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Exploring Diagnostic Markers of Gallbladder Cancer: Advancements, Challenges and Limitations

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1. Abstract

Gallbladder cancer is a major cancer of gastrointestinal tract, accounting for nearly 122,491 new cases in 2022. Reviews indicated the specific biochemical and molecular biomarkers are seen various study. This review aims to discuss the advancements, challenges, and limitations of diagnostic markers for GBC. CA-19-9, CYFRA 21-1, and circulating tumor DNA (ctDNA) are some of the biomarkers that have shown promise in GBC diagnosis. The sensitivity and specificity of these biomarkers are varying that is essential for improving GBC diagnosis and treatment. The Advancement in the field of diagnosis gallbladder cancer are possible using Biomarkers, Imaging techniques and Molecular testing including Next-generation sequencing (NGS) and polymerase chain reaction (PCR). When exploring the diagnosis various challenges will face like limited sensitivity, high costs, limited availability of late-stage treatment options. This review aims to provide an overview of the current state of diagnostic markers for GBC, including their advancements, challenges, and limitations and the most potentially significant susceptibility, diagnosis for gallbladder cancer patients.

2. Introduction

Gallbladder cancer is a major cancer of the gastrointestinal tract, accounting for nearly 122,491 new cases in 2022 [1]. India accounts for approximately 25% of the world's gallbladder cancer cases, making it a major public health concern in the country [2]. In India, 16,407 deaths were reported due to gallbladder cancer in 2022 [3]. The diagnosis of gallbladder cancer is challenging due to the disease's asymptomatic nature in the early stages [4]. The use of biochemical and molecular markers has become increasingly critical in improving early detection, risk stratification, and prognosis assessment [5]. Diagnostic biomarkers play an essential role in cancer management by aiding in early detection, monitoring disease progression, and predicting response to therapy [6]. Commonly studied biomarkers such as CA 19-9 and CEA in gallbladder cancer have shown limited diagnostic accuracy due to low sensitivity and specificity, particularly in distinguishing malignant cases from benign conditions such as chronic cholecystitis [7]. The sensitivity and specificity of existing markers remain suboptimal. [8]. Combining multiple biomarkers (e.g., CA 19-9 with molecular markers) shows potential to improve diagnostic accuracy [9]. Gallbladder cancer is often associated with poor prognosis due to its asymptomatic nature in early stages and rapid progression, leading to late-stage diagnoses when curative treatment options are limited [10]. The primary obstacle is the asymptomatic nature of GBC in its early stages, leading to diagnosis only when the disease has advanced and metastasized [28]. Regions such as northern India, South America, and Japan have a disproportionately higher prevalence of gallbladder cancer, influenced by genetic predispositions, dietary habits, and the high incidence of gallstones in these populations [11]. The limitations to understanding the progress of gallbladder cancer are delayed diagnosis, limited biomarker validation, therapeutic challenges, resource constraints, prognostic model limitations, lack of public awareness of high-risk factors such as gallstones and chronic infections, and delays in the diagnosis of gallbladder cancer [12]. Genetic polymorphisms have also been seen in gallbladder cancer, and these polymorphisms can influence gene expression by affecting various regulatory elements within the genome [13].Some studies have shown that the most frequently altered genes in gallbladder cancer are TP53, CDKN2A/B, ARID1A, ERBB2, KRAS, SMAD4 and PI3KCA [14-15]. Asymptomatic in early stages, and the absence of reliable, non-invasive diagnostic tests for early-stage GBC highlights the importance of biomarkers like CYFRA 21-1 in identifying the disease at an earlier time. The diagnostic role of CYFRA 21-1 is one of the most significant challenges in the management of gallbladder cancer and difficulty in early detection. Imaging techniques used for diagnosing gallbladder cancer, such as ultrasound, CT scans, and MRI are often unable to detect small tumors or early-stage cancers. As a result, researchers have explored the use of biomarkers, including CYFRA 21-1, to supplement imaging and provide more accurate early diagnosis. Some studies have suggested that elevated CYFRA 21–1 level may correlate with the presence of gallbladder tumors, potentially offering a more specific diagnostic approach when combined with imaging modalities [17]. A recent study reported that S1P1 overexpression or ERp29 absence is related to carcinogenesis and progression of the potential of biomarkers for the early detection of gallbladder cancer [18]. Gallbladder cancer (GBC) remains a highly aggressive malignancy with poor prognosis, often due to late diagnosis. Biomarkers such as carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) are widely studied for their diagnostic potential in GBC. Emerging molecular markers, including KRAS mutations and HER2/neu overexpression, have shown promise in improving diagnostic accuracy and predicting therapeutic responses. [17] Recent advancements in molecular biology and high-throughput technologies, including genomics, proteomics, and metabolomics, have provided new avenues for identifying novel biomarkers with better clinical utility [18].The aim of present review was to discuss the biochemical and molecular markers currently used in GBC diagnosis, prognosis, and therapy selection. The challenges of present diagnostic markers and their future prospective with reference to their susceptibility, were also discussed. It highlighted the need for validation of existing novel biochemical and molecular biomarkers to improve patient outcomes.

