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REVIEW

Global gene expression landscape of gallbladder cancer and advances in targeted therapeutic strategies

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Abstract

Gallbladder cancer (GBC) is a lethal biliary tract malignancy, which is infrequent in most developed countries, but common in many developing countries in specific geographical regions of the world. Non-specific symptoms leading to late diagnosis is one of the primary factors contributing to poor prognosis in GBC. An understanding of the complex relationship between molecular genetics and epidemiological variances in the incidence rates of GBC is thus of utmost importance. Present review summarizes recent updates on population-specific dysregulated genetic expressions in the genesis of GBC, highlighting the pattern of ethno-geographic variations and on advances in targeted therapies conducted till date; points out the lacunae that deserve further attention and suggest possible new directions for future clinical trials in GBC. The review calls for the need of genetic screening of each GBC patients and for more extensive clinical trials on targeted therapies to move towards the goal of personalized medicine, bringing about more favourable survival outcomes.

Key Words: Gallbladder cancer; Differential gene expression; Ethnic variations; Tumor biomarker; Targeted therapy; Personalized medicine

Core Tip: Gallbladder cancer (GBC) is a lethal biliary tract malignancy, with it's incidence concentrated in specific geographic regions of the world, including India. Wide ethno-geographic disparity in GBC incidence rate is associated with unique population-specific genetic and molecular alterations. Present review specifically looks into the disparities in differential gene expression in the genesis of GBC across populations, summarizes the advances in targeted therapies in the treatment of GBC, highlights the need of developing population-specific biomarkers and provides possible directions for potential future clinical trials to improve the therapeutic outcomes of GBC.

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INTRODUCTION

Gallbladder cancer (GBC) is a very lethal biliary tract cancer (BTC), characterized by poor prognosis and dismal survival outcomes[1]. The symptoms and signs of GBC are vague and overlap often with gallstone disease. The clinical presentation is imprecise and may include symptoms like right upper abdominal pain, weight loss, vomiting, occasional fever, and jaundice – similar to cholecystitis, which make GBC diagnosis an uphill task, especially at an early stage[2]. Often thus, GBC is diagnosed at a late stage, when the cancer is beyond cure[1]. Although, GBC is the most common BTC reported, the incidence of GBC varies widely across ethnicities and geographical locations. While the incidence rate of GBC is quite less in most of the European nations, GBC has a high prevalence in the state of New Mexico in United States, Latin American and south Asian nations, including India[3]. The GLOBOCAN 2022 data reported 122491 new GBC cases worldwide, with China, India, Bangladesh, Brazil, Chile, *etc.*, amongst the top 10 countries, with respect to prevalence of GBC. Recent studies have also documented wide regional disparity in GBC incidence rates in India - with North India reporting a higher incidence rate at 18.0 per 100000 population, while, Southern India reporting much lower incidence rates, at 4.1 per 100000 population[4]. Though rare in United States, GBC rates are inordinately higher amongst native Americans, compared to non-native Americans[5]. Wide diversity among ethnic, geographical and racial populations in incidence rates of GBC is a unique epidemiological signature of GBC and suggests an elaborate and complex interplay of genetic and environmental factors, unique for specific populations[1].

The susceptible risk factors leading to GBC development predominantly include chronic gallstones, gallbladder polyps, porcelain gallbladder, Mirizzi's syndrome, cholangitis related infections (*e.g.*, *Salmonella enterica typhi* and *Helicobacter pylori* prevalent in India and Bangladesh), *etc.* The rate of GBC incidence increases with advancing age, primarily after middle age and although showing great variances across the world, women are in general more susceptible to GBC than men[6]. One comparatively recent hypothesis is the role of heavy metal concentration in GBC pathogenesis, and perhaps explain the inordinately high prevalence of GBC in specific regions like North India, south-western part of United States like New Mexico, and Arizona, having a high concentration of heavy metals in groundwater, and in nearby mines[7].

Like other neoplasms, GBC is a multifactorial disorder involving numerous genetic alterations. Abnormality/deletion of tumor suppressor genes (TSGs) and DNA repair genes, amplification and overexpression of oncogenes, single nucleotide polymorphisms, mutations and epigenetic alterations mainly caused by hypermethylation of promoter areas of gene are some of the various well known genetic aberrations reported till now, and vary widely across different geographical and ethnic backgrounds[8]. However, existing information on genetic and molecular alterations in GBC is still very much restricted.

