinoma, and adenosquamous carcinoma. There are few rare types of GBC, such as small cell carcinomas, lymphomas, and sarcomas. Neuroendocrine tumors of the gallbladder have also been described in available literature [46]. Most cancers originate in the fundus (60%), 30% in the body, and 10% in the neck of the gallbladder [47]. The commonest predisposing conditions in the decreasing order are gallstones, APBDJ, and gallbladder polyps. The adenoma-carcinoma sequence has been found in gallbladder polyps and seen in less than 1% of cases. (**Figure 2**)

In 2018, the eighth edition of the American Joint Committee on Cancer (AJCC) was published, which is a simplified Tumor Node Metastasis (TNM) classification (**Figure 3**) and is presently the most widely used system. When restricted to the gallbladder wall, primary GBC is regarded as early-stage (Tis, T1, T2), whereas T3 and T4 lesions signify advanced GBC that has penetrated the

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wall and infiltrated nearby tissues or organs. GBC categorized as stages I or II are potentially resectable with curative intent; stage III generally indicates locally unresectable disease as a consequence of vascular invasion or involvement of multiple adjacent organs; and stage IV represents unresectability with distant metastases [48].

5. CLINICAL PRESENTATION

GBC has been quite difficult to diagnose in the early stages, as the symptoms and signs are vague and non-specific. This is probably due to coexisting stone disease, inflammation, or both, which can produce similar symptoms. The clinical difference between benign and malignant disease is probably only when carcinoma has advanced enough to produce persistent pain or a palpable mass. In a large series, it was suggested that clinical signs mimic benign gallbladder disease until the invasion of surrounding structures gives a clue regarding the correct diagnosis. The most common symptoms at presentation are abdominal pain or biliary colic. Patients with advanced disease may also present with jaundice, either from direct invasion of the biliary tree or from metastatic disease to the hepatoduodenal ligament; systemic signs, such as malaise and weight loss, may also be present [49].

6. ETIOLOGY/RISK FACTORS FOR GBC

Numerous etiological factors are linked to GBC, making it a complex disease. However, little is known about the underlying mechanisms of GBC pathogenesis. GBC is linked to both genetic and environmental risk factors, including lifestyle factors like food habits, obesity, and diabetes that can be avoided, as well as unpreventable risk factors including age, gender, ethnicity, region, and family history [50]. The main etiological variables linked to GBC are cholelithiasis, calcified or Porcelain Gallbladder, Gallbladder Polyp, bacterial infections environmental pollutants, female gender and family history.

6.1. Cholelithiasis (Gallstones)

The presence of long-standing gallstones in gallbladder is considered as the most important risk factor for the development of GBC [51]. This association is seen in 60-90% of cases in different populations around the world. The incidence of GBC parallels the prevalence of cholelithiasis [52]. However, the incidence of GBC is out of proportion to the prevalence of gallstones in India [53]. The risk of GBC is directly proportional to the size of gallstones [54]. The relative risk of GBC in subjects with gallstones >3cm in size is found to be 9.2-10.1 times more as compared to subjects with gallstones smaller than 1cm. The relationship seems to depend on how long the stones stay in the gallbladder, and found no relationship between gallstone size and GBC [55].

It is typically recommended that gallstones that are asymptomatic, do not require surgery [56]. Controversial studies in regions with a high incidence, like North India, suggests it removal. This is because these galltones may create abnormal pathology and frequently lead to cancer if treatment is not received [57]. In a large human study, cholelithiasis and cholecystitis have been found to produce a series of pathologic changes such as simple epithelial hyperplasia, atypical hyperplasia, and carcinoma in situ, which represents the precancerous conditions of GBC [58]. However, several other factors may be important in the development of gallbladder carcinoma because about 10–25% of patients with this disease do not have associated cholelithiasis and only a small proportion (1–3%) of patients that do have gallstones actually develop cancer. Some ethnic and racial groups have higher incidences of gallstone-related carcinomas suggesting that other environmental or genetic factors may contribute to gallbladder carcinogenesis in patients with cholelithiasis, and hence a matter of investigation **(Figure 4)**.