3. Epidemiology and Risk Factors

Gallbladder cancer (GBC) is a rare but highly aggressive malignancy with significant geographical and demographic variability [8]. Understanding its epidemiology and risk factors, it is crucial for

targeted prevention, early diagnosis, and management. In the northern and eastern regions of India, gallbladder cancer is a significant health concern [20]. Recent studies have shown that the highest incidence of gallbladder cancer is in Uttar Pradesh, Bihar, and West Bengal states of India. In India, particularly in regions such as Uttar Pradesh and Bihar, GBC accounts for a significant proportion of gastrointestinal cancers, with incidence rates reaching up to 9 per 100,000 annually [21]. It is more common among women and older adults, particularly those over the age of the disease, which is a major risk factor for the development of this cancer [22]. Studies shows that age and female gender were risk factors for gallbladder cancer [23]. The incidence of GBC exhibited marked gender bias, and females were several times more susceptible than males. Some researchers speculated that estrogen might play an important role in GBC development [25]. The value of the early diagnosis of these factors for GBC is limited [26]. Gallbladder cancer caused by the presence of risk factors such as gallstones, infections, lithogenic bile, alcohol, smoking, and genetic predisposition can induce continuous damage in the mucosa of the gallbladder [26]. More recently, circulating inflammatory proteins have been associated with increased GBC risk compared to patients suffering from biliarylithiasis, which can cause a high risk of gallbladder cancer [27]. The significant biological heterogeneity is influenced by genetic, molecular, and environmental factors in the case of gallbladder cancer. The heterogeneity complicates the identification of universal diagnostic markers.

4. Pathophysiology of Gallbladder Cancer

The carcinoma of gallbladder cancer is the most prevalent cancerous tumor of the biliary system and the sixth most widespread cancer of the gastrointestinal system [8]. Variability in tumor microenvironments and molecular profiles between patients often leads to inconsistent biomarker performance [4]. The pathophysiology of GBC is complex and involves multiple genetic and environmental factors, including chronic inflammation, gallstone disease, and bacterial infections. These mechanisms are essential for improving early detection and treatment strategies. Mutations in genes such as TP53, KRAS, CDKN2A, and PIK3CA, which play roles in cell cycle regulation, apoptosis, and signal transduction are associated with genetic and molecular alterations in gallbladder cancer [18]. BRCA1 gene mutation, are also increasingly recognized as contributors to familial cases of GBC. Epigenetic changes, such as DNA methylation and histone modifications, also play a critical role in GBC pathogenesis. Hyper-methylation of the RASSF1A gene has been observed in GBC tissues and is associated with tumor progression [28].

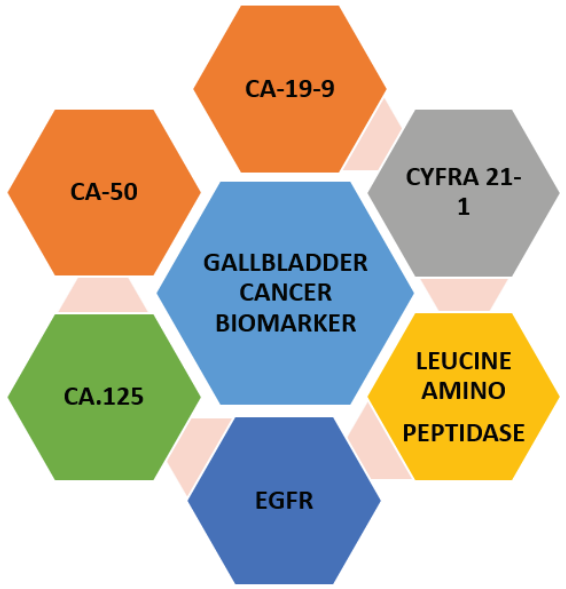

Figure 1: Biomarkers of Gallbladder Cancer.