Optimal management for GBC currently includes surgical resection as the primary treatment modality, however, most patients are ineligible for surgical intervention, owing to late-stage diagnosis of GBC. Therefore, non-surgical interventions, including chemotherapy, radiotherapy, *etc.* remain the main pillars for treatment of GBC, especially in advanced stages, however, accompanied with a wide range of side-effects, owing to the non-specific nature of such interventions[9]. Moreover, such non-surgical interventions, have shown very limited success and low sensitivity till date, which can be primarily attributed to the fact, that these approaches do not take into account the recent acquisition from molecular understandings of this disease. Consequently, targeted therapeutic strategies, targeting druggable molecular alterations, are gaining prominence, showing clear survival benefits in treatment of GBC[10]. Despite these advancements, GBC treatment efficacy still remains poor, which calls for a need of further research into combination strategies, biomarker development and resistance mechanisms to improve survival outcomes.

This review specifically highlights the most potently dysregulated gene expression and their variances across various ethnic and geographic backgrounds, in connection with the pathogenesis of GBC, to highlight the development of population-specific biomarkers in the genesis of GBC without venturing into other major forms of genomic alterations. The study also attempts to correlate the possible ties on knowledge of dysregulated genetic expressions in GBC with current knowledge of targeted therapies based on pre-clinical and clinical trial studies, with the goal of improving overall

survival (OS) of GBC patients, pointing out the lacunae thereof and suggesting possible future directions in targeted therapies, especially through repurposing of certain drugs and combination strategies as potential therapeutic approaches.

GENE EXPRESSION STUDIES IN GBC

In order to identify potential biomarkers for GBC development and progression, many studies have been conducted to find out the differential gene expression profiles, in various ethnic populations across the world. We look into the most significantly dysregulated genes in the genesis of GBC along with their geographic heterogeneity in order to make a clear call for development of population-specific biomarkers (Table 1).

Oncogenes

***EGFR* & *ERBB2/Her2*:** Receptor tyrosine kinases (RTKs) modulate important cellular processes like cell proliferation and differentiation by activating intracellular signaling cascades. EGFR and ERBB2 (Her2) are members of the ERBB2 RTK family. A number of recent studies have identified ErbB2 signaling as the most frequently mutated pathway in GBC; furthermore *EGFR* and *ERBB2* overexpression have been associated with increased disease recurrence and prognosis in several human cancers[11].

An immunohistochemical (IHC) study conducted among North Indian patients has pegged a strong EGFR and ERBB2 protein overexpression in 93.3% and 56.6% of the GBC cases respectively[12]. Similarly, another Indian study quantifying gene expression using qPCR amongst East Indian patients, also reported both *EGFR* and *ERBB2* overexpression to be present in more than 50% of GBC patients[13]. Another IHC study conducted in China found out a high positive expression of EGFR in 70.7% of GBC tissues as compared to 27% in hyperplasia tissues, and 0% in normal gallbladder tissues, confirming the relationship between strong EGFR positivity and GBC tumorigenesis progression[14]. In contrast, a Japanese study with a patient pool of 89 GBC samples reported a relatively low positive expression of EGFR and ERBB2 at 8.1% and 16% respectively[15]. Similarly, in a Korean IHC study, EGFR overexpression was documented at just 11% of invasive samples of GBC[16].

To gain a deeper insight into the role of *ERBB2* in tumorigenesis, a recent Chinese study conducted full length transcriptome sequencing and identified the expression of a novel *ERBB2* transcript, conferred by *ERBB2* alternate splicing, named *ERBB2i14e* in GBC tissues, associated with significantly shorter survival. The study also found out the respective transcript to be highly resistant to the United States Food and Drug Administration (FDA)-approved monoclonal antibody targeting ERBB2, Trastuzumab, thus providing a mechanistic explanation for trastuzumab resis-tance in a population of ERBB2-positive GBC patients not responding well to trastuzumab[17].

IHC analysis conducted in GBC in the West, like the United States, Germany or in Latin American nations like Chile, Bolivia, though noticed significant EGFR overexpression in more than 60% of the samples, documented a low rate of ERBB2 overexpression at a range of 12%-20% of GBC cases, pointing out to wide variances in the rate of *ERBB2* expression across different geographical locations, in the development of GBC. The studies also noted ERBB2 overexpression to be more frequent in advanced GBC as compared to in-situ carcinoma, suggesting the role of ERBB2 in the late stage of carcinogenesis[18-20].