6.2. Calcified or Porcelain Gallbladder

Calcification of the gallbladder wall (porcelain gallbladder) is a relatively rare disease and is usually asymptomatic. Porcelain gallbladder has been associated with carcinoma in 12·5–62% of patients. GBC incidence is low with diffuse intramural calcification (type I; complete) as compared to selective mucosal calcification (types II and III; incomplete) [59].

6.3. Gallbladder Polyp

The presence of polyps is another predisposing factor for GBC, and polyps with a diameter larger than 10 mm have the greatest malignant potential. Removal of the gallbladder is recommended if a polyp is diagnosed in asymptomatic patients, even in the absence of gallstones. Small polyps (less than 10 mm in diameter) need to be removed only if they are producing symptoms or are associated with gallstones. Gallbladder polyps are relatively common and are found in 3 to 6% of the population on sonographic examination. The majority of gallbladder polyps are benign without malignant potential, while adenomatous polyps with malignant potential are observed only in approximately 1% of cholecystectomy specimens. Surgical treatment is advised for polyps that exceed 1.0 (in number), polyps with a

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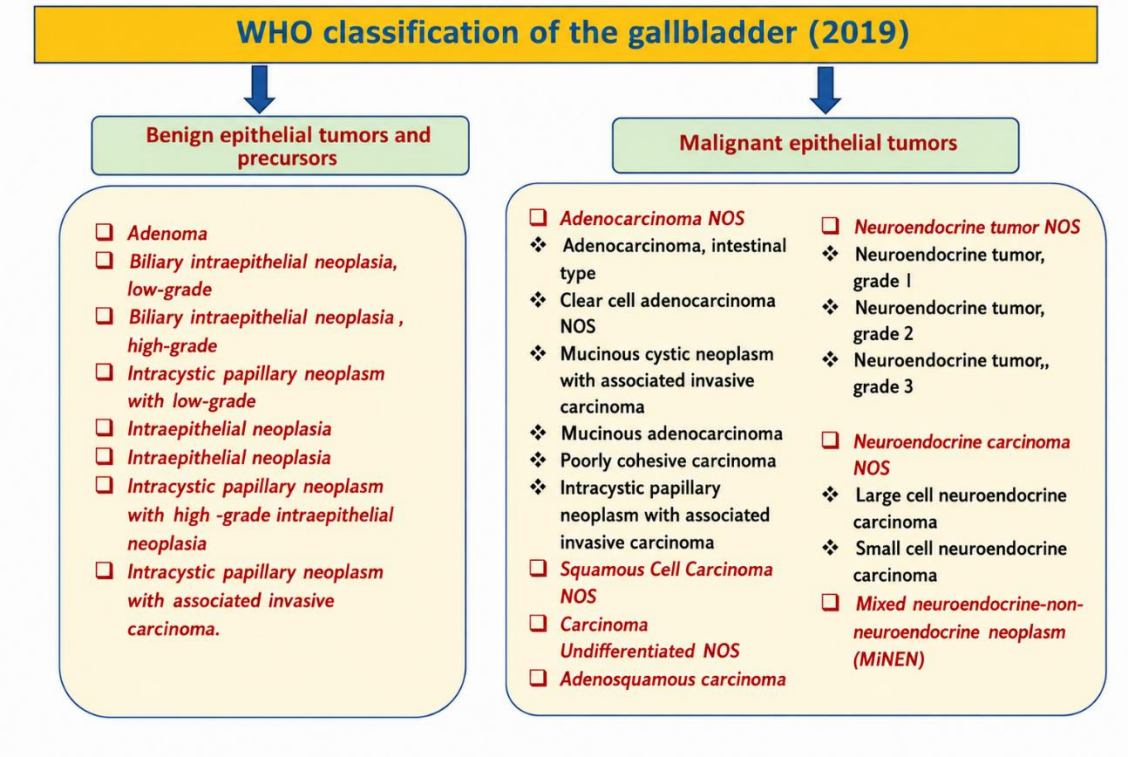

Figure 2. World Health Organization (WHO) classification of the gallbladder (2019)