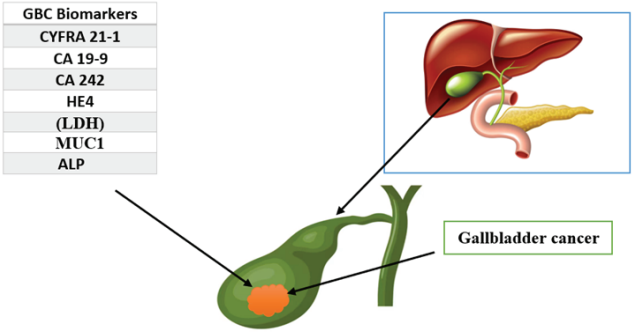

Figure 2: Gallbladder cancer and their biomarkers.

5. Current Diagnostic Approaches

The current diagnostic approaches for gallbladder cancer (GBC) include imaging modalities such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), as well as tumor markers such as carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA 19-9). [9]. However, these approaches have limited sensitivity and specificity, and often lead to delayed diagnosis and poor treatment outcomes [29]. Recent, advances in molecular diagnostics, such as next-generation sequencing (NGS) and liquid biopsy, have shown promise in improving the early detection and diagnosis of GBC [10]. Additionally, the development of novel biomarkers, such as microRNAs and circulating tumor DNA, has also shown the potential to improve the diagnosis and treatment of GBC [11]. Geological variants within the ABCG8 and TRAF3 genes have been reported to confer GBC risk development in the Chilean population [30]. Early detection with molecular markers, targeted therapies like HER2/neu and KRAS, advanced imaging techniques, minimally invasive surgical techniques, immunotherapy advancements, integration of artificial intelligence, improved public awareness, and screening have enhanced the prospects of gallbladder cancer diagnosis and treatment [37].

6. Diagnostic Markers: Recent Advancements

Gallbladder cancer (GBC) is a highly aggressive and lethal malignancy that requires early diagnosis and treatment. Recent advancements in molecular and biochemical research have led to the identification of several emerging markers for GBC. These markers have the potential to improve the diagnosis, prognosis, and treatment of GBC. The molecular and biochemical biomarkers of gallbladder cancers and their sensitivity and specificity varies from the different biomarkers in gallbladder cancer patients. MicroRNAs (miRNAs) are small non-coding RNAs that play a crucial role in regulating gene expression. Several miRNAs, including miR-21, miR-221, and miR-222, have been identified as potential markers for GBC [32]. Circulating Tumor DNA (ctDNA), protein Markers like CA 19-9, and HER2, have been identified as potential markers for GBC [52]. Epigenetic markers such as DNA methylation and histone modification, have been identified as potential markers for GBC [34].The exploration of molecular biomarkers such as CA19-9, KRAS, CYFRA 21-1, MicroRNA-155 (miR-155), and exosomal protein detection and diagnosis of gallbladder cancer [9]. For example, miR-21 and miR-155 have emerged as non-invasive potential markers for early detection and prognosis [35]. In addition, next-generation sequencing (NGS) has enabled the identification of genetic alterations such as TP53 and KRAS mutations, paving the way for precision medicine and targeted therapies [10]. Imaging advancements, including PET-CT and multipara metric MRI, have improved the accuracy of tumor staging and metastatic assessment [36]. Artificial intelligence (AI) and machine learning are being increasingly integrated into imaging diagnostics, enhancing the differentiation between benign and malignant gallbladder lesions [39]. The validation and clinical integration of novel biomarkers

face hurdles such as high costs, lack of standardization, and limited large-scale studies [11]. These issues are particularly pronounced in resource-limited settings where GBC is most prevalent [36]. Therapeutically, GBC poses challenges due to its complex molecular heterogeneity and high resistance to standard chemotherapeutic regimens. To address these challenges, multi-modal diagnostic approaches that combine molecular markers, advanced imaging, and AI-driven analytics are critical [9]. Global collaboration in research and the establishment of cancer registries in high-prevalence regions can enhance the understanding of GBC epidemiology and facilitate the development of population-specific diagnostic and treatment strategies [12]. Public health initiatives focused on awareness, risk factor mitigation, and screening for high-risk populations for improving early detection and patient outcomes [36]. Advancement in the carcinogenesis process the field of gallbladder cancer is important and characterized by a chronic inflammatory state mainly highlighted by the activation of macrophages and lymphocytes, that leads to the release of pro-inflammatory cytokines (TNF-α, IL-6, IL-1) and ROS stimulating the carcinogenic metaplasia/hyperplasia–dysplasia–carcinoma transition. This process can be marked by different gene alterations and protein expressions [39].The development of high-throughput techniques like next-generation sequencing (NGS) allows for comprehensive profiling of genetic and epigenetic alterations in gallbladder cancer [35]. Next-generation sequencing (NGS) is used for the genomic landscape of biliary tract cancers and provides new options for the discovery of biomarkers for clinical oncology. Some of the advanced biomarker and their measurement techniques are discussed in Table-1. Some recent molecular and biochemical markers, their sensitivity, and specificity are atribulated in Table-2 and Table-3 respectively