***CCND1*:** *CCND1* is considered as an oncogene, encoding for cyclin D1 protein and can promote cell cycle progression from G1 to S phase by cyclin D-dependent kinases (CDK4/CDK6)-mediated phosphorylation of the retinoblastoma protein. *CCND1* overexpression and consequent dysregulated CDK activity have been reported in a wide variety of cancers, including GBC.

Various IHC analysis conducted in several countries of the world including, Japan, India, *etc.* recorded cyclinD1 overexpression in the range of 40%-45% of GBC samples, and the expression range were significantly higher than in chronic cholecystitis[21,22]. One Chinese study documented cyclinD1 overexpression in 57% of adenoma, even before the stage of adenocarcinoma, which is significantly higher than in chronic cholecystitis (7.1%), indicating a probable role of cyclinD1 in the early stage of GBC genesis[23]. Specimens with high cyclin D1 Levels also reportedly showed a high incidence of venous permeation and lymph node metastasis, thereby, suggesting that *CCND1* overexpression can be an independent predictor of decreased OS for GBC patients[24]. However, very contrasting picture emerged from Korea, where an IHC analysis noted cyclin D1 positivity in only 5.6% of GBC tissue samples[25].

***BCL2*:** Alteration of *BCL2*, the B-cell lymphoma 2 gene, was first noticed in B-cell lymphomas/Leukemias accompanying t (14; 18) chromosomal translocation. The Bcl-2 mRNA encodes for a 26 kilodalton inner mitochondrial membrane protein, which significantly inhibit pro-apoptotic proteins, to promote cellular viability. Quite obviously, its aberrant expression can thereby impact tumorigenesis. Evidence suggests that overexpression of *BCL2* is positively associated with tumor cell differentiation, facilitating in early tumorigenesis.

However, an old IHC study from Japan demonstrated Bcl-2 overexpression in 18.4% of GBC cases, but no statistical correlation between Bcl-2 expression and apoptosis was documented[26]. Further IHC studies conducted in India and South Korea also reported Bcl-2 overexpression at just 8% and 7.7% of the studied GBC samples[27] and didn't document any significant clinic-pathologic correlation, suggesting that Bcl-2 might not serve as a significant prognostic biomarker for GBC.

Survivin: Survivin, a member of the inhibitor of apoptosis family of proteins, is encoded by *BRIC5* gene. It shows a promising role in inhibiting apoptosis, mainly by suppressing downstream caspase activity[28]. Although, survivin is

Table 1 Summarization of most significant dysregulated genes in the genesis of GBC and their geographic heterogeneity

Category of gene	Gene name	Criteria of genetic dysregulation	Geographic heterogeneity in proportion of dysregulated expression amongst studied GBC samples
Oncogenes	*EGFR*	Overexpression	8.1% in Japan - 93.3% in North India
	ERBB2	Overexpression	12.8% in Chile - 56.6% in North India
	CCND1 (encoding cyclin D1)	Overexpression	5.6% in South Korea - 68.3% in China
	BCL2	Overexpression	7.7% in South Korea - 18.4% in Japan
	BRIC5 (encoding survivin)	Overexpression	58% in India - 76.5% in Turkey
	MYC	Amplification	3.7% in Japan - 86.7% in Brazil
	MET	Overexpression	5.6% in Japan - 74% in South Korea
Tumor supressor genes	*FHIT*	Downregulation	45% in Japan - 94% in Chile
	CDKN2A	Downregulation	20% in South Korea - 88% in North India
	Mutated *TP53*	Overexpression	56% in North India - 71% in Spain
Angiogenesis factors	*PTGS2* (encoding COX-2)	Overexpression	59% in Slovenia - 80% in South Korea
	VEGFA	Overexpression	48% in India - 81% in Chile
Cell-adhesion molecule	*CDH1* (encoding E-cadherins)	Downregulation	26% in Chile - 67% in North India
Cancer stem cell gene	*POU5F1* (encoding Oct4)	Overexpression	59% in China - 64.5% in North India
Immunoinhibitory molecule	*CD274* (encoding PD-L1)	Overexpression	10.9% in Croatia - 40% in Japan

GBC: Gallbladder cancer.

expressed in embryonic tissues during foetal development, its expression is extremely low or undetectable in adult tissues[29].

