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DECODING GALLBLADDER CARCINOMA: AN OVERVIEW OF ITS TRENDS, MECHANISMS, AND GENETIC UNDERPINNINGS

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ABSTRACT

Gallbladder cancer (GBC) is a rare but highly aggressive malignancy with a poor prognosis, especially in advanced stages. The disease is frequently diagnosed at advanced stages due to its asymptomatic nature in early progression, resulting in poor prognosis and limited treatment options. This review offers a thorough examination of the current state of GBC, focusing on its diagnosis, treatment, and emerging research directions. Using a systematic literature search, we identified key studies related to GBC's diagnostic challenges, treatment modalities, and innovative therapeutic approaches. Our findings highlight the key points associated with achieving early and precise diagnosis of GBC, thus leading to potentially curative surgical interventions. Molecular insights demonstrate frequent mutations in TP53, KRAS, PIK3CA, BRAF, and EGFR, along with promoter hypermethylation of tumor suppressor genes (APC, CDKN2A, ESR1) and deregulation of miRNAs (miR-155, miR-29c-5p, miR-133a-3p) and lncRNAs (H19, LINC00152, CRNDE). Dysregulated signalling pathways, including PI3K/AKT, MAPK, and TGF-β/SMAD, contribute to tumor proliferation, invasion, and chemoresistance. Current treatment options are largely limited to gemcitabine-based chemotherapy regimens, such as Gem Cis, which, despite their use, come with notable limitations and adverse effects. Nevertheless, the review points to promising future developments, must prioritize large-scale, collaborative research, clinical validation of biomarkers, and equitable access to advanced therapies, including the need of diagnostic tools for early detection, improved chemotherapy protocols, targeted therapies informed by molecular insights into GBC, and the exploration of immunotherapy. Addressing these challenges and leveraging emerging therapeutic strategies could substantially enhance patient outcomes in GBC.

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Keywords - Gallbladder cancer (GBC), epidemiology, pathogenesis, gene mutation and alteration, tumour suppressor.

1. Introduction

Gallbladder cancer, while relatively rare, poses a significant challenge due to its aggressive nature and poor prognosis, particularly when diagnosed at advanced stages. As a major global health issue, cancer overall contributes to over 9.6 million deaths annually (World Health Organization, 2023). Gallbladder cancer, specifically, is notable for its high incidence in regions such as East and Southern Asia, Europe, and Central and South America (Marcinak et al., 2024). It predominantly affects women and individuals over sixty (*What Is Cancer? - NCI*, n.d.), and often remains asymptomatic in its early stages, leading to late diagnoses and complicating treatment strategies (Adson, 1973). This cancer's rarity contrasts with its severity, underscoring the need for a deeper understanding of its epidemiology, pathogenesis, and molecular genetics. Research highlights the critical importance of identifying and addressing risk factors such as age, gallstones, family history, and conditions like primary sclerosing cholangitis. Knowledge of these factors is vital for implementing effective preventive measures and improving early detection. Despite its low incidence compared to other cancers, gallbladder cancer's aggressive progression and the absence of a serosal layer—which may facilitate hepatic invasion and metastasis—make early detection and intervention crucial. Ongoing research into the disease's epidemiology, aetiology, and molecular genetics is essential for developing novel prevention strategies, diagnostic tools, and treatments. By enhancing our understanding of these aspects, we can improve screening methods and therapeutic outcomes, ultimately leading to better management and reduced mortality associated with gallbladder cancer (Xu et al., 2017); (Andrén-Sandberg & Deng, 2014); (Azevedo et al., 2020).

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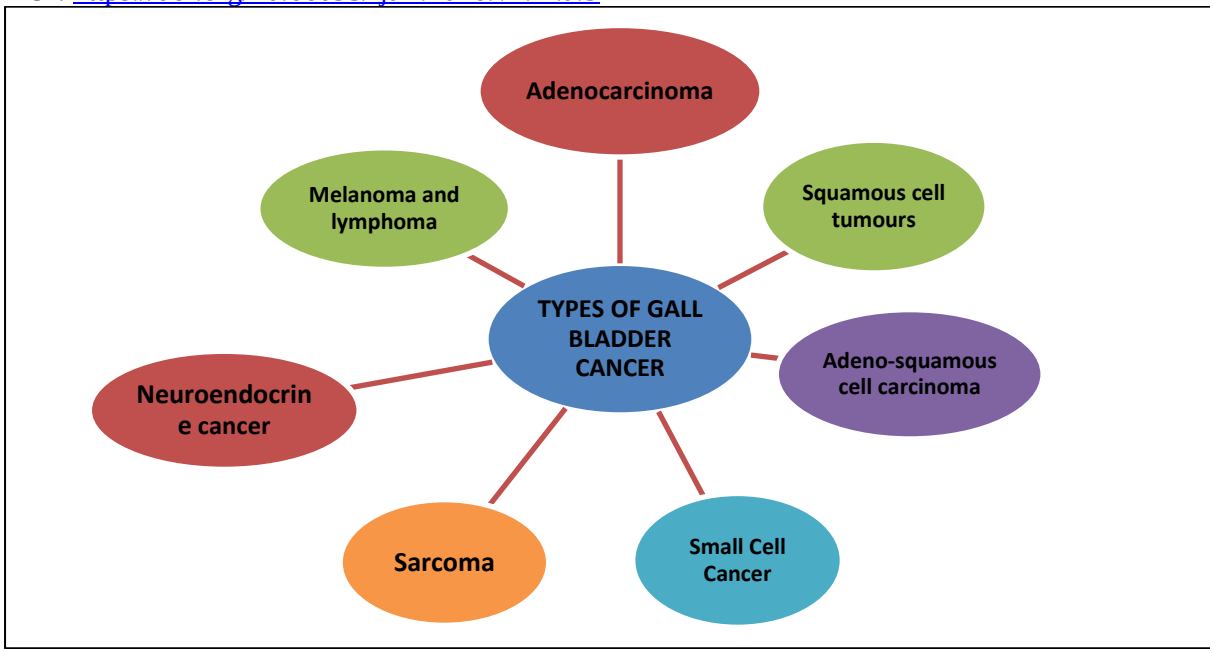

Figure 1: Types of gall bladder cancer.

1.1 Normal Cells vs Cancerous cells

Significantly different from the normal cells are these cancer cells, in their development, appearance, and functionality within our bodies. Cancer cells multiply rapidly and uncontrollably unlike normal cells, disregarding growth limits. They do not respond to other cells and cannot be replaced or repaired. Cancer cells manipulate the immune system, tricking it into supporting their survival and growth. Unlike normal cells, they lack defined tasks and can hide and grow indefinitely. Carcinogens can infect surrounding tissues and spread to different parts of the body through metastasis, whereas normal cells stop growing when they encounter other cells. Cancer cells also exhibit genetic abnormalities that enhance their proliferation and spread. Metastatic cancer cells resemble the original tumour cells, indicating the role of genetic alterations in metastasis. Disrupted regulatory mechanisms in cancer cells lead to uncontrolled division, invasion of nearby tissues, and the characteristic symptoms of cancer. Research focuses on identifying and targeting metastatic cancer cells to improve treatment and prevention (*Cancer Cells vs. Normal Cells: How Are They Different?*, n.d.).

2. Gallbladder Cancer: Types

Gallbladder cancer is categorized into multiple varieties because the gallbladder includes many distinct kinds of cells *(Figure 1).* Any of these cells can proliferate into Carcinogens (Types of Gallbladder Cancer) (Liang et al., 2020).

2.1. Adenocarcinoma

Adenocarcinoma, accounting for around 85% of all gallbladder cancer cases, stands as the prevailing form of this disease. This type of cancer originates from the glandular cells present in gallbladder lining, responsible for producing mucus that aids in the process of digestion. Papillary, non-papillary, and mucinous adenocarcinoma are the three subtypes (KrishnaPriya et al., 2022). Papillary adenocarcinoma has a better prognosis while non-papillary adenocarcinoma is aggressive and spreads quickly. With floating cancer cells in the mucus, mucinous adenocarcinomas are more difficult to treat but have a better prognosis than other forms (Albores-Saavedra et al., n.d.) (Akazawa et al., 2022).

2.2. Adenosquamous cell Cancer (ASC)

Different organs may be affected by adenosquamous carcinoma, a malignancy having glandular and squamous cell characteristics. A variety of treatment options are accessible to patients, including surgery, chemotherapy, radiation therapy, and immunotherapy. These methods can be employed to address the individual's specific medical needs. The selected treatment is influenced by variables including disease stage and general health. If necessary, additional therapy could be used after surgery. To create a personalized treatment plan that can be modified depending on the patient's response, collaboration with healthcare specialists is crucial.

2.3. Cancerous Squamous Cells

Squamous cell carcinoma originates from the epidermis and gland cells lining the gallbladder. It is treated similarly to adenocarcinomas and accounts for about 5% of gallbladder cancers. Squamous cells are found throughout the body, lining organs like the lungs, throat, thyroid, and skin. This type of cancer can occur anywhere squamous cells are present. While typically not life-threatening in the skin, SCC can grow slowly and deeply, potentially damaging nerves, blood vessels, and surrounding tissues. The progressive growth of cancerous cells can give rise to the formation of substantial tumours (Gordon, 2013)

2.4. Small cell Carcinoma

Small cell carcinoma, commonly referred to as oat cell cancer, represents a highly formidable variant of lung cancer distinguished by its swift-growing, diminutive cells exhibiting a substantial nuclear to cytoplasmic ratio. The standard treatment approach generally encompasses chemotherapy and radiation therapy; however, the prognosis frequently remains discouraging, with limited survival rates observed following diagnosis (Fujii et al., 2001).