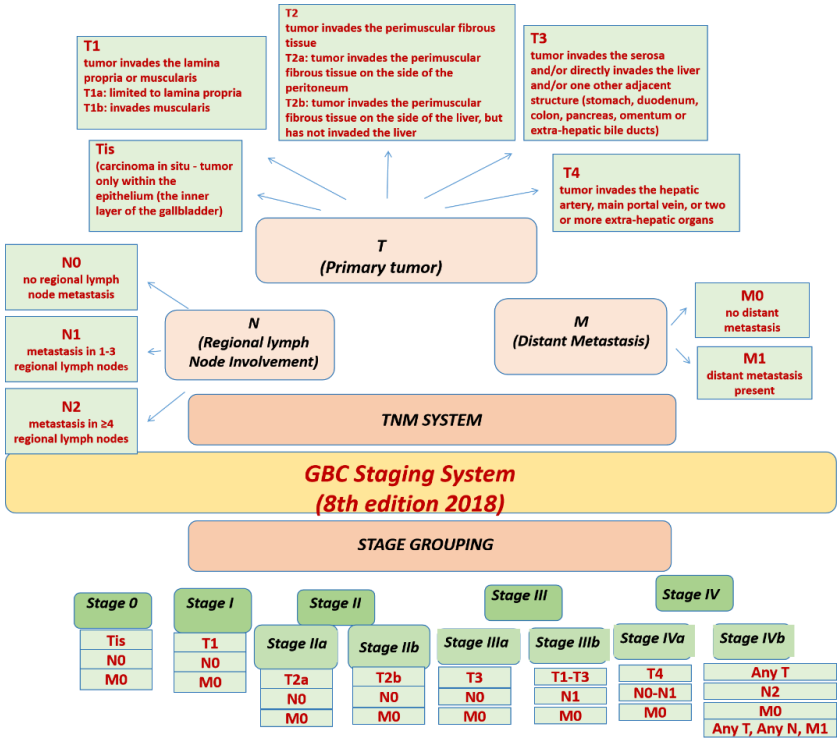

Figure 3. American Joint Committee on Cancer (AJCC), 8th edition TNM staging system for gallbladder cancer.

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diameter >1 cm, associated gallstones, elderly patients (age >50 years), and when clinical symptoms are apparent [60].

6.4. Anomalous pancreaticobiliary duct junction

Anomalous Pancreatico-Biliary Duct Junction (APBDJ) is a rare congenital malformation of the biliary tract. It is

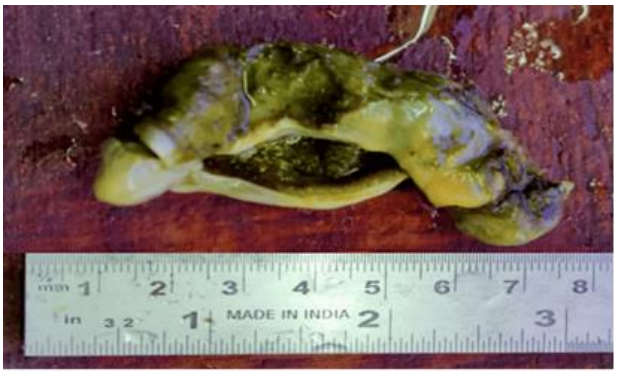

Figure 4. Gross morphology of GBC associated with cholelithiasis.

defined as the junction between the choledochus and the pancreatic duct outside of the duodenal wall and beyond the influence of the sphincter. Studies have suggested that APBDJ is a risk factor for GBC. It is thought that this anomalous junction allows the free reflux of pancreatic juice into the gallbladder, the stasis of which damages the gallbladder mucosa and causes precancerous changes [61].

6.5. Chronic Infections

Chronic infection by Salmonella (S. typhi and S. paratyphi) and Helicobacter (H. bilis and H. pylori) has been associated with an increased risk of GBC. Studies from India also found a risk of developing GBC in positive H. pylori carriers [62]. Recent PCR-based studies show an association between the presence of Helicobacter species in bile and the development of GBC [63, 64]. A recent study conducted on the North Indian population revealed a controversial result: it could not find any significant association between the presence of *H. pylori* infection and GBC [65]. The production of secondary bile acids by bacteria from the breakdown of main bile acids is linked to carcinogenesis through a number of pathways, such as producing DNA damage and oxidative stress, encouraging chronic inflammation, and damaging cell membranes. Deoxycholic acid and other secondary bile acids have the ability to promote tumor growth, and elevated levels of these acids are associated with a higher risk of GBC.