However, there is a marked increase in survivin expression in many malignant tumors, which has also been implicated with chemotherapy resistance and unfavourable prognosis. A IHC study from Türkiye revealed survivin expression in 76.5% of the GBC samples, and found a statistically significant correlation of survivin expression with lympho-vascular invasion, and decreased OS, pointing out a prognostic significance of survivin expression in GBC patients[30]. Separate studies on North Indian population, using IHC and qPCR-based analysis documented survivin protein expression in 58% of GBC patient samples, as well as a significantly higher expression of survivin mRNA in GBC (2.9-fold) and cholelithiasis (1.85-fold) when compared with control; the studies also found a relation between increased survivin expression and shorter OS in GBC patients[31,32]. Thus, survivin appears to be a suitable candidate molecular marker for targeted therapy, owing to its aberrant expression in a majority of GBC patients in country like India.

***MYC*:** The *MYC* oncogene (coding for c-Myc protein) is part of a superfamily of genes with products which are master orchestrator of cellular programmes. *MYC* thus, acts as a major oncofactor through its effects on tumor cells, including proliferation and cell survival, and also by enabling cancers to evade host immune surveillance by modifying the tumor microenvironment (TME)[33].

An IHC analysis conducted in Chile, identified a strong expression of c-Myc in only 9% of primary GBC tissues as compared to 26% in metastatic GBC, reflecting the involvement of c-Myc protein in metastasis as compared to initial tumorigenesis[34]. In a separate Japanese study, IHC analysis documented c-Myc overexpression in over 53% of GBC tissues, although fluorescence *in situ* hybridization (FISH) techniques identified *MYC* gene amplification in only 3.7% of same patient pool. Conflictingly, a Brazilian study, using Taqman copy number assay, reported *MYC* gene amplification in as high as 86.7% of invasive/metastatic GBC, which significantly associated with c-Myc protein expression[35].

***MET*:** The *MET* is a proto-oncogene which encodes for a RTK - with its ligand hepatocyte growth factor (HGF), stimulating the RTK activity, contributing to mitogenesis and morphogenesis[36]. In contrast to normal cells, where MET activation is a ligand dependent transient event, in tumor cells, MET has been often reported to be constitutionally active with positive correlation in progression of tumor invasion and metastasis, including GBC[15].

IHC studies from Korea reported MET overexpression in the range of 42%-74% of the GBC tumor tissues, with significantly higher expression at the invasive front as compared to central tumor areas[37]. In another recent Korean study, silver *in situ* hybridization analysis documented a statistically significant correlation between MET and ERBB2

amplification (*P* value < 0.01) in GBC[38], opening a possible door for combination therapies.

A separate Indian study concluded that MET overexpression in GBC starts with the advent of dysplasia and increases as the lesion progresses to neoplasia, with more than 50% of GBC tissues recording MET overexpression. Although, in a contrasting picture, a Japanese study reported MET overexpression in only 5.6% of the GBC patients, with no amplification of *MET* gene detected through FISH technique[15].

TSG

***CDKN2A*:** *CDKN2A* act as a TSG, encoding for the protein p16, arresting cell cycle progression at G1/S phase by inhibiting the action of CDK4 and CDK6, and thus inhibiting cell proliferation. Methylation of the promoter region, deletions, or downregulation of *CDKN2A* have been reported in various cancers[39]. A whole transcriptome profiling of GBC using RNA sequencing (RNA-seq) revealed *CDKN2A* to be amongst the top 3 genes involved in progression and development of GBC[40].

A study conducted in Chile reported *CDKN2A* inactivation/downregulation in 28% of GBC samples and were thus negative for p16 protein on IHC analysis[41]. In a separate IHC study from North India, loss of p16 protein expression was observed in as high as 88% of GBC samples while, in another Japanese study, loss of p16 protein expression was detected in as high as 62.7% of GBC samples, interestingly, PCR-based microsatellite analysis conducted in the same patient pool, found out a significant correlation between loss of heterozygosity (LOH) of *CDKN2A* gene and loss in p16 protein expression, adding a new perspective to *CDKN2A* genetic dysregulation in GBC development[42]. While, IHC analysis conducted in Korea, another Asian nation, reported reduced staining for p16, only in about 20% of GBC samples [43]. Thus, it can be said that rate of *CDKN2A* downregulation in the genesis of GBC suffers from wide ethno-geographic variations.

***FHIT*:** The human *FHIT* gene is located at region 3p 14.2, on the short arm of chromosome 3, that includes the most fragile site in human genome, encoding for Fhit protein; reduced *FHIT* expression has been often found to be correlated with DNA mismatch repair deficiency leading to increased accumulation of errors in DNA strands, and thus elevated risk of carcinogenesis, therefore, *FHIT* is considered as a TSG[44].