2.5. Sarcoma

Sarcoma is a rare cancer originating from connective tissue. Gallbladder sarcomas, specifically leiomyosarcomas, arise from smooth muscle cells in the gallbladder wall. Symptoms include abdominal discomfort, nausea, vomiting, and jaundice. Diagnosis involves imaging tests and biopsy. Treatment involves surgery, radiation, and chemotherapy. Prognosis depends on various factors like tumour stage, grade, patient's health, and metastasis (*Sarcoma Symptoms, Treatment, and Malignant Tumor Specialists*, n.d.).

2.6. Neuroendocrine cancer

Neuroendocrine tumours (NETs) arise as sporadic malignancies originating from hormone-producing cells scattered across multiple organs. They can occur in the digestive system, lungs, pancreas, and other organs. Carcinoid tumours, a type of NET, originate from the neuroendocrine system and commonly affect the small intestine, rectum, appendix, and lungs. Symptoms vary based on location and hormone production, including abdominal pain, diarrhoea, flushing, wheezing, and weight loss, although some individuals may be asymptomatic (Raphael et al., 2017).

2.7. Melanoma and lymphoma

Gallbladder lymphoma and other rare types of gallbladder cancer are infrequent and require specialized treatment. Unlike other cancers, gallbladder lymphoma is unlikely to be treated with surgery. Instead, chemotherapy and radiation therapy are commonly used due to the systemic nature of lymphoma. Rare types of gallbladder cancer may also demand different treatment methods than common types like adenocarcinoma (Verwer et al., 2010).

3. Gallbladder Cancer: Causes

There are three main causes of gallbladder cancer: genetic mutations, exposure to environmental toxins, and inherited genetic mutations. Cancer is generally caused by genetic

abnormalities that alter the genes that control cell growth and division. These mutations might be passed down via families or occur spontaneously during cell division. Inherited genetic mutations, which are handed down from our parents, can raise our chance of acquiring certain forms of cancer. Toxins in the environment: Toxins in the environment, such as cigarette smoke, UV radiation from the sun, and pollution, can damage. DNA damage increases the likelihood of developing cancer. Inherited genetic mutation, for example, some people are born with genetic mutations that predispose them to types of cancer. We can, however, minimise our risk and enhance our chances of early identification and treatment by knowing the causes of cancer. Gene mutations associated with gallbladder cancer are often acquired rather than inherited. For instance, mutations in the TP53 tumour suppressor gene have been found in numerous cases of gallbladder cancer. BRAF, PIK3CA, and KRAS are additional genes that could be involved in gallbladder cancer. Gallbladder cancer-causing gene changes may be triggered by chronic inflammation. But sometimes, the cause of these changes goes unnoticed. Many gene changes may simply be the result of random events occurring inside a cell without any external influence. In addition, women are more likely than men to get gallbladder cancer, and this increased risk is associated with factors such as obesity, ageing, smoking, and consuming a diet high in fat and low in fibre (Rock et al., 2020). Gallbladder cancer is also increased by some medical diseases, such as primary sclerosing cholangitis and porcelain gallbladder. While inherited gene changes can enhance the risk of some malignancies, gallbladder cancer gene mutations are frequently acquired rather than inherited. These mutations may occur due to factors such as chronic inflammation or exposure to environmental toxins, but some mutations may also occur randomly without any clear cause. The TP53 tumour suppressor gene, KRAS, BRAF, and PIK3CA are among the genes that have been linked to gallbladder cance (Wang et al., 2018). Understanding the genetic basis of gallbladder cancer may help researchers develop new strategies for early detection and treatment of this disease (Cooper, 2000).

3.1. Factors involved

The disparity of inherited and environmental factors has been linked to gallbladder cancer. In addition to female hormones, chronic inflammation caused by gallstones or infections, as well as genetic mutations can cause gallbladder cancer. Due to their ability to induce persistent inflammation and damage to the gallbladder's cells, gallstones pose a serious risk for gallbladder cancer. The risk of developing gallbladder cancer may also be increased by exposure to certain chemicals, heavy metals, and nitrosamine, which are found in some

processed foods and cigarette smoke. The occurrence of gallbladder carcinoma ranges across different geographical regions, particularly in Central and South America, Asia, and selectable areas of Africa. This discrepancy could be attributed to various environmental influences, including dietary patterns and exposure to harmful substances. Additionally, variations in genetic susceptibility may contribute to the differing prevalence rates observed. The development of gallbladder cancer is a multifaceted interplay between genetic, hormonal, and environmental factors. Extensive research is required to comprehensively grasp the fundamental causes behind this disease.

3.2. Risk Factors: Gallbladder Cancer

Identifying the elements that contribute to the emergence of cancer in particular individuals while others remain unaffected can present a formidable undertaking. Nonetheless, a thorough investigation has illuminated distinct risk factors that augment the probability of encountering carcinogens. These risk elements encompass exposure to chemicals or medications and particular cellular behaviours in reaction to these compounds. Furthermore, there exist uncontrollable variables, including age and family history (indicated by a genealogical chart), that contribute to the susceptibility to cancer. Concerning gallbladder cancer (GBC), aside from ethnic background, multiple other factors associated with increased risk have been identified. One prominent factor is the presence of pre-existing gallstones, referred to as cholelithiasis, which exhibits a strong correlation with GBC. Nonetheless, it is crucial to acknowledge that the occurrence of GBC in individuals with gallstones is relatively rare, standing at a mere 0.5%. This implies that the greater part of people with gallstones will not develop gallbladder cancer throughout the course of their lives.

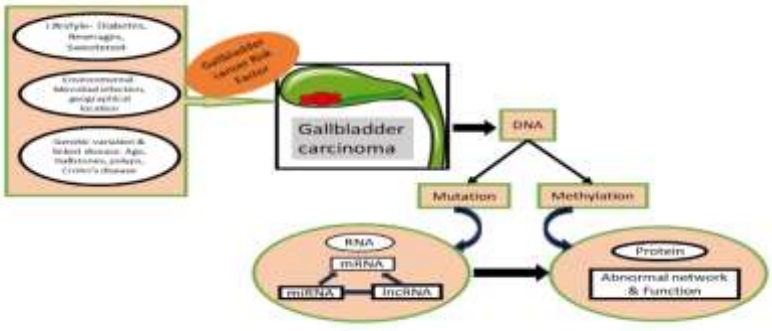

Figure 2: "Risk Factors Associated with Gallbladder Cancer (GBC)"

Furthermore, advanced age represents a noteworthy risk factor for GBC, typically diagnosed between the ages of 67 and 72. In addition, there is a higher susceptibility for women to develop gallbladder cancer (GBC) compared to men, with a two to six times increased risk. Furthermore, several characteristics, such as being overweight and working in the chemical processing, textile manufacturing, and oil refining industries, have been associated with an increased risk of gallbladder cancer (GBC). Gallbladder cancer has been connected to salmonella infection in areas where the disease is prevalent, like the Indian subcontinent and portions of Central and South America. Additionally, individuals with Lynch syndrome, an inherited predisposition to certain types of cancer, including GBC, are more prone to developing this disease. In the US, different ethnic groups have different gallbladder cancer (GBC) incidence and fatality rates. Women of American Indian and Hispanic descent had the greatest rates, but African Americans have seen an increase in recent years. These disparities emphasize the influence of ethnicity as a contributing factor in GBC. Numerous of these cancer risk factors, and preventive measures have been discovered through epidemiological studies. Researchers have examined large populations and contrasted individuals with cancer to those without, to identify significant associations and patterns. Although the development of cancer is a multi-faceted process with various factors involved, research has identified several risk factors linked to gallbladder cancer. There are numerous variables that can raise a person's risk of gallbladder cancer. These include having gallstones already, being older, female, overweight, working in a particular field, having a history of Salmonella infections in areas where the illness is widespread, and having a genetic predisposition such as Lynch syndrome. Knowing these risk factors can help with targeted interventions, early detection, and prevention to lower the incidence and death rates of gallbladder cancer.