6.6. Environmental exposures and other factors

GBC occurs due to several environmental factors, especially exposure to environmental pollutants. Patients with GBC have been identified in the textile, shoe, chemical, paper, and oil manufacturing sectors, suggesting occupational exposure to chemical carcinogens. Studies show the involvement of heavy metals in the development of GBC. In Indian GBC, chromium, lead, arsenic, and zinc are heavy metals that can cause cancer in endemic regions. Other risk factors that might be associated with GBC are diet, family history, obesity, and tobacco use.

7. DIAGNOSIS OF GBC

The gallbladder is an inaccessible organ from the perspective of histology. GBC patients can be present with one of the three different clinical scenarios: (1) malignancy suspected preoperatively; (2) malignancy found at the time of cholecystectomy for presumed benign disease; and (3) malignancy diagnosed incidentally on pathological examination after simple cholecystectomy for cholelithiasis. Most cases of GBC (about 75%) are diagnosed when the disease is beyond the limits of resection. The following modalities play an important role in diagnosis and staging, as well as follow-up.

7.1. Ultrasonography

It is usually the initial screening modality. GBC may have three distinct appearances on ultrasound: (1) a mass replacing the gallbladder or invading the gallbladder bed, (2) an intraluminal gallbladder growth or polyp, or (3) asymmetric gallbladder wall thickening. Ultrasound has a sensitivity of 85% and an accuracy of 80% for the diagnosis of GBC. The addition of high-frequency probes, color Doppler, and the use of contrast agents has enhanced the discriminative ability of ultrasound [66].

7.2. Computed tomography (CT)

It can accurately detect gallbladder abnormalities and the extent of disease. The main purpose of CT is to evaluate the extent of tumor growth and establish whether there is direct infiltration into adjacent tissues or vessels, nodal involvement, and distant metastases. It has proved extremely useful for assessing the extent of resection in patients with advanced disease. However, a CT scan is poor in detecting small metastases on the liver surface and peritoneal metastasis.

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7.3. Magnetic resonance imaging (MRI)

It is another modality for evaluation of GBC. Its sensitivity for hepatic invasion is 70-100%, and for lymph node metastasis, it is 60-75%. However, it does not offer any additional benefits over a CT scan for preoperative staging.

7.4. Magnetic resonance cholangiopancreatography (MRCP)

It can provide more detailed information than ultrasonography or CT, and this technique has replaced the more invasive cholangiography at many centers. [67]

7.5. Positron emission tomography (PET)

It is an attractive imaging modality, as the tumor cells show an avid uptake of fluorodeoxyglucose. It is useful in differentiating malignant from benign disease, preoperative staging, and detecting postoperative residual disease. PET is better than CT in detecting lymph nodal involvement and distant metastasis and can be combined with a CT scan to provide structural and functional assessment in a single setting. PET-CT is a useful technique for post-therapy surveillance for recurrence in GBC patients as well as for ruling out metastatic disease when choosing individuals for surgery. The precise function of PET-CT in this illness may eventually be clarified with the aid of larger prospective investigations [68].

7.6. Fine needle aspiration cytology (FNAC)

It is useful in establishing the diagnosis in patients with unresectable GBC. Though safe, it has limited utility in obtaining diagnostic tumor tissue due to the fear of dissemination along the needle tract.

7.7. Endoscopic ultrasound (EUS)

It has emerged as an important tool to diagnose early GBC, stage GBC more accurately than a CT scan, and provide direct access to GB and lymph nodal tissue through fine needle aspiration. The accuracy of EUS staging is 100% for tumor in situ (Tis), 76% for T1, 85% for T2, and 93% for T3–4.

7.8. Tumor markers

CEA, CA-19-9, CA-125, and CA-242 have been extensively studied. CA 242 is particularly useful in differentiating malignant from benign biliary disorders with a specificity of 84%. It performed better than CA 19-9 or CEA. These markers may have a role in assessing tumor burden and response to therapy. Bile obtained during endoscopic retrograde cholangiography can be centrifuged and analyzed for malignant cells as well as molecular markers such as hTERT and others. However, the technical difficulties as well as low diagnostic yield have precluded their routine use.