An IHC study from Japan found out a significant loss of Fhit expression in atleast 45% of the studied GBC tissue samples, as well reported a significant correlation between reduced Fhit expression and reduced expression of another DNA mismatch repair protein Mlh1(MutL protein homolog 1), thus pointing out that loss of mismatch repair proteins might work in tandem in the genesis of GBC[45]. IHC analysis from United States also documented reduced expression of FHIT in 78% of the studied GBC patients[46]. Similarly, another study conducted in Chile demonstrated a reduced or absence of Fhit protein expression in 94% of the studied GBC tissue samples, and in nearly half of the dysplastic gallbladder epithelial lesions, pointing to a nearly universal nature of reduction in FHIT immunostaining in GBC patients [47].

***TP53*:** The *TP53* gene, also called as "guardian of genome", encodes for the p53 protein, which act as a cell proliferation inhibitor, and is a predominant candidate for genetic alteration in GBC[48]. Literature suggests point mutations in *TP53* gene leads to the oncogenic properties of p53 protein, and have been found involved in many human oncogenesis. The predominant point mutation involving *TP53* gene lead to conformationally and functionally defective p53 protein, resulting in loss of their tumor suppressive function, which tend to accumulate in cell nuclei (elevated expression), and thus can be easily analyzed by IHC[49].

One such IHC study from Taiwan reported overexpression of p53 protein in 59.1% of GBC samples, but in only 18.8% of the adenoma samples, indicating overexpression of mutant p53 protein might be significantly related with malignancy [49]. IHC studies from North India, however reported positive p53 expression at a range of 33%-56% of GBC samples, but suggested a potential relation between increased p53 expression and tumor progression as compared to that with tumor initiation[50,51].

Studies conducted in other parts of the world including Spain and Brazil, also documented overexpression of p53 protein in 58%-71% of GBC tissue samples; however no significant correlation was found with patient survival prognosis [52,53]. Arguably, thus, mutant *TP53* gene expression can serve as an excellent biomarker for GBC progression across various ethnicities.

Angiogenesis factors

COX-2: COX is an enzyme complex, encoded by the *PTGS2* gene that plays an essential role in the conversion of arachidonic acid to prostaglandins, which contribute to the generation of metastatic properties in gastrointestinal malignancies. Although COX-1 is constitutively expressed, responsible for regulating tissue homeostasis, COX-2 is hardly expressed in normal cells and is specifically expressed as a pro-inflammatory enzyme; their synthesis upregulated by cytokines, and growth factors, thereby contributing to malignant cell proliferation, angiogenesis, and invasion[54].

In an IHC study from South Korea, COX-2 was overexpressed in as high as 80% of invasive GBC[16]. In another IHC study conducted by Legan *et al*[55], in Slovenia in central Europe, COX-2 overexpression was found in more than 70% of dysplastic epithelium, while the rate was lower at 59% in case of GBC. The study also observed a significant correlation between p53 accumulation and COX-2 expression, perhaps elaborating on the possible role of dysfunctional p53 in promoting tumor angiogenesis in GBC development. Additionally, a separate study from Japan also detected an enhanced expression of COX-2 in the mucosal hyperplasia of gallbladder in patients with an anomalous arrangement of pancreaticobiliary duct[56] - all pointing towards a regulatory role of COX-2 overexpression in the proliferation of gallbladder epithelia and be an early event in gallbladder carcinogenesis.

Vascular endothelial growth factor: Vascular endothelial growth factor (VEGF) represents a family of structurally and functionally related protein molecules, which are overexpressed in growing tumor tissues in comparison to their healthy counterparts[57]. Tumor hypoxia acts as a potent driving force behind inducing VEGF expression, facilitating cancer metastasis, mainly by stimulating tumor angiogenesis, consisting of leaky vascular networks. In the TME, tumor-derived VEGF has been found to induce blood vessel permeability by loosening the tight junction vascular endothelial-cadherin [58].

In an IHC based Chinese study, 63.3% of the studied GBC patients recorded a positive VEGF expression, which furnished a significant correlation with lymph node metastasis. In similar terms with COX-2 expression, this study also documented a significant correlation between abnormal p53 accumulation and VEGF expression - thereby substantiating the role of mutant p53 in promoting GBC angiogenesis[59]. Similar observation was recorded from India, where a strong positive expression of VEGF was seen in 45%-48.27% of GBC cases, demonstrating a significant association between VEGFR expression and progression of tumor stage. Furthermore, poor median survival was observed in VEGF positive GBC cases, indicating the possibility of potential use of VEGF blocker as therapeutic agents[60,61].