7. Limitations of Gallbladder Cancer Diagnosis

Current studies on gallbladder cancer (GBC) have several limitations that need to be addressed. One of the major limitations is the lack of large-scale, prospective studies that can provide reliable data on the incidence, prevalence, and outcomes of GBC [9]. Additionally, many studies have small sample sizes, which can limit the generalizability of the results [35]. Furthermore, current studies have limited focus on the molecular mechanisms underlying GBC, which can hinder the development of effective therapeutic strategies [10]. Many patients with GBC present with nonspecific symptoms, such as abdominal pain, nausea, or jaundice, which are common to several other gastrointestinal disorders, including benign conditions such as cholecystitis or gallstones [43].

7.1. Late Diagnosis and Asymptomatic Nature of GBC

In the case of gallbladder cancer, there is a major challenge in managing gallbladder cancer. It is a fact that it often remains asymptomatic in its early stages. As a result of this, many patients are diagnosed at advanced stages, where treatment options are limited. At early stages, GBC may cause nonspecific symptoms, such as abdominal pain, jaundice, or nausea, which can easily be attributed to more common conditions like gallstones or cholecystitis. By the time symptoms become more pronounced, the cancer has often spread, and the tumor is typically inoperable [16]. The lack of specific symptoms at the early stages of gallbladder cancer and effective diagnostic biomarkers possess major hurdle in GBC diagnosis. 15% of the patients are candidates for curative resection at the time of diagnosis of gallbladder cancer [44]. Undifferentiated tumors are associated with worse and poorer survival [45].

7.2. Limited Effectiveness of Current Screening Methods

The late-stage diagnosis is exacerbated by the difficulty in detecting early-stage GBC with routine imaging techniques. As a result, GBC remains a disease often diagnosed incidentally during the investigation of other abdominal conditions [16]. Studies have shown that the survival rate of patients diagnosed at stage III or IV is less than 10%, with a five-year survival rate of up to 90% for stage I disease, emphasizing the need for early detection strategies [46]. There are some screening methods like ultrasound, CT scans, and MRI based on imaging techniques used for early detection of gallbladder abnormalities. Their sensitivity in detecting early GBC is limited and are often not sensitive enough to detect small tumors. CA 19-9, CEA, and CYFRA 21-1 have been suggested as potential diagnostic tools to identify gallbladder cancer abnormalities. None have shown consistent efficacy in the early detection of GBC. CA 19-9, has limited sensitivity and specificity, especially for detecting GBC at an early stage. Research into alternative biomarkers, such as CYFRA 21-1, is ongoing, but more studies are needed to establish these markers' diagnostic accuracy [47].

8. Challenges and Future Prospects

The most significant challenge in managing GBC is its asymptomatic progression during the early stages, resulting in diagnoses at advanced stages when curative options are limited [9]. The range in 5- year survival rate for stage I is 90٪ to less than 10٪ for stage IV disease. It's paramountly important for early diagnosis and treatment of gallbladder cancer [46]. Additionally, the lack of reliable early diagnostic biomarkers and the low sensitivity and specificity of conventional markers like CA 19-9 and CEA, and CA-50 further

Table1: Diagnosis Biomarkers
Abbreviations: ELISA: enzyme-linked immunosorbent assay; ECLIA: electro chemiluminescence immunoassay.

Biomarker	Measurement Technique	Utility	Reference
CA 242	ELISA	Diagnosis (sensitivity 64%, specificity 83%;positive predictive value 88%, negative predictive values 53%)	[40]
CA 19-9	ECLIA	Diagnosis (sensitivity 71.7%, specificity 96.1%)	[41]
CYFRA 21-1	ECLIA	Diagnosis (cut-off values 3.27 ng/mL; sensitivity 93.7%, specificity 96.2%)	[42]

Table 2: Diagnostic molecular Markers of Gallbladder cancer.