8. TREATMENT FOR GBC

8.1. Surgical therapy of GBC

Surgical resection remains the mainstay of therapy for GBC. With laparoscopic cholecystectomy emerging as the gold standard for treatment of benign gallbladder diseases, the issues related to GBC need to be viewed with a different perspective. It has been recently recognized that even with early carcinoma gallbladder (Stage I, II), where cholecystectomy alone is considered sufficient treatment, patients develop dissemination in the form of port site metastasis.

A simple cholecystectomy is curative for Tis and T1a tumors, and result in a 100% 5- year survival. These tumors are recognized incidentally at the time of histopathologic examination, and as long as the cystic duct margin is negative, no further surgery is indicated. Lymph node metastasis is almost nonexistent in the setting of T1 disease. Patients with T2 tumors are best treated with an extended cholecystectomy. In a multiple institution review of 1686 GBC resections in Japan, the authors reported 12.8% morbidity for a simple cholecystectomy, 21.9% for extended cholecystectomy, and 48.3% for hepatic lobectomy. The mortality rates were 2.9%, 2.3%, 18% respectively. They reported a series of 150 hepatopancreaticoduodenectomies for GBC with 54% morbidity and 15.3% mortality [69].

8.2. Neoadjuvant chemotherapy

Neoadjuvant therapy is preoperative treatment intended to decrease tumour growth, improve survival, and increase the likelihood of complete surgical resection (R0 resection). it is being investigated more and more, especially for locally advanced or marginally resectable instances of gallbladder cancer. Select cases of incidental GBC discovered after cholecystectomy with high-risk characteristics (e.g., T2b/T3, positive margins, lymphovascular invasion), locally advanced (T3/T4) GBC without distant metastases, and borderline resectable tumours involving nearby organs or vessels are candidates for neoadjuvant therapy. Gemcitabine and cisplatin were the most often utilised neoadjuvant chemotherapy medications. Although neoadjuvant

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chemotherapy has been demonstrated to increase survival for other cancers, there is little data to support its use in advanced gallbladder carcinoma [70]. Over the last ten years, research has demonstrated that neoadjuvant chemotherapy will only help patients with advanced gallbladder cancer who will eventually undergo a R0 resection [71,72]. Furthermore, Tata Memorial Hospital developed criteria, which emphasise the need for neoadjuvant treatment in cases of advanced gallbladder cancer and high-risk factors for disease recurrence based on clinicoradiologic characteristics [73]

8.3. Postoperative Adjuvant Therapy

The high incidence of locoregional spread and recurrence rates in patients with GBC makes adjuvant chemotherapy and radiotherapy a very rational and attractive therapeutic option. Many studies include attempts at therapy with intraoperative or external-beam radiotherapy and chemotherapy, including 5-fluorouracil and/or mitomycin C. However, GBC is generally considered relatively radioresistant, although the studies are too few and too small to allow any effective judgement of the value of various types of radiotherapy. Adjuvant chemotherapy and/or radiotherapy have not altered the dismal prognosis of patients but may marginally improve survival. The three classes of cytotoxic agents used are gemcitabine, fluoropyrimidines, and platinum compounds. A recent landmark study established the combination of gemcitabine and cisplatinum as the standard of care for GBC [74]. There is a paucity of quality data regarding the role of adjuvant radiotherapy for GBC. In a meta-analysis of 6,712 patients with gallbladder cancer (66.2%), it was found that adjuvant therapy was most beneficial for patients with lymph nodes ($P<0.01$) and was linked to nonsignificant improvement ($P=0.06$) with no difference between tumor sites [75]. Additionally, another meta-analysis has demonstrated the benefits of adjuvant therapy for survival in patients with R1 gallbladder cancer who had lymph node positivity and stage II or higher malignancy [76]. Primarily, the Surveillance, Epidemiology, and End Results (SEER) project served as the basis for the retrospective investigations. According to recent trial, gallbladder cancer that has been removed do not shows better results when chemo-radiation is added to chemotherapy as opposed to chemotherapy alone [77].