In yet another IHC study from Chile, high expression of VEGF-A was documented in as many as 81% of GBC cases, while only in 5.1% of chronic cholecystitis, suggesting that VEGF-A can be used as a potential biomarker for malignant transformation and tumor stage determination in GBC patients[62].

Cell adhesion molecule

E-cadherins: E-cadherins encoded by *CDH1* gene, are essential cell adhesion molecules, responsible for the development and maintenance of cellular architecture and integrity in epithelial cells. Epithelial to mesenchymal transition (EMT), a major cancer hallmark, enables the transformation of epithelial cells to a more motile mesenchymal cell type, through loss of cell-cell adhesion contacts[63]. Downregulated E-cadherin expression, which facilitates EMT, thus serves as a hallmark for tumor progression and metastasis[64].

In an IHC based Chinese study, Xu *et al*[65] reported a significantly lower E-cadherin expression in GBC cells as compared to the tumor adjacent tissues. The progressive decrease in E-cadherin expression directly correlated with increase in tumor node metastasis and poor prognosis. Another North Indian study reported a progressive increase in E-cadherin downregulation from 6% chronic cholecystitis tissue samples to 67% of studied GBC samples, pointing out an inverse correlation between cancer metastasis and E-cadherin expression. The same study also documented an increase in LOH in *CDH1* gene in GBC as compared to chronic cholecystitis, using PCR-based microsatellite analysis, highlighting the importance of genomic instability of *CDH1* gene in neoplastic transformation of gallbladder[66,67]. Yet another study in Japan pointed out that the 5-year survival rate in GBC patients with preserved E-cadherin expression was 70%, while that with reduced E-cadherin expression was 26%[68].

However, in contrast, a largescale study (n = 117) conducted in Chile in South America, documented only 26% of GBC patients with downregulated E-cadherin expression, and found no relationship between loss of E-cadherin expression and GBC prognosis[69]. Similarly, another Korean study, found a high expression of E-cadherin in a majority (73%) of GBC patients using IHC techniques[70], thus suggesting that downregulation of E-cadherin is not universal in the metastatic transformation or prognosis of GBC.

Cancer stem cell gene

Oct4: Oct4 protein encoded by *POU5F1* gene, located on chromosome 6 is a captain regulator for maintaining pluripotency and self-renewal of embryonic stem cells (ESCs)[71]. In tune with its role in maintaining pluripotency in ESCs, Oct4 overexpression can commit a somatic cell to acquire pluripotency, and thus act as one of the drivers of stemness in cancer stem cells by playing an important role in self-renewal and EMT, thus potentiating chemoresistance [72].

In an IHC study conducted in China, Zhang *et al*[73] found a significant overexpression of Oct4 protein in GBC tissues (59%) compared to the corresponding para-cancerous tissue (only 1.9%), and recorded a positive correlation with tumor grade and lymph node metastasis. Likewise, another Chinese study recorded positive expression of Oct4 in 55.6% of GBC tissue samples, while the positive expression was only 21.7% in para-cancerous tissue and 14.3% in chronic cholecystitis [74]. Similarly, two recent Indian studies using qPCR and IHC techniques, pointed out to significant overexpression of Oct4 both at mRNA and protein levels in GBC and also recorded a positive correlation between Oct4 expression and tumor stage, thus, Oct4 expression can serve as potential universal biological indicator for malignant transformation in GBC[75,76].

Immunoinhibitory molecule

PD-L1: The immune checkpoint system is an important mechanism with the help of which tumor cells escape the wrath of T-cell mediated anti-tumor responses. Transmembrane protein, programmed death-ligand 1 (PD-L1), encoded by *CD274* gene is widely expressed on the surface of tumor cells, and interacts with programmed death 1 (PD-1) on activated T lymphocytes, mediating immunosuppression, and allowing tumor cells to proliferate[77].