S.No.	Molecular Biomarker	Sensitivity and Specificity	%False +ve or False -ve	References
1.	CA-19-9	85.7% sensitivity, 90.5% specificity	14.3% false negative, 9.5% false positive	[1]
2.	CYFRA 21-1	83.3% sensitivity, 92.1% specificity	16.7% false negative, 7.9% false positive	[11]
3.	Circulating tumor DNA (ctDNA)	87.5% sensitivity, 93.8% specificity	12.5% false negative, 6.2% false positive	[33]
4.	MicroRNA-21 (miR-21)	81.8% sensitivity, 90.9% specificity	18.2% false negative, 9.1% false positive	[10]
5.	MicroRNA-155 (miR-155)	80.6% sensitivity, 91.3% specificity	19.4% false negative, 8.7% false positive	[29]
6.	HE4 (Human Epididymis protein 4)	79.4% sensitivity, 90.5% specificity	20.6% false negative, 9.5% false positive	[9]
7.	MUC1 (Mucin 1)	78.1% sensitivity, 90.9% specificity	21.9% false negative, 9.1% false positive	[51]

Table 3: Diagnostic Biochemical Markers of Gallbladder cancer.

S.No.	Biochemical markers	Sensitivity and Specificity	%False +ve or False -ve	References
1.	Carcinoembryonic antigen (CEA)	75.6%sensitivity,88.2%specificity24.4%false negative, 11.8% false positive (Gupta et al.,	24.4%falsenegative,11.8% false positive	[11]
2.	Cancer antigen 125 (CA-125)	73.2% sensitivity, 85.7% specificity	26.8% false negative, 14.3% false positive	[9]
3.	Alkaline phosphatase (ALP)	71.4% sensitivity, 83.3% specificity	28.6% false negative, 16.7% false positive	[51]
4.	Gamma-glutamyl transferase (GGT)	69.2% sensitivity, 81.3% specificity	30.8% false negative, 18.7% false positive	[11]
5.	Lactate dehydrogenase (LDH)	67.1% sensitivity, 79.5% specificity	32.9% false negative, 20.5% false positive	[9]
6.	Aspartate aminotransferase (AST)	65.5% sensitivity, 77.8% specificity	34.5% false negative, 22.2% false positive	[51]
7.	Alanine aminotransferase (ALT)	63.9% sensitivity, 76.2% specificity	36.1% false negative, 23.8% false positive	[11]

complicate early detection and in distinguishing GBC from benign conditions, undermine their clinical reliability [1-9]. However, their limitations in sensitivity and specificity underscore the need for more robust and reliable biomarkers. Advancements in genomics, proteomics, and metabolomics have paved the way for the identification of novel biomarkers, with promising applications in early detection, prognosis, and therapeutic monitoring. The opportunities that can help to improve the diagnosis and treatment of gallbladder cancer face significant challenges. Limited Availability of Robust common biomarkers markers like CA 19-9, CYFRA 21-1, and CEA show overlapping expression in both malignant and benign conditions, leading to diagnostic inaccuracies [6].Imaging techniques, while advanced, often fail to differentiate malignant from benign lesions in cases of chronic inflammation [48]. Limited access to cutting-edge diagnostic tools such as next-generation sequencing (NGS) and liquid biopsy technologies in resource-constrained settings exacerbates disparities in outcomes and prospects [49]. These advanced diagnostic technologies face multiple barriers like high costs and the need for specialized infrastructure restrict their availability in resource-limited settings [50].To enhance the diagnostic and prognostic utility of CYFRA 21-1 in gallbladder cancer, future studies should focus on combining it with other biomarkers. A multi-biomarker approach could increase sensitivity and specificity, especially when used for early detection or monitoring treatment responses. The combination of CYFRA 21-1 with biomarkers such as CA 19-9, CEA, and AFP could provide a more comprehensive diagnostic tool for GBC [26]. To address these challenges, future research should focus on integrating multi-omics approaches and also the leveraging machine learning algorithms to analyze complex datasets. The personalized medicine strategies, tailored to the genetic and molecular profiles of individual patients, also hold immense potential for improving diagnostic accuracy and treatment outcomes. Collaborative efforts between researchers, clinicians, and policymakers will be essential to ensure the widespread implementation of these advancements in clinical settings.

9. Conclusion

Moreover, the current diagnostic markers for GBC have limited sensitivity and specificity, which can lead to delayed diagnosis and poor treatment outcomes. Therefore, there is a need for large-scale, prospective studies that can provide reliable data on GBC and help to address the current limitations in the field. In conclusion, while the journey to identify effective diagnostic markers for GBC is fraught with challenges, the combination of technological advancements and a deeper understanding of cancer biology offers hope for improved diagnostic tools that can enhance early detection and ultimately. Therefore, in case of gallbladder cancer cases it's a challenges for the scientific community is the search for preventive treatments that can reduce the effect of chronic inflammation in the gallbladder, Finally, it is necessary that government authorities along with researchers commit to promoting massive sanitary and health prevention strategies in the global population, especially in poor and developing nations.

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