Table 1: The significant risk factors for gallbladder cancer

Sr. No.	Strength of association	Risk factor
1.	Cholelithiasis	Strong
2.	Bacterial and Salmonella infections	Strong
3.	Porcelain gallbladder	Strong
4.	Gallbladder polyps	Strong
5.	Anomalous pancreato-biliary duct junction	Moderate to strong

6.	Endogenous and exogenous estrogens	Moderate to strong
7.	Industrial exposure to carcinogens	Moderate to strong
8.	Pregnancy	Moderate
9.	Familial tendency	Moderate
10.	Segmental adeno-myxomatosis of gallbladder	Weak to Moderate
11.	Chronic inflammation	Weak to Moderate
12.	Polyposis coil	Weak to Moderate
13.	Mirilzzal syndrome	Weak to Moderate

The risk factors linked to the emergence of gallbladder cancer (GBC) are depicted in Figure 2. Important components of microRNA biogenesis, dysregulation, function, and protein networking in GBC are included in the systematic representation. Photos from Servier Medical Art were used to make the figurines. A Creative Commons Attribution 3.0 Unported Licence (https://creativecommons.org/licenses/by/3.0/) governs Servier Medical Art by Servier. Gallstones, also known as cholelithiasis, give a substantial danger for gallbladder cancer to spread. The prolonged presence of gallstones in the gallbladder, especially over a period of 20 years or more, greatly increases the likelihood of this association. Studies support this, demonstrating that 70–94% of GBC patients have gallstones (Table 1). It is crucial to remember that there is no connection between the type of gallstone and the likelihood of gallstone cancer. According to the study, cholelithiasis affects roughly 10% to 15% of adults in developed nations. This means that cholelithiasis affects many people—between 20 and 25 million Americans, according to estimates—and is therefore a serious public health concern. Ultrasonography is the most reliable method for epidemiological screening of cholelithiasis. This non-invasive diagnostic equipment creates pictures of the gallbladder and detects the presence of gallstones using high-frequency sound waves. This method is widely available, affordable, and has high sensitivity and specificity for detecting gallstones. It is the most reliable method for screening cholelithiasis, and individuals with symptomatic cholelithiasis should seek medical evaluation and treatment to prevent the

development of gallbladder cancer. Certainly, there is a link between bacterial infections and gallbladder cancer, according to various research. Persistent infections produced by pathogenic bacteria can result in chronic inflammation, which leads to the generation of toxins and metabolites that can harm cells and promote cancer formation. The bacteria that cause typhoid fever, *Salmonella typhi*, is syndicated to a higher threat of gallbladder in endemic locations like India, Pakistan, Chile and many more. Other bacterial infections, such as *Helicobacter pylori* and *Streptococcus bovis* linked to the bacterial causes of gallbladder cancer. It is crucial to highlight that not everyone who has a bacterial infection will develop gallbladder cancer and that other variables such as genetics and lifestyle have a role in cancer development. Understanding the association between infections and cancer, on the other hand, can assist identify high-risk individuals and create preventative and treatment techniques. A lot of variables can contribute to inflammation, including physical blockage caused by cholelithiasis. Diseases, environmental infections, polyps and adenomas, people who are self-immune, and structural abnormalities such as pancreato-biliary. According to research, each of these is a threat linked to gallbladder cancer. The precise involvement of inflammation in the cellular process of gallbladder tumour progression has been demonstrated to be weakening. Porcelain and polyp gallbladder are observed in 12.5% to 62% of gallbladder individuals with cancer. Additionally, polyps bigger than 10 to 15 mm cause cancer in around 45% and 67% of cases, respectively. Cholecystectomy for polyps greater than 10mm relates to diseases such as advanced-age adherent polyps, and concomitant cholelithiasis. Anomalous pancreato-biliary duct junction represents an additional susceptibility factor for gallbladder cancer (GBC), prevailing in approximately 17% of GBC patients while occurring in fewer than 3% of individuals with alternative hepatobiliary conditions. Pancreatic water accumulates in the gallbladder forming gallstones which cause inflammation and bile duct obstruction. Obesity, particularly in women, is known to be a potential factor for GBCs. According to the meta-analysis you referenced, obese persons had a 1.56 relative chance of having gallbladder cancer compared to those who were normal weight. Even people who were overweight had a little higher risk, with a relative risk of 1.14. Surprisingly, the link between fat and gallbladder cancer appears to be greater in women than in males. Nevertheless, several studies have shown no link between overweight or obesity and the occurrence of GBC in Men. It is also important to note that the link between weight increase and gallbladder cancer is not obvious. While obesity is a risk factor, some research suggests that increasing weight may reduce the chance of gallbladder

cancer. Research done by Weider Pass et al., for example, discovered that women who acquired more than 20 kg of weight had a considerably reduced risk of gallbladder cancer than those who gained less than 5 kg. Weight and gallbladder cancer risk are complex and require further study. Drinking, smoking, and dieting increase the risk of this disease. Red meat and smoking raise risk, but vegetables and fruits prevent. While increasing calorie intake reduces gallbladder cancer risk, fibre and vitamins also do. Smoking and drinking may contribute to this condition, although how is unknown. Cigarette smoking greatly increases gallbladder cancer risk. Alcohol usage is linearly associated with risk variables for gallbladder cancer, according to one study. More research is needed to understand these gallbladder cancer risk variables' processes and connections. Carcinogen exposure is another key risk factor of GBC. According to retrospective research, chemical pollution from pesticides, vinyl chloride as industrial or occupational coatings & excessive exposure to heavy metal, and radiation, have been linked to an increase in the prevalence of GBC. A study of 1808 GBC cases in California discovered a relationship between the automobile, furniture, and rubber industries to the gallbladder. According to the findings of the study done in the United States, 27.6% of GBC patients were rubber workers. Several medicines raised the chance of gallbladder cancer (including isoniazid and oral contraceptives). The link between ulcerative colitis and biliary carcinoma is widely established. Individuals who have had a transplant and have ulcerative colitis have a tenfold increased chance of acquiring gallbladder cancer compared to the general population. Although colitis enacts GBC emergence, inflammation is a major driver of cancer advancement in the gallbladder. While oestrogen is thought to be performed in the production of gallstone, The connection between stages of oestrogens & the creation of biliary stones (also known as bile duct stones) is less apparent. Biliary stones arise when the composition of bile becomes imbalanced, resulting in the creation of crystals that eventually grow into stones. Some data suggest that high oestrogen levels may raise the chance of biliary stone development, although the mechanism is unknown. One explanation is that oestrogen changes the makeup of bile, increasing the chance of stone development. Further study is needed, however, to completely understand the link between oestrogen levels and biliary stones. In terms of the danger of infection and inflammation in the biliary system, independent of oestrogen levels, this can be a complication of biliary stone disease. When stones become trapped in the bile duct, they can prevent bile flow and cause inflammation and infection. If left untreated, this can produce symptoms such as stomach discomfort, nausea, and fever, and can progress to serious

problems. Thus, while there may be a link between oestrogen levels and biliary stone formation, it is important to remember that there are other variables that can contribute to the production of biliary stones, and oestrogen levels are just one of many potential causes. Female hormones may play a role in GBC formation during pregnancy, but the exact mechanisms are unknown. Some studies have found that women who have had multiple pregnancies or have given birth to many children. However, other studies have not found a significant association between parity (the number of pregnancies) and gallbladder cancer. One research published in the Journal of Gastroenterology and Hepatology found that women who had their first menstrual period (menarche) at a younger age (less than 12 years old) may be more likely to get gallbladder cancer than women who had their first period later in life. The study also discovered that women with more than three children had also increased risk of gallbladder cancer than women with fewer children. While there may be a link between female hormones, and fertility, it is crucial to remember that many other variables, such as age, obesity, family history, and certain medical disorders. As with any other health condition, it is vital to voice any concerns or questions you may have to your healthcare provider. Gallbladder Cancer (GBC) causes are uncertain. Polyposis coli, gallbladder segmental adenomyomatosis, and chronic inflammatory bowel illness may contribute. Segmental gallbladder adenomyomatosis is a rare benign disorder that thickens the gallbladder wall and develops tiny nodules or tumours. However, the exact link between this disease and gallbladder cancer is unknown. A rare genetic disorder, polyposis coli causes many colon and rectum polyps. Although not directly connected to gallbladder cancer, polyposis coli may increase the risk of gastrointestinal cancers. Gallstones in the bile duct cause inflammation and obstruction in Mirizzi syndrome, an uncommon gallstone complication. Mirizzi Syndrome does not cause GBC, although it can cause gallbladder inflammation and injury. Rare kidney stone complications include this condition. Mirizzi Syndrome may be linked to gallbladder cancer in limited research. The condition affects 0.2%–2.7% of biliary stone patients (Satake et al., 2022).

4. Epidemiology

GBC is India’s major public health concern, with a high incidence rate that is rising in both genders. GBC is the most widespread in the nation's northern, north-eastern, central, and eastern parts. GBC is typically identified at an advanced stage in India, contributing to its dismal prognosis. Unlike what happens in the West, gallbladder cancer (GBC) mainly strikes

younger people in India in their fifth and sixth decades of life. Gallstones account for 80% of GBC cases in India, making them a serious threat to the disease. To reduce the number of GBC-related deaths in India, it is necessary to carry out comprehensive, cooperative study at several sites to determine the corresponding risk linked to each relevant risk factor. This valuable information can be utilized to formulate cost-effective national strategies to prevent gallbladder cancer (GBC). Meanwhile, it is critical to maintain heightened attention over gallbladder cancer (GBC) and increase the availability of healthcare services to enable successful gallstone therapy. These interventions are critical in lowering the mortality rates associated with GBC (Randi et al., 2006).