The goal of adjuvant chemotherapy plus radiation therapy for GBC is to increase survival following surgery and lower the chance of recurrence. Researchers demonstrated the survival benefit of chemotherapy plus radiation therapy using the SEER data of 1,137 patients with chemotherapy plus radiation therapy (11%), particularly for those with T2–4 and/or lymph node positivity [78]. According to Mantripragada et al.'s analysis of the National Cancer Database, which included 4,775 patients, patients with gallbladder cancer who had chemotherapy and radiation therapy had a 0.25-year survival advantage over the observation group ($P<0.01$) [79]. The American Society of Clinical Oncology (ASCO) clinical practice guideline revealed that patients with gallbladder cancer with R1 resection may receive chemotherapy in addition to radiation therapy, based on the SWOG S0809 findings [80]. Moreover, chemo-radiotherapy has not been considered standard care because of the lower availability of randomized trials.

8.4. Targeted Therapy and immunotherapy

Emerging treatments for gallbladder cancer include targeted therapy and immunotherapy, especially when the disease has spread or is in advanced stages. By targeting specific vulnerabilities in cancer cells, these medicines seek to increase the immune system's capacity to identify and combat cancer cells. Ivosidenib is a kind of targeted treatment that stops a specific mutation in the IDH1 gene, which inhibits the growth of malignant cells. Pemigatinib is another type of targeted treatment that prevents particular alterations in the EGFR2 gene; it could kill cancer cells and prevent them from proliferating. Pembrolizumab has acceptable toxicity and has persistent anticancer efficacy in 6% to 13% of patients with advanced BTC, regardless of PD-L1 expression, according to the KEYNOTE 28 subgroup studies [81].

Immunotherapy stimulates the body's antitumor immune system, which improves the identification and destruction of cancer cells. The most widely used immunotherapeutic drugs are programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) antibodies. These antibodies are used to treat GC with varying degrees of effectiveness [82]. According to genomic sequence advancements, GBC patients have genetic alterations in ERBB2 (16%), PIK3CA (14%), KRAS (11–19.2%), CDKN2A/B (19%), ARID1A (11–13%), and BAP (4–13%) [83]. Additionally, inhibitors of PD-1/PD-L1 have become a viable targeted therapy approach for GBC patients [84]. According to a study using IHC analysis, GBC tumor cells from 19 out of 237 (8.0%) tumors showed upregulation of PD-L1. Using Next generation sequencing (NGS), elevated MSI-H and TMB-H were observed in 1 out of 104 tumors (1.0%) and 6 out of 104 tumors (5.8%), respectively. These findings collectively indicated that PD-L1 in GBCs serves as

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Table 1. Molecular biomarkers for predicting prognosis in gallbladder cancer.