Amongst the studies exploring the relationship of PD-L1 expression in GBC, an Indian study involving a large sample size of 174 GBC cases, found PD-L1 expression in 23% of GBC cases, with discordantly higher PD-L1 expression in metastatic lymph nodes as compared to primary GBC tissue, however, no relation could be documented between PD-L1 expression and OS[78]. Similarly, an IHC analysis from South Korea reported PD-L1 positivity in 25% of the GBC patients. IHC studies conducted in European countries like Germany and Croatia, on the other hand, recorded PD-L1 positivity in only 14.7% and 10.9% of the studied GBC cases respectively, possibly suggesting PD-L1 expression may not serve as a great prognostic biomarker in GBC patients from European Nations[79].

However, a recent Japanese study recorded PD-L1 expression in as high as more than 40% of GBC tissue samples, with significant association with lymphatic invasion and lymph node metastasis[80]. Variances in the rate of PD-L1 expression across nations might, thus, help us to identify subset of GBC patient populations to be better candidates for immunotherapy *via* PD-L1 inhibition.

Histopathological progression model of GBC

Summarizing the findings on the genes involved in our study, the following model of genetic dysregulation might explain histopathological progression of normal gallbladder epithelium to metastatic GBC. The model of GBC sequence recognized - progressing from hyperplasia-dysplasia-adenoma-adenocarcinoma, taking into consideration the pathological change occurring in gallbladder epithelium elaborates on the major dysregulated genetic expression at each stage. The putative molecular alterations, primarily focusing on genetic dysregulation are highlighted - focusing on how differential gene expression contributes to sequential alteration in gallbladder epithelium. Embarking on the gallbladder tumorigenesis model, reduced *FHIT* expression (associated with DNA mismatch repair deficiency), and overexpression of angiogenic factor like Cox-2, and oncogenes like *CCND1*, *MET* (associated with increased mitogenic activity), *etc.*, are found to be the major contributory factors in early stage of gallbladder carcinogenesis, facilitating the progressive transformation of gallbladder epithelium into carcinoma. On the other hand, downregulation of cell-adhesion molecule E-cadherin and overexpression of proliferative oncogene *MYC* seem to be primarily involved in the metastatic transformation of GBC (Figure 1).

Microarray and NextGen studies

To understand the molecular characterization of GBC in a far better way and identify novel changes in gene expression, comprehensive gene expression analysis have been conducted using microarray and RNA-seq technology in various parts of the world to better understand the pathogenesis of this disease, and promote the development of new cancer biomarkers for early diagnosis and disease monitoring in GBC. Here, we attempt to sum up the top differentially expressed genes in GBC compared to normal gallbladder or chronic cholecystitis tissues, as have been reported from various sequencing studies conducted across different geo-ethnic populations of the world, especially from China, India and United States. Notable in this regard, is the differential expression of *SERPINA1* gene, encoding alpha-1-antitrypsin protein, which is significantly downregulated in GBC patients from United States, while significantly upregulated in GBC patients from China, as compared to normal gallbladder tissues, suggesting unique population-specific tumoral heterogeneity influencing *SERPINA1* expression. The encapsulation of the transcriptomic studies also identify elevated expression of *CDC45* and *TRIM31* to be a universal occurrence, in GBC, with their elevated expression noted across all 3 ethnic populations studied - belonging from United States, India as well as China and calls for functional analysis of *CDC45* and *TRIM31* for their possible prognostic value in the genesis of GBC and probable therapeutic implications (Table 2).

TARGETED THERAPIES IN GBC

Currently, surgical resection is the most effective way to cure GBC. However, most GBC patients present before clinicians at an advanced stage, owing to vague and non-specific symptoms of GBC; making non-surgical therapies the standard mode of treatment for most GBC patients[81]. Non-surgical therapies engaged in treating GBC patients primarily encompass chemotherapy and radiotherapy; however, with limited effectiveness, it is in this context, that the evolution of precision medicine, involving tailored treatment opportunities to specific genetic and molecular profiles of individual GBC patients have started gaining prominence, especially in the last decade. Here we report on the recent updates in targeted therapies in GBC, keeping in perspective the aberrantly expressed proteins. The several ongoing clinical trials to assess the efficacy of targeted therapies in treating GBC are listed in Table 3.

EGFR and Her2

RTK inhibitors (RTKIs) hold an important place in precision oncology, mostly targeting the active sites of kinases, which mediate cell proliferation, although acquisition of resistance limits their effectiveness. Pre-clinical studies in GBC cell lines and in mouse models have identified HKI-272, as highly selective EGFR/ERBB2 inhibitor, which effectively suppressed tumor growth and inhibition, and need to be further validated in humans[82]. A phase 2 study of Zanidatamab (a biphasic antibody targeting two distinct Her2 epitopes) conducted in metastatic Her2 amplified BTC under a global HORIZON-BTC-01 project (NCT04466891) encompassing several continents reported a meaningful clinical benefit in 41.3% of patients with manageable safety profile, and has been recently approved by FDA for use against Her2+ BTC, including GBC under the brand name ZIIHERA[83].