Table 2: Some essential mutational genes in GBC

Sr. No.	Genes	Mutational Position
1	P53	Exon 5, 6, 7, 8
2	K-ras	Codon 12 (GGT change to GAT)
3	Keapl	C249Y/S338L
4	PIK3CA	Exon 9
5	EGFR	Exon 19, 20, 21
6	P16	Exon 15
7	B-raf	Exon 1, 2

4.1. Prevalence

Based on data from the World Health Organisation (WHO), gallbladder cancer ranks 28th in the world among cancers that cause death. It ranks 19th among females, showing a greater incidence among women. In the year 2020, approximately 219,000 fresh instances of GBC were reported worldwide, with a higher occurrence observed in the female population compared to males (Figure 3A). Projections made by the American Cancer Society for the year 2023 in the United States suggest a total of 12,220 newly diagnosed cases of gallbladder and adjacent major bile duct cancer. Of these cases, 5,750 will affect males, while women will account for 6,470 instances (Figure 3B) (Dutta et al., 2019). These malignancies claimed the lives of around 4,510 people: 1,900 males and 2,610 women. Four out of every ten new cases will be of gallbladder cancer (Figure 3C). As previously said, gallbladder cancer is very frequent in India, although the condition is less common in Western nations (Bledsoe et al., 2022). The causes for these regional discrepancies are unclear, although they are most likely

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due to differences in risk factors, genetics, and availability of healthcare. Overall, gallbladder cancer remains a substantial public health concern across the world, and efforts to increase disease prevention, early identification, and treatment are required. It is critical to recognise that the prevalence and death rates of GBC vary significantly across various areas and people (Jha et al., 2018).

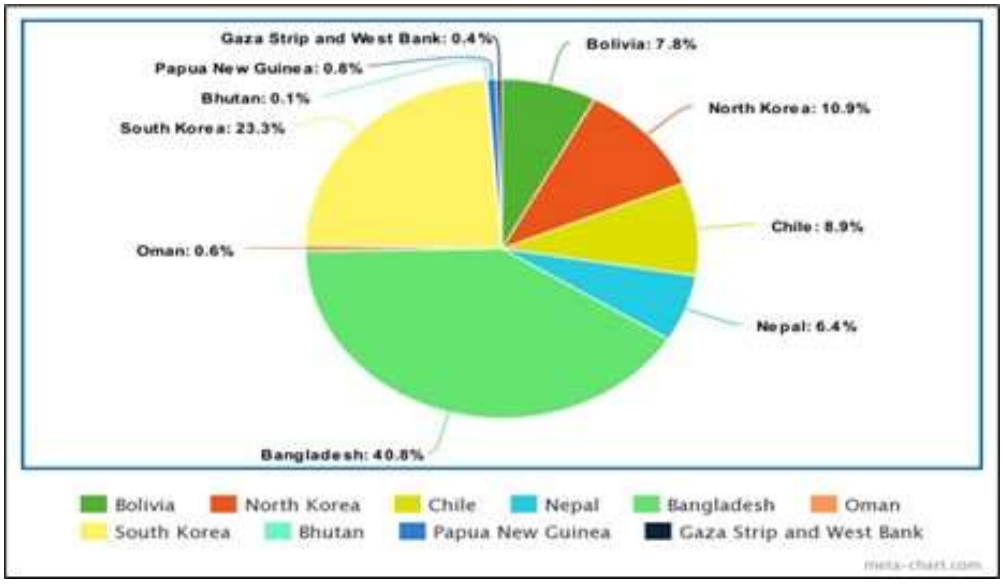

Figure 3A: Worldwide Mortality Rate of Gallbladder Cancer in Men, 2020"

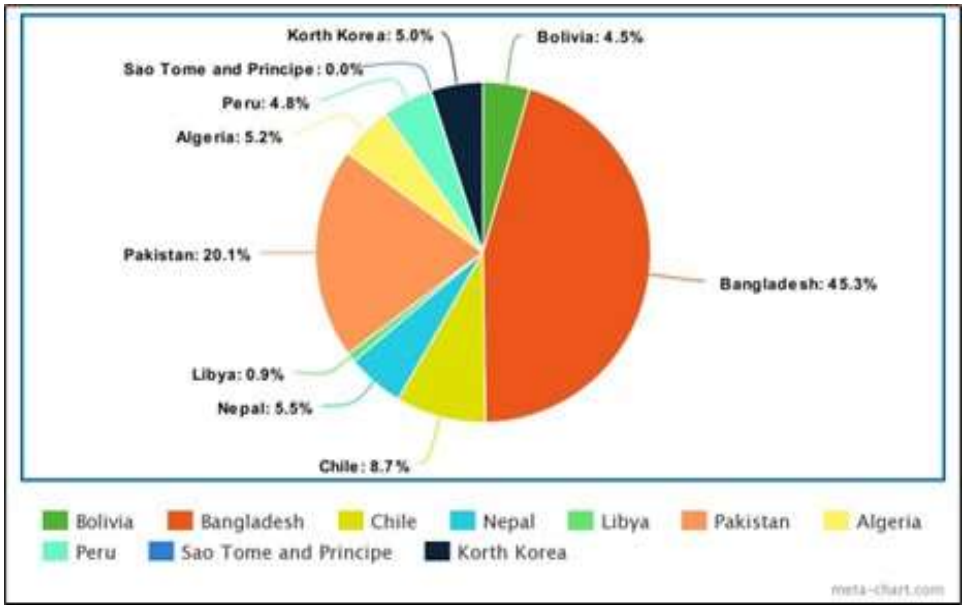

Figure 3B: Worldwide Mortality Rate of Gallbladder Cancer in Women, 2020

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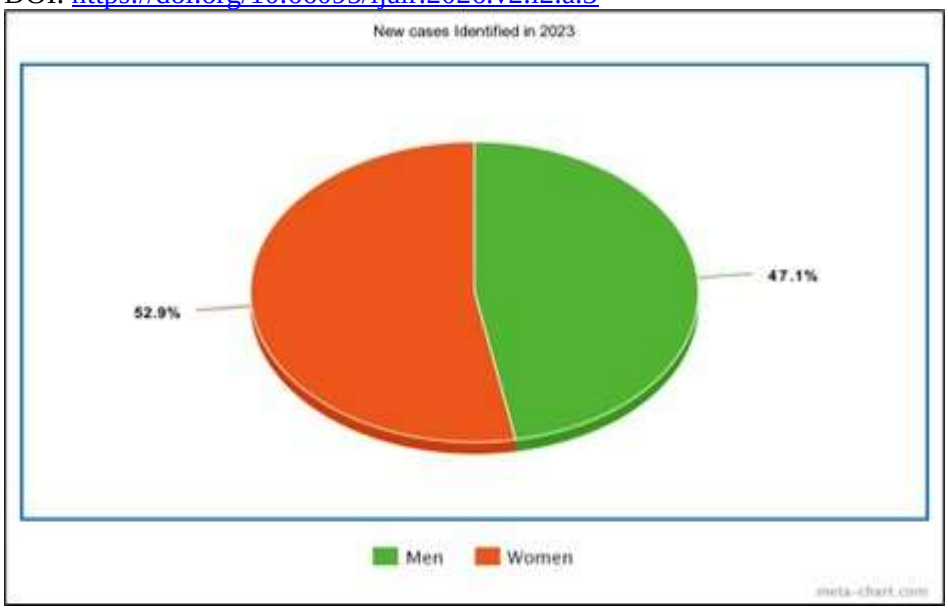

Figure 3C: Newly Identified Cases of Gallbladder Cancer in 2023

Figure 3(A)world morality rate of gall bladder cancer men prevalence 2020, (B) world mortality rate of gall bladder cancer women prevalence 2020 (C) new cases identified in 2023.

5. Prevention

The gallbladder is a tiny organ situated in the upper right side of the abdomen. Gallbladder carcinoma (GBC) is a very deadly but uncommon type of cancer that starts there. Bile, a digestive fluid produced by the liver, is kept in storage in the gallbladder. Although the specific causes of gallbladder cancer are still unknown, there are several known risk factors that can raise your chance of getting the disease. Reducing or completely avoiding smoking is a vital step in lowering the risk of cancer, including GBC. The risk of cancer is greatly reduced when one stops smoking. Furthermore, being fat or overweight increases the risk of developing breast, colorectal, and kidney cancers, among other cancers. Individuals can lower their risk of cancer by maintaining a healthy weight by regular physical activity and eating a balanced diet. Incorporating a wide variety of fruits, vegetables, complete grains, and lean meats into one's diet can significantly reduce the risk of acquiring cancer. Aiming for at least 30 minutes of moderate physical activity most weekdays, regular physical exercise can help people reach a healthy weight and reduce their risk of cancer, particularly breast and colon cancer. Drinking alcohol is another thing that can make you more likely to have some cancers, like liver, colon, and breast cancer. It is imperative to use caution when consuming alcohol and to think about cutting back to reduce the risks involved. Individuals should wear

protective clothes, seek shade when possible, and apply sunscreen to protect their skin. Furthermore, it is critical to be cognizant that radiation from medical imaging procedures can also contribute to the risk of developing cancer. It is best to consult with a healthcare practitioner about the potential dangers and advantages of any imaging testing. Furthermore, ionising radiation and some types of air pollution can increase the risk of acquiring cancer. Individuals who operate in locations where these drugs are present must take proper steps to limit their exposure. Understanding the potential risk factors linked to gallbladder cancer and embracing proactive measures to counteract those risks can greatly contribute to diminishing the chances of developing the disease. Individuals can protect their health and lower their risk of gallbladder cancer and other types of cancer by adopting a healthy lifestyle that includes not smoking, eating a balanced diet, engaging in regular physical activity, limiting alcohol consumption, shielding the skin from UV radiation, and minimizing exposure to radiation and air pollution.