Authors [Ref]	Country	Sample size	Biomarker	Methods	Conclusion
Jin et al. (2018) [90]	China	50 paired GBC/ Normal tissue xenograft model (rat) GBC cell lines (NOZ, GBC-SD, SGC-996, EH-GB1, OCUG-1)	LncRNA *MEG3*	RT-PCR/ Flow Cytometry/ IHC	MEG3 executed its functions via EZH2 to regulate the downstream target gene LATS2
Lui (2020) [91]	China	40 GBC/ adjacent tissue GBC cell lines (GBC-SD, SGC-996, NOZ, OCUG, and EHGB-1) and control cell line (293T) Nude mouse xenograft model	LINC01694	RT-PCR	LINC01694 participated in the growth of GBC cells via regulating miR-340-5p/Sox4 axis.
Wu et al (2017) [92]	China	77 GBC/ 77 Non canceous adjacent tissue Xenograft Model: Male athymic BALB/c nude mice	lncRNA-PAGBC	RT-PCR/ Flow Cytometry/ IHC	lncRNA-PAGBC competitively absorb miR-133b and miR-511 to upregulate SOX4 and PIK3R3, which further promotes tumorigenesis and activates AKT/mTOR pathway.
Chen et al. (2019) [93]	China	53 GBC/ 27 adjacent non-tumorous tissues cell lines (GBC-SD and NOZ) Xenograft :Female BALB/c nude mice	lncRNA PVT1	RT-PCR/ Flow Cytometry/ IHC	Long non-coding RNA PVT1 promotes tumor progression by regulating the miR-143/HK2 axis in gallbladder cancer
Garcia et al. (2020) [94]	Chile (South America)	236 GBC/ 173 chronic cholecystitis GBC cell lines G-415, TGBC1TKB, TGBC2TKB	Hippo-YAP1	RT-PCT/ IHC	Hippo-YAP1 pathway may be a candidate for targeted therapy in advanced GBC patients
Rawal et al. (2025) [95]	North India	40 GBC 40 Inflammatory lesions	S100P, PIGR, C1QBP, TAGLN, and CNN1	LC-MS/MS/ELISA/RT-PCR	S100P, PIGR, C1QBP, TAGLN, and CNN1 emerge as potential protein-based biomarkers involved in the progression from gallbladder inflammatory lesions to invasive cancer.
Wang et al. (2018) [96]	China	125 GBC	Interleukin-6 (IL-6)	Electrochemiluminescence Immunoassay (ECLIA)	IL-6 affected tumor metastasis-related cells and the environment, such as the regulation of immune cells34 and control of liver metabolism.
Niyaz et al. (2018) [97]	India	268 GBC	EGFR, VEGF, HER2/Neu and p53	fluorescent in situ hybridization (FISH) using tissue microarray (TMA). and NGS	RAS pathway molecules like HER2/Neu and EGFR showed significant expression suggesting that interactions take place among different members of the ErbB family during tumor development.
Xu et al () [98]	China	130 GBC tissue Human GBC (GBC-SD and NOZ) and 293T cell lines Xenograft Model:Female BALB/c mice	TRIM47	IHC/ RT-PCR/ MOlecular Docking	TRIM47 promotes tumor progression through regulating K63-linked ubiquitination of PARP1
Fatma et al (2023) [99]	India	100 GBC/ 51 Normal tissue		IHC	BMI-1 gene deregulation is implicated in the progression of GBC in the North-Indian population.
Misra et al (2022) [100]	India	36 GBC tissue	SMAD4, NOTCH1, ERBB2&4, PIK3CA, MET, PTEN, EGFR,	22 gene panel examined NGS based approach	Metastatic disease was associated with high frequency of CTNNB1, KRAS and NRAS gene mutations.

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			KRAS and BRAF		
Albrecht et al (2021) **[101]**	Germany	131 GBC tissue	PD-L1	IHC	PD-L1 expression confers a negative prognostic value in Western-world GBC and highlight the TIGIT/CD155 immune checkpoint as a potential new target for GBC immunotherapy.
Zhang et al. (2021) **[102]**	China	50 GBC/adjacent tissue GBC-SD, SGC-99	miR-204	qRT-PCR	miR-204-mimics and sh-Notch2 were similar to those with miR-NC+si-NC in proliferation, invasion, migration as well as apoptosis.
Lu et al (2020) **[103]**	China	46 GBc/ adjacent tissue	miR-7-2-3p and miR-29c-3p	qRT-PCR	the deficiency of miR-7-2-3p and miR-29c-3p was closely associated with poor prognosis of GBC patients.
Yang et al (2017) **[104]**	China	70 GBC/ adjacent non-carcinoma gallbladder epithelial tissue yangCell lines, TYGBK-1, TYGBK-8, OCUG-1, and NOZ	miR-125b	qRT-PCR	MicroRNA-125b in gallbladder cancer was significantly correlated with patients' clinical stage, tumor differentiation, lymph metastasis, and tumor invasion.
Chen et al.2018 **[105]**	China	53 GBC and 27 adjacent non tumour tissues	MiR-139-5p	qRT-PCR/ IHC	MiR-139-5p is associated with poor prognosis and regulates glycolysis by repressing PKM2 in gallbladder carcinoma
Yang et al. (2017) **[106]**	China	98 GBC blood 60 Healthy control blood GBC-SD cells and SGC996 cells	Circulating miR-141	qRT-PCR	high expression level of circulating miRNA-141 was significantly associated with tumor invasion, lymph node metastasis and advanced pTNM stage.
Lin et al. (2020) **[107]**	China	243 GBC and paired non-tumor tissue GBC cell lines (NOZ, GBC-SD, and EGH1) Xerograft Model: BALB/c nude mice	deoxycholic acid (DCA	qRT-PCR/ IHC/NGS/ UHPLC-MS/MS	Deoxycholic acid modulates the progression of gallbladder cancer through N6-methyladenosine-dependent microRNA maturation
Zhou et al. (2017) **[108]**	China	80 GBC tissue GBC cell lines G-415, OCUG-1 and SGC-996	hsa-miR-372	qRT-PCR	Decreased expression of hsa-miR-372 predicts poor prognosis in patients with gallbladder cancer by affecting chloride intracellular channel 1
Shu et al (2017) **[109]**	China	40 GBC/40 Cholelithiasis GBC cell lines GBC-SD, SGC-996	MicroRNA-29c-5p	qRT-PCR/ IHC	MicroRNA-29c-5p suppresses gallbladder carcinoma progression by directly targeting CPEB4 and inhibiting the MAPK pathway
Wang et al. (2017) **[110]**	China	82 GBC/ 82 non cancerous GB GBC cell lines GBC-SD, SGC-996, and NOZ	miR-218-5p	qRT-PCR/ IHC/ Bioinformatics	Reduced miR-218-5p expression in GBC well correlated with tumor prognosis
Fatima et al (2019) **[111]**	India	50 GBC/ 50 Gallbladder inflammatory disease	MiR 335-5p	qRT-PCR	miR-335 is an independent prognostic factor for patients with GBC, and patients with low miR-335 expression have poorer prognosis than those with high miR-335 expression.
Fatima et al. (2019) **[112]**	India	48 GBC/ 55 Non neoplastic tisuue	cancer stem cell markers Oct-4 and CD133	IHC	high expression level of Oct-4 may provide a new insight for the prognosis of the disease in terms of clinical staging and grade.