6. Genetic Involvement in Gallbladder Cancer

Detection and treatment signatures for GBC were developed, showcasing the interplay between DNA, RNA, and protein levels.

6.1. GBC Genomic Signatures

DNA mutations and methylation pathways are important concepts for the diagnosis and treatment of many malignancies, including gallbladder cancer (GBC). To appropriately manage the growth of GBC, several pathways are essential. As listed in Table 3, some genes, such as P53, K-ras, Keap1, PIK3CA, EGFR, P16, and B-raf, have been connected to mutations linked to GBC. Allele-specific mutations may have an impact on the occurrence of GBC, according to research from Chile. Rare germline mutations that are inherited have also been linked to GBC. Modifications in the epidermal growth factor receptor have shown promise in the management of gastrointestinal cancer (gastroenterology & 2019, 2019).

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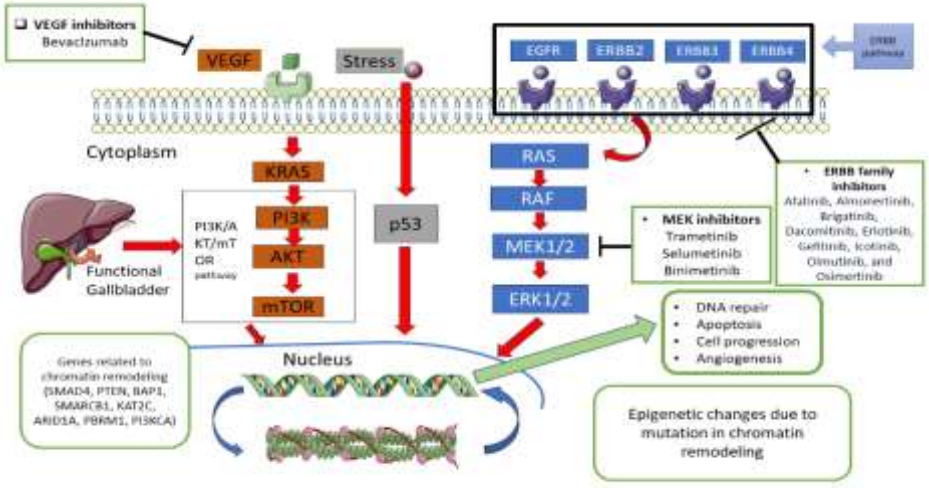

Figure 4: GBC Molecular Pathogenesis and Pathway Inhibitors"

GBC has been specifically linked to P53 mutations in exons 5-8 and K-ras mutations in codon 12. GBC can arise because of Keap1 mutations at C249Y and S338L, which can cause the lack of Nrf2 repression action. Gene mutations and other DNA-based molecular markers are useful tools for the diagnosis and management of GBC. Important gene mutations help to develop efficient treatment plans and shed light on the biology of GBC. Additionally, a major biological marker for gallbladder cancer at the DNA level is gene-specific DNA methylation. Early and progressive aberrant hypermethylation of promoter regions is a hallmark of GBC. Like mutations, gene-specific DNA methylation affects GBC diagnosis and therapy planning. Examples of these genes are APC, CDKN2A, ESR1, PGP9.5, and SSBP2. When diagnosing and treating GBC, DNA molecular markers such as mutations and gene-specific DNA methylation are essential. Tailored treatment techniques may target specific gene mutations and methylation patterns.

Figure 4 illustrates the widely accepted framework known as the dysplasia-carcinoma sequence, which outlines the genomic and molecular alterations involved in the molecular pathogenesis of gallbladder cancer (GBC). The figure also depicts pathway inhibitors associated with these alterations. The images in the figure were created using illustrations from Servier Medical Art, and Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

Table 3: Some anomalous miRNAs in GBC and their target mRNAs

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Sr. No.	miRNA	Expression(miRNA)	mRNA	Expression(mRNA)
1	miR-146b-5p	Down	GFR	Up
2	miR-20a	Up	Smad7	Down
3	miR-29c-5p	Down	CPEB4	Up
4	miR-133a-3p	Down	RBPJ	Up
5	miR-26a	Down	HMGA2	Up
6	miR-122	Down	PKM2	Up
7	miR-143a-3p	Down	ITGA6	Up
8	miR-101	Down	ZFX	Up
9	miR-30d-5p	Down	LDHA	Up
10	miR-182	Up	CADM1	Down
11	miR-30b	Down	NT5E	Up
12	miR-340	Down	NT5E	Up
13	miR-125b-5p	Down	Bcl2	Up
14	miR-143-5p	Down	HIF-1 alpha	Up
15	miR-33a	Down	IL-6	Up
16	miR-223	Down	STMN1	Up
17	miR-218-5p	Down	PRKCE	Up

A tumour suppressor gene known as **TP53** is essential in halting the development and spread of cancer. The TP53 gene frequently develops mutations in a variety of malignancies, including gallbladder cancer. The **KRAS** gene controls the division and development of cells. It is common to find KRAS mutations in a variety of malignancies, including gallbladder cancer. Tumour growth and unregulated cell division are both possible outcomes of these mutations. The **PIK3CA** gene encodes a protein known as PI3K that participates in signaling pathways for cell growth and survival. Gallbladder cancer has been linked to PIK3CA mutations, which may help explain why these pathways are activated abnormally. The genes **KEAP1, EGFR, P16, and BRAF**, are not frequently linked to gallbladder cancer. They are connected to other cancers, though. In non-small cell lung cancer (NSCLC), KEAP1 (Kelch-like ECH-associated protein-1), a gene implicated in cellular responses to oxidative stress, is

frequently associated with mutations or dysregulation. Even though it is not frequently linked to gallbladder cancer. Mutations or overexpression of the gene encoding the receptor protein EGFR (Epidermal Growth Factor Receptor), which is involved in cell division and development, have been found in lung, colorectal, and other head, and neck malignancies. Gallbladder cancer is rare when EGFR mutations are present. By preventing cell division, the tumour suppressor gene P16, sometimes referred to as CDKN2A, controls the cell cycle. Gallbladder cancer is not commonly related to P16 mutations or inactivation, although it has been connected to melanoma, pancreatic cancer, and certain forms of head and neck cancers. In melanoma and some colorectal cancers, the gene BRAF, which codes for a protein implicated in cell signalling pathways regulating cell growth and division, frequently exhibits mutations, particularly the V600E variation. Nonetheless, gallbladder cancer is uncommon to have BRAF mutations (Table 2) (Gallbladder cancer statistics | World Cancer Research Fund International n.d.).

7. Pathogenesis

The leading cause of gallbladder cancer (GBC) correlates with persistent inflammation. According to the current theory of gallbladder cancer development, persistent inflammation in the gallbladder triggers a series of cellular alterations. This includes the progression, after a progressive process, from excessive growth and abnormal tissue creation to precancerous changes, early-stage carcinoma, and invasive carcinoma. In research by Roa et al., aberrant tissue development, pre-cancerous changes, and early-stage carcinoma were shown to often present close to invasive malignancies in the gallbladder (66%, 81.3%, and 69%, respectively). Various ethnic groups may experience chronic gallbladder inflammation for various reasons. Persistent inflammation creates a pro-cancerous environment that supports tumour growth and development when gallstones are present. Gallstone-induced chronic inflammation and gallbladder cancer are largely associated in South America. For example, with 9.2 instances per 100,000 individuals, Chile has one of the highest rates of gallbladder cancer (GBC) worldwide. Additionally, gallstones are thought to affect 27% of the adult population in Chile. Notably, gallstones are more common and fatal in indigenous Mapuche Indian women in Chile. Gallbladder abnormalities and cancer are being intensively investigated in the ongoing Chile Biliary Longitudinal Study (Chile BiLS), which enrolled 4,726 Chilean women with gallstones between 2016 and 2019. The BLS study found that the 200 Mapuche people had greater levels of the inflammatory cytokine IL-8 in their inflammatory profile when compared to 200 non-Mapuche females with gallstones. This

finding raises the possibility of ethnic differences in the study participants' inflammatory reactions to gallstones. APDJ abnormalities are rare congenital abnormalities that have been associated to gallbladder cancer (GBC) in several studies from China and Japan. This disease keeps the biliary system operating normally by causing pancreatic juice to continuously reflux into the bile duct. The bile ducts may eventually develop cancer if inflammation continues because of excessive development, aberrant tissue creation, or other factors. APDJ was more common in GBC patients than in controls, according to a meta-analysis of nine case-control studies (10.60% vs. 1.76%, odds ratio: 7.41, 95% confidence interval: 5.03 to 10.87, p 0.00001) (Khan et al., 2013).

8. Essential miRNAs& ncRNAs in gallbladder cancer

The importance of miRNA, mRNA, and long-coding RNA in the management of gallbladder cancer cannot be overstated. These RNA molecules play vital roles in various physiological and pathological conditions in gallbladder cells. One specific mRNA of interest is the human telomerase (hTERT) mRNA, which contains a telomerase catalytic component. This substance has been shown to be particularly useful in diagnosing pleomorphic lesions in the gallbladder (Jia et al., 2021). Another important mRNA is SUMO-1, which exhibits conditional expression changes in gallbladder cancer as well as surrounding gallbladder tissues and adenomatous polyps. This specific mRNA is an intriguing target for diagnostic reasons. Furthermore, the expression of many factors, including VEGF, FLT-1, CD-146, and KDR, has been linked to the development of gallbladder cancer. These components' expression levels can be evaluated to detect diagnostic markers as well as give insight into progression, prognosis, staging, and possible treatment action. Furthermore, miRNA expression has emerged as an important tool in understanding gallbladder cancer. The level of miRNA expression is directly related to the patient's survival. For example, high levels of miRNA-155 expression have been related to considerably worse overall survival when compared to low levels of expression. The increased expression of miR-155 in gallbladder cancer implies that it might be used as a prognostic, diagnostic, and therapeutic target (Kono et al., 2012). Other miRNAs, including miR-146b and miR-335, have been linked to gallbladder cancer. MiR-146b suppresses gallbladder development via binding to the epidermal growth factor receptor, whereas miR-335 expression is associated with aggressive tumour characteristics and clinical outcomes and may be a therapeutic target for primary gallbladder cancer. Furthermore, miR-29c-5p operates as a tumor-reducing miRNA, potentially functioning as a prognostic biomarker or therapeutic target by suppressing tumour

growth via direct interaction with CPEB4 and This element has proven to be extremely beneficial in detecting pleomorphic lesions in the and inhibition of the MAPK pathways. Similarly, miR-133a-3p inhibits tumour growth by selectively targeting the recombination signalling protein jk (RBPJ), and miR-25a promotes GBC proliferation by targeting HMGA2. miRNA, mRNA, and long-coding RNA molecules are vital components in the comprehension and treatment of gallbladder cancer. Their expression patterns and regulatory mechanisms provide valuable insights into diagnosis, prognosis, and potential therapeutic targets. Ongoing research in this field continues to unravel the intricate molecular mechanisms underlying gallbladder cancer, offering hope for improved treatments and patient outcomes (*Table 3*) (Cao et al., 2022).

8.1. mRNAs

8.1.1. Smad7

Smad7 is a flexible intracellular protein that can serve an essential part in the control of several signalling pathways, including the TGF- signalling pathway. The TGF- pathway regulates cell differentiation, proliferation, apoptosis, and its disruption associated with the formation and recurrence of many malignancies. Smad7 was first shown to be a negative regulator of TGF signalling. By attaching to TGF receptor type I, Smad7 prevents Smad2/3 from activating downstream. Smad7's cooperation with other intracellular proteins has been shown in recent studies, suggesting that it is involved in TGF-independent signalling pathways and may have a deeper impact on the development and progression of cancer (Capelle et al., 2020). According to experimental research, Smad7's influence on the growth of tumours differs according to the situation. It has shown promise in preventing the growth and metastasis of some cancers, including colorectal and hepatocellular carcinomas, by inhibiting angiogenesis, inflammation, and the epithelial-mesenchymal transition (EMT). On the other hand, Smad7 has been observed to influence cell migration, survival, and proliferation in various situations, which aid in the formation and spread of cancer. Given its simultaneous involvement in both the genesis and progression of cancer, Smad7's function may vary depending on the type of cancer and stage of tumour growth. Furthermore, Smad7 expression abnormalities are frequently seen in a variety of human cancers, suggesting that it may play a part in the initiation and spread of cancer. As such, Smad7-targeting therapeutic approaches offer a promising new direction in cancer treatment. Preclinical models have been utilised to produce and test Smad7 inhibitors, which have demonstrated the capacity to obstruct tumour growth and metastasis (Stolfi et al., n.d.).

8.1.2. PKM2/ Pyruvate kinase M2

The results of the study show that the PKM2 mRNA expression in gallbladder cancer (GBC) tissue is higher than in the surrounding normal gallbladder tissue. It was noteworthy that almost half of the GBC tissue samples that were paraffin-preserved showed this increased expression. In addition, using a sizable cohort of GBC patients, the researchers investigated the relationship between the expression level of PKM2 and several clinical or pathological traits. An isoform of pyruvate kinase called PKM2 is essential for controlling cellular metabolism. This enzyme functions as a tetramer in normal cells and is crucial to the glycolysis process because it converts phosphoenolpyruvate (PEP) to pyruvat. On the other hand, within cancerous cells, it predominantly manifests as a dimer, resulting in altered glucose metabolism and increased generation of lactate. This alteration in glucose metabolism is a distinguishing feature of cancer cells and is believed to facilitate their survival and growth. The control of PKM2 gene expression is influenced by multiple factors, including oncogenes, tumour suppressor genes, and miRNAs (Lu et al., 2016). Fluctuations in the expression of these factors can lead to modified PKM2 levels and function, thereby promoting the initiation and advancement of cancer. The regulation and functioning of PKM2 in cancer cells are intricate and ever-changing, necessitating further exploration to gain a comprehensive comprehension of its involvement in the formation of cancer and to devise effective treatment strategies targeting this protein (Christofk et al., n.d.).

8.1.3. Bcl-2 gene

Also known as B-cell lymphoma or leukaemia-2, plays a significant role in gallbladder cancer (GBC) tissue by controlling cell apoptosis. To investigate a potential treatment approach, scientists explored the use of small interfering RNA (siRNA) that specifically targets the Bcl-2 gene. They aimed to assess the effectiveness of introducing Bcl-2 siRNA (Yang et al., 2017). The study involved constructing a eukaryotic expression vector containing Bcl-2 siRNA, which was then transferred into GBC-SD cells, a type of human gallbladder cancer cells. The outcomes showed that utilising a Bcl-2 siRNA vector successfully reduced the expression of Bcl-2 in the cells (Marie Hardwick & Soane, 2013). As a result of this suppression, cell apoptosis was suppressed, and 5-fluorouracil chemotherapy sensitivity was raised. Additionally, research conducted in vivo utilising a mouse xenograft model of gallbladder carcinoma showed that the Bcl-2 siRNA vector

significantly reduced tumour development. These results show that siRNA, which blocks Bcl-2 expression, has the potential to be a useful treatment for GBC (Garner et al., 2017). According to the study, synthetic inhibitors that target Bcl-2 may be an effective treatment option for gallbladder cancer. To investigate the therapeutic usefulness of this method, more study is needed. The study's findings offer a foundation for further research and inspire the creation of prospective GBC therapies based on siRNA-mediated inhibition of Bcl-2 expression (Geng et al., n.d.).

Table 4: The relation between lncRNAs and miRNAs in GBC

Sr. No.	**miRNA**	**Expression (miRNA)**	**mRNA**	**Expression (mRNA)**
1	miR-146b-5p	Down	GFR	Up
2	miR-20a	Up	Smad7	Down
3	miR-29c-5p	Down	CPEB4	Up
4	miR-133a-3p	Down	RBPJ	Up
5	miR-26a	Down	HMGA2	Up
6	miR-122	Down	PKM2	Up
7	miR-143a-3p	Down	ITGA6	Up
8	miR-101	Down	ZFX	Up
9	miR-30d-5p	Down	LDHA	Up
10	miR-182	Up	CADM1	Down
11	miR-30b	Down	NT5E	Up
12	miR-340	Down	NT5E	Up
13	miR-125b-5p	Down	Bcl2	Up
14	miR-143-5p	Down	HIF-1 alpha	Up
15	miR-33a	Down	IL-6	Up
16	miR-223	Down	STMN1	Up
17	miR-218-5p	Down	PRKCE	Up

8.1.4. CADM1

The important cell adhesion molecule CADM1 has garnered a lot of attention because of its function in controlling the growth of tumours. Research has shown that CADM1 plays a complex role in the development of tumours. It promotes the death of tumour cells, inhibits the growth of cancer, and controls several signalling pathways, including AKT, EMT, and STAT3. The prevention of tumour cell invasion and migration is facilitated by the actions of CADM1. On the other hand, aggressive tumour behaviour has been linked to decreased expression of CADM1. Interactions between CADM1 and long non-coding RNAs (LncRNAs) and microRNAs (miRNAs) are an interesting part of CADM1 regulation in carcinogenesis. These non-coding RNA molecules could affect CADM1 expression, which in turn affects tumour growth and mortality, either directly or indirectly. More specifically, in some cancer types, particular LncRNAs have been found to be CADM1 regulators. In adult T-cell leukaemia/lymphoma (ATLL), for example, CADM1's role appears to involve the NF-kB pathway. Shifting the focus to gallbladder cancer (GBC), recent studies have emphasized the crucial roles of LncRNAs in GBC pathogenesis. LncRNAs such as SPRY4-IT1, CRNDE, HOXA-AS2, UCA1, and lncRNA-H19 have been implicated in promoting GBC development and progression. These LncRNAs exert influence over various cellular processes, including proliferation, metastasis, and epithelial-mesenchymal transition (EMT) (Qiu et al., 2014). Their dysregulation in GBC suggests their potential as therapeutic targets for inhibiting tumour metastasis and as prognostic indicators. Furthermore, lncRNAs in GBC have been found to interact with mRNAs and miRNAs, thereby adding another layer of complexity to the regulatory network. For instance, H19 has been identified as a molecular sponge for miR-342-3p, controlling the expression of FOXM1. Similarly, LINC00152 and CCAT1 act as sponges for miR-138 and miR-218-5p, respectively, regulating target genes involved in cell proliferation. Additionally, lncRNA-LET has a significant impact on gallbladder tumour development. Overexpression of lncRNA-LET under hypoxic conditions confers a proliferative advantage to tumour cells. Conversely, abnormal expression of lncRNA-LET inhibits gallbladder tumour growth, indicating its potential as both a prognostic marker and therapeutic target. Overall, the complex interplay between CADM1, LncRNAs, miRNAs, and mRNAs shows the complexity of tumour biology and the potential of these molecules as indicators for early detection and therapy targets for cancer (*Table 4*). Undoubtedly, more interactions will be found as this field of study develops, and this information will help with the creation of novel treatment approaches for cancer patients (Zhu et al., 2022).