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a therapeutic marker for immune checkpoint blockade [85]. In addition, several therapeutic techniques have been used to identify possible targets for GBC patients receiving treatment with MAPK pathway inhibitors. The study documented an instance of advanced secondary GBC treated with BRAF and MEK inhibitors following surgical excision. After 8 months of treatment, there was no sign of metastasis, with PFS lasting 14 months and OS lasting 26 months [86]. Tumor immunotherapy, however, has enabled an exciting new therapeutic strategy to improve the efficacy of GBC treatment.

9. PROGNOSIS AND SURVIVAL OF GBC

The prognosis of GBC remains extremely poor because of the highly aggressive malignant behavior of the tumor. The 5-year survival rate for all stages of GBC is about 5% [87]. The incidental GBC shows a minimally better prognosis because they are often detected earlier, without severe clinical signs. The median survival for suspected carcinomas is 9.2 months, and for incidental carcinomas it is 26.5 months [88]. The data from the international medical literature for patients with T1 tumors show survival between 60% and nearly 100% following a simple and extended cholecystectomy. The survival of patients with T2 tumors varies, depending on lymph node involvement (extent of surgery) and margin. Patients with T2N0M0 who did not undergo a second radical operation have a survival rate between 10% and 22%, while after a radical resection, survival rates are 60% to 80%. For patients with T2b GBC in particular, further systemic treatment may be necessary to prevent systemic recurrence. T2b showed a greater recurrence rate and more numerous recurrence patterns than T2a [89] (**Table1**).

10. CONCLUUSION

Numerous lines of evidence indicate that different environmental risk factors may play a part in gallbladder cancer. There is no recognized genetic marker for gallbladder cancer, despite the fact that numerous articles have been written about its hereditary risk. Additionally, there are currently very few genome-wide association studies (GWAS) on gallbladder cancer. Increased knowledge of the pathogenic mechanisms behind the neoplastic changes occurs in the mucosa of gallbladder can be facilitated by technological innovation. Moreover, the tumor markers for GBC diagnosis have a low specificity and are not identified until the disease is progressed, which makes treatment more difficult. The current review offers a thorough summary of all the research done on its pathogenesis, epidemiology, and molecular genetics under one roof. The researchers will find this useful in understanding the state of research today and the extent of our progress to date. Future research projects can be designed in the right directions based on available literature.

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Conflict of interest

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Ethical statement

This review article is based on published literature. One figure was adapted from an author's PhD thesis approved by the Institutional Ethics Committee, Era's Lucknow Medical College, India (ELMC/R_Cell/EC/2014/01).

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