8.2. GBC-related proteins

In addition to the substances previously discussed, it is critical to acknowledge the significance of critical proteins in the detection and management of gallbladder cancer. Protein acetylation and phosphorylation are two mechanisms that can lead to altered protein expression. Numerous proteins that impact gallbladder cancer have been found and investigated in detail (see Table 5).

Examining the complex interactions between different proteins and their expression levels is essential because it provides important information about gallbladder cancer (GBC) diagnosis, prognosis, and treatment. Many proteins have been identified in GBC, and the expression levels of these proteins may have an impact on how the disease develops. Notably, Bcl-2 promotes the proliferation of cancer cells, suggesting that it could be a target for therapeutic intervention in GBC. On the other hand, overexpression of c-erb-B2 is linked to a poor prognosis in GBC. Reduced FHIT expression has been linked to Mlh1 expression during GBC formation, and the MMP-2/TIMP-2 ratio may be used as a diagnostic marker for early GBC diagnosis. P16INK4 is inhibited by the retinoblastoma protein, and higher P16INK4 expression is associated with worse survival results in GBCs. In addition, overexpression of S100A4 and P53 as well as decreased expression of p27, Smad4, FHIT, E-cadherin, p16, and RB are associated with poor survival in GBC. In GBC, some proteins, like P53 and PML, show promise as therapeutic targets. Research conducted on GBC cell lines indicates that SP1 and CDX2 are frequently overexpressed, with CDX2 expression being linked to the generation of MUC2. Comprehending these patterns of protein expression provides essential insights into GBC, directing the creation of efficacious diagnostic and treatment approaches. Furthermore, understanding GBC and improving treatment approaches depend heavily on deciphering protein expression and phosphorylation patterns. For example, cyclin D1 and P16 have a negative association that affects GBC in its early phases, and GBC diagnosis and treatment are associated with phosphorylation events. CD133, when phosphorylated, enhances GBC cell motility, while MUC4 interacts with ErbB2 to promote tumour formation through ErbB2, MAPK, and Akt hyperphosphorylation. Studies have shown that blocking Akt phosphorylation can reduce the pro-apoptotic effects of cirsimaritin, a compound under investigation. PHLPP, a protein phosphatase, has demonstrated its potential in GBC treatment by inhibiting surviving phosphorylation. Additionally, increased expression of the CCK1 receptor has been associated with enhanced protein lysine acetylation, suggesting potential diagnostic applications using histone deacetylase inhibitors. Understanding the complex patterns of protein expression and phosphorylation in GBC provides crucial insights into the

disease and aids in the development of improved diagnostic and treatment strategies (Wu et al., 2017)

9. Therapeutic Implications

Gallbladder cancer (GBC) is a subtype of biliary tract tumours (BTC), which also includes extra- and intrahepatic cholangiocarcinoma. Recent advancements in next-generation sequencing (NGS) have demonstrated the genetic distinctions between GBC and cholangiocarcinoma. Despite its extremely low incidence, GBC is notable for its aggressive characteristics and dismal prognosis. The only curative therapy available today is still complete surgical excision, although it is limited to use in early-stage cases. Regrettably, systemic medications are required for palliative care or to enable surgery because most GBC cases are discovered at advanced stages when surgery is not an option. Unresectable, locally progressed, and metastatic GBC have traditionally been treated primarily with gemcitabine and platinum-based chemotherapies. However, during the past ten years, the therapeutic landscape has seen some notable breakthroughs. These innovations cover a range of tactics. For circumstances when initial chemotherapy failed, creative chemotherapeutic methods have been developed. Targeted medicines have also been developed to treat certain gene mutations linked to GBC, including those in the HER2, FGFR, and BRAF genes. Immune checkpoint inhibitors have also been researched to boost the body's anti-tumour response. It is important to note that because of the rarity of these bile duct malignancies, clinical studies frequently include both GBC and cholangiocarcinoma.

Table 5: Key genes in GBC.

Sr. No.	miRNA	Expression(miRNA)	mRNA	Expression(mRNA)
1	miR-146b-5p	Down	GFR	Up
2	miR-20a	Up	Smad7	Down
3	miR-29c-5p	Down	CPEB4	Up
4	miR-133a-3p	Down	RBPJ	Up
5	miR-26a	Down	HMGA2	Up
6	miR-122	Down	PKM2	Up
7	miR-143a-3p	Down	ITGA6	Up

8	miR-101	Down	ZFX	Up
9	miR-30d-5p	Down	LDHA	Up
10	miR-182	Up	CADM1	Down
11	miR-30b	Down	NT5E	Up
12	miR-340	Down	NT5E	Up
13	miR-125b-5p	Down	Bcl2	Up
14	miR-143-5p	Down	HIF-1 alpha	Up
15	miR-33a	Down	IL-6	Up
16	miR-223	Down	STMN1	Up
17	miR-218-5p	Down	PRKCE	Up

9.1. miRNAs as Therapeutics Target

Investigations into genomic sequencing have produced findings on the genetic variety of biliary tract malignancies (BTCs). Different BTC groups display distinct arrangements of genetic changes. Mutations in genes including FGFR1, FGFR2, IDH1, IDH2, BAP1, and ARID1A are usually associated with intrahepatic cholangiocarcinoma (Artegiani et al., 2019). Contrarily, SMAD4 changes are commonly seen in extrahepatic cholangiocarcinoma. Compared to other biliary tract tumours, gallbladder malignancies (GBCs) show molecular differences. Increased EGFR gene cluster activation and mutations in the genes TP53, SMAD4, ARID1A, PIK3CA, CDKN2A, and CDKN2B separate GBCs from other types of cancer (Chen et al., n.d.). Studies employing various genomic methodologies have revealed increased frequencies of Her2/neu overexpression and amplification, alongside heightened TOP2A expression and amplification, in gallbladder cancers (GBCs) in contrast to cholangiocarcinoma. Additionally, a subgroup of GBCs exhibited mutations in genes responsible for homologous repair. Intriguingly, the genetic characteristics of GBCs may exhibit divergence depending on the geographical region (Lau et al., n.d.). Diverse groups exhibit discrepancies in the presence or absence of certain mutations. Examples include the absence of ARID1A and PIK3CA mutations in the Japanese group and the absence of ARID2 and ERBB3 mutations in the Chilean individuals (Farshidfar et al., n.d.). The relationship between HER2/neu overexpression and overall survival and disease-free survival is still unclear in gallbladder malignancies (GBCs), as indicated by the conflicting findings of

several studies. There may be two distinct genetic pathways involved in the molecular aetiology of GBC. While GBCs in people with cholelithiasis in Chilean communities have a higher prevalence of TP53 mutations, GBCs coming from aberrant pancreaticobiliary ductal junctions (APDJs) typically reveal KRAS mutations (Roessler et al., n.d.). These findings highlight the variety of genetic alterations in BTCs and their potential effects on therapeutic strategies and patient outcomes. To provide more individualised therapies for people, additional research is required to get a greater understanding of the molecular subtypes of BTCs and their medicinal significance.

9.2. Targeted therapy (BRAF/MEK pathway)

Raf/MEK/ERK signalling pathway activation has been reported in 3% of biliary tract neoplasms (BTCs), which are tiny tumours with BRAF V600E mutations. Clinical trials have investigated inhibitors targeting this route for the treatment of BTC considering these findings. In a phase 1/2 study of BTC patients, a cohort of 34 patients who had progressed after initial gemcitabine-based treatment saw an overall lifespan (OLS) of 7.8 months, a duration of disease control (DDC) of 4.1 months, and a collective response rate (CRR) of 20.6% when the MEK inhibitor binimetinib was combined with gemcitabine and capecitabine (Long et al., n.d.). After receiving cisplatin, gemcitabine, and binimetinib therapy, a subgroup of 35 untreated BTC patients demonstrated a 36% response rate (ORR), a 6-month progression-free survival (PFS), and a 13.3-month overall survival (OS). For advanced BTC cases, phase 1b research (ABC-04) assessed the combination of gemcitabine, cisplatin, and the MEK inhibitor selumetinib. Only two of the eight people that were tested gave a complete or partial answer. In patients with BRAF V600E mutant tumours, including BTCs, the phase 2 ROAR basket research showed encouraging outcomes when dabrafenib and trametinib, two MEK inhibitors, were combined. The overall response rate (ORR) was 47%, the overall survival rate (OS) was 14 months, and the median progression-free survival (PFS) was 9 months among the 43 BTC patients who received treatment. These results point to the possibility of treating BTCs, especially those with BRAF V600E mutations, by focusing on the BRAF/MEK pathway. Nevertheless, further thorough investigation is required to confirm the effectiveness and security of these specialty medications for BTC patient (Wainberg et al., 2019).

9.3. Therapeutics

The aggressive nature and rarity of gallbladder cancer (GBC) have made the development of viable treatment alternatives difficult. To address this problem, several biliary system tumour forms, such as extrahepatic and intrahepatic cholangio carcinomas and gallbladder cancer (GBC), have been the subject of substantial phase 3 clinical research. This approach aims to overcome the limited number of cases and the heterogeneity among these rare malignancies. By grouping these cancers, researchers can evaluate potential treatment strategies more comprehensively and identify therapies that may benefit multiple subtypes of biliary tract cancer. The goal is to leverage shared characteristics and commonalities among BTCs to improve treatment outcomes (Edeline et al., 2019).

9.4. Neoadjuvant Therapy for BTCs

There is currently little research to support any therapy regimens or certain benefits, making it difficult to determine the best preoperative treatment for gallbladder cancer (GBC). Nevertheless, several studies have looked at the possible role of preoperative intervention as a workable substitute for people with GBC. In a review of 74 patients with GBC, Creasy and colleagues identified a subset of people who showed positive responses to preoperative treatment, exhibiting improved results after the final surgical surgery. In addition, phase 2 research by Shroff and colleagues worked with 60 patients with advanced biliary tract tumours, including 13 patients with GBC. The effectiveness of preoperative regimens comprising gemcitabine, cisplatin, and nab-paclitaxel was carefully assessed in this work (Shroff et al., n.d.). With a complete response rate (ORR) of 45%, illness control was successfully achieved in 84% of cases. Surprisingly, the preoperative treatment allowed 12 patients with previously inoperable diseases to endure surgery. For preoperative treatment of gallbladder cancer (GBC), other chemotherapeutic options to gemcitabine include 5-FU, standalone capecitabine, standalone gemcitabine, gemcitabine with a platinum agent, or 5-FU with a platinum agent. Preoperative chemotherapy regimen selection may be influenced by patient features, tumour stage, and doctor preferences. Emphasizing the necessity lies in conducting additional investigations and clinical experiments to ascertain the efficiency and optimal approach of preoperative intervention in gallbladder cancer (GBC) (surgery et al., n.d.).

9.5. Adjuvant Therapy

Surgery is currently the only treatment option for gallbladder cancer (GBC). Most GBC patients (66%) still have disease return after two years, typically in remote locations, despite

having had entire excision. There have been new reports of clinical trials looking at possibilities for supplemental therapy in biliary tract tumours, even though neoadjuvant therapy, administered before surgery, has not yet been categorically acknowledged as a typical method for BTCs.

9.6. Systemic Treatment

The mainstay of care for patients with incurable gallbladder cancer (GBC) is still cytotoxic chemotherapy. An important study in this field was the phase 3 randomised ABC-02 trial, which compared the effectiveness of gemcitabine plus cisplatin (Gem CIS) to gemcitabine alone in patients with ampullary cancer, gallbladder cancer, or locally advanced or metastatic cholangiocarcinoma. The Gem CIS group had a considerably longer median progression-free survival (PFS) of 8.0 months compared to 5.0 months, while the Gem CIS group had a median overall survival (OS) of 11.7 months compared to 8.1 months for the gemcitabine group. Additionally, 81.4% more tumours were controlled in the Gem CIS group than in the Gemcitabine group. Gemcitabine and cisplatin were the main treatment options for locally progressed and metastatic biliary tract cancers after the ABC-02 study.

Later research investigated other combinations of treatments to improve results. The phase 2 research demonstrated encouraging outcomes for both nab-paclitaxel and GemCis, with a median PFS of 11.8 months and an OS of 19.2 months. We anticipate a phase 3 randomised investigation contrasting this combo with gemcitabine and cisplatin. In the ABC-06 trial, FOLFOX was suggested as a possible second-line treatment. Patients with gallbladder cancer (GBC) had a median overall survival (OS) of 5.1 months for the FOLFOX group, versus 4.6 months for active symptom control (ASC) alone. Despite not reaching statistical significance, FOLFOX showed a tendency towards increased survival.

Another viable second-line approach is liposomal irinotecan plus 5-FU/leucovorin, which demonstrated a substantially higher median PFS (7.1 months) in a phase 2b study than 5-FU/leucovorin alone (1.4 months). In the US, ongoing studies, such as the NAPOLI-2 study, are assessing the safety and effectiveness of 5-FU/leucovorin and liposomal irinotecan for biliary cancer.

To sum up, the principal treatment for incurable gallbladder cancer is still cytotoxic chemotherapy, especially regimens based on gemcitabine. Significant improvements in overall survival, progression-free survival, and tumour control rate have been shown with

gemcitabine and cisplatin. To enhance outcomes for patients with biliary tract malignancies, FOLFOX and liposomal irinotecan with 5-FU/leucovorin are being closely examined. Ongoing study of alternative combinations, such as nab-paclitaxel with GemCis or FOLFOX, shows promise in clinical studies.

10.Discussion

The findings from this study underscore the significant challenges in diagnosing and treating gallbladder cancer (GBC). The persistent difficulty in achieving early and accurate diagnosis contributes to high rates of misdiagnosis and delays in identifying patients who could benefit from early intervention. This diagnostic challenge is compounded by the fact that GBC is often discovered at advanced stages, which severely limits treatment options and diminishes survival prospects. The grim reality that no patient has surpassed a five-year survival without surgery further emphasizes the critical need for improved early detection and treatment strategies. The limited success of current therapeutic approaches highlights a substantial gap in effective GBC treatment. While operative resection remains the sole curative option, only a small fraction of patients is eligible, leaving many without potentially life-saving interventions. The promising potential of targeted therapy, though still not a definitive cure, particularly in advanced cases, points to an urgent need for ongoing research. This research should focus on developing novel treatments and enhancing current methodologies to improve patient outcomes. Furthermore, exploring new diagnostic technologies and approaches could aid in earlier detection, thereby increasing the likelihood of curative treatment and improving survival rates.

The current landscape of GBC treatment reflects both progress and limitations. While targeted therapies and chemotherapy offer some promise, they are not yet a cure. Chemotherapy, when combined with surgery, improves five-year survival rates, but it also introduces potential side effects such as decreased appetite and reduced white blood cell count. This reinforces the need for novel and more effective treatments to overcome these limitations. Future research must focus on enhancing the effectiveness of current treatment regimens, exploring novel therapeutic targets, and improving early diagnostic techniques. The continuous evolution of understanding in the molecular mechanisms of GBC and the development of innovative treatment strategies is crucial for advancing patient outcomes. As we progress, addressing the challenges of GBC through dedicated research efforts will be essential for improving survival rates and treatment efficacy.

Conclusions

Diagnosing and treating gallbladder cancer (GBC) is extremely difficult. Many times, early and accurate diagnosis is still difficult to come by, which makes misdiagnosis more common in clinical settings and makes it more difficult to identify patients who would benefit from early intervention. Although operative resection is the only treatment that can be used to cure GBC, only 38% of patients have met the eligibility requirements over the previous 20 years. This highlights the reality that a significant portion of patients are not able to receive potentially curative care. The fact that GBC is frequently discovered at advanced or intermediate stages, which further restricts treatment options and lowers survival chances, exacerbates these difficulties. The reality that no patient has lived more than five years without surgery serves as a stark reminder of the need of early detection and treatment. It is imperative to address the challenges associated with diagnosing and treating GBC, which calls for additional research to improve patient outcomes by using more efficient diagnostic and treatment modalities. Targeted therapy is not yet a cure for GBC, even though it offers promise, particularly in advanced stages. Patients with GBC who receive chemotherapy, which is frequently combined with surgery, have better 5-year survival rates than those who only have surgery. On the other hand, decreased appetite and a decrease in white blood cell count are possible side effects of chemotherapy. It is imperative to look on novel and effective GBC treatments given the shortcomings of the available choices.

The goal of ongoing research is to improve the effectiveness of chemotherapy regimens and find new targets for targeted treatment. Immunotherapy, which uses the body's defences against cancer cells, is a promising new therapeutic option for gastric cancer. New insights into the aetiology and prognosis of GBC have led to the discovery of putative genetic prognostic markers. Research has demonstrated that lupeol interacts with the EGFR/MMR-9 pathway to cause GBC to undergo programmed cell death. The PI3K-AKT pathway has been linked to long non-coding RNAs including LINC00152 and CRNDE, which may offer a treatment option for GBC. These results highlight the significance of figuring out the molecular causes of GBC and locating viable therapeutic targets. It is essential to conduct more research in this area to create GBC treatments that work and enhance patient results. The path to better knowledge and creative solutions is a continuous one, and it is essential to improving the treatment of gallbladder cancer.

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Author contribution

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Data Availability

Data will be made available on request.

Conflict of interest

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