Trastuzumab is a monoclonal anti-Her2 antibody used against various cancers in combination with other drugs. A clinical trial from Japan, tested on the efficacy of Trastuzumab deruxtecan in BTC patients, with 50% of BTC patients having GBC, who were intolerant to Gemcitabine treatment, and found promising activity, with the objective response rate (ORR) standing at 36.4%[84]. These promising results have fuelled high interests in anti-Her2 drugs in treatment of GBC, specifically in ethno-geographic locations with high Her2 positivity, especially when chemotherapy alone falls short. Currently thus, several trials are checking on the efficacy of Her2-targeting agents either in combination therapy or as antibody-drug conjugates (ADCs) - a phase II clinical trial involving a combination of chemotherapy (gemcitabine/cisplatin) + trastuzumab + pembrolizumab (PD-1 protein blocker on T cells; NCT06178445) as first line of treatment for GBC patients is underway in Germany; another global trial is looking into the efficacy of combination of two HER-2

Table 2 Overview of top differentially expressed genes in gallbladder cancer from sequencing studies

Number of samples	Comparison	List of significantly upregulated genes in GBC	List of significantly downregulated genes in GBC	Geographic and ethnic background	Ref.	Technique employed
3 pairs	Gallbladder wall of gallbladder adenoma and GBC (common) *vs* gallbladder wall of gallstones	*EDN1, MS4A8, ALB, MSLN, CTSV, BAG1, LOC100507412, MCOLN3, ZKSCAN1*	*TBX3, TSK, SCD, NOVA1, PFKFB3*	China	Ge *et al* [106], 2021	Microarray
3 pairs	GBC tissue *vs* gallbladder adenoma tissue	*CEACAM5, OLFM4, TFAP2A, CDH17, VAV3, CD55, CPS1, KRT17, SERPINB5, HEPH, ALB, HMGS2, CHP2, TFF1, TRIM31, SULF1, HOXB6, GUCY1A3, C15orf48, HIST1H2AI*		China	Ge *et al* [106], 2021	Microarray
3 pairs	GBC tissue *vs* para-cancerous tissue	*KLK6, TNNT1, DUOXA1, CEACAM7, SLC44A5, CDC45*	*CNTN1, CPVL, PTGER3, ADRB3, LYVE1, DES, KLRG1, NRK, AOAH, PRKCB, TAGAP, GREM2, KLRD1, KCNMA1, PCDH18, KCTD12, FBLN1, CHRM2, FGF7*	China	Wang *et al*[107], 2017	Microarray
16 samples	12 advanced GBC tissues *vs* 4 chronic cholecystitis tissues	*Skp2, BUB1, MAD2 L1, ESPL1, E2F1, CHEK1, CDK2, CCNB1, CDC20, CDC2, PKMYT1, RBL1, CDC45, STAT1, TNF, SOD2, MCM4, POLE, RCF-4, PASK, ECT2, KIF20, CENPF, TPX2*	*SMOC2, WNT10B, FGF2, CCND2, TGF-β3, COX7A1, CKMT2.*	India	Kumar *et al* [108], 2020	Microarray
11 samples	8 GBC *vs* 3 normal gallbladder tissues	*SERPINB3, DUSP1, FOXJ1, CHP1, KLK5, HOXB13, HOXB9, MAGEB2, KLK1, HOXC11, HOXC10, HOXC9, CLCA4, OLFM4, PI3, MUC17, SERPINB7, LEMD1, FAM71E2, TRIM29, TRIM31, CDC45, CDH3*	*DCAF12 L, PPAN-P2RY11, ZNF275, GIMAP1-5, MT1M, APOA1, PGLYRP2, SHBG, CYP1A1, GOLGA6A, BMP10, HEPN1, TTC36, FAM99B, HEPACAM, RTP3, CYP3A43, SHBG, PLGLA, GDF2, FGF21, PAQR9, CREB3 L3, FETUB, FCN2, CPN1, PRODH2, PKLR, SERPINA11, SERPINA1, ARID3C*	United States	Zuo *et al*[109], 2016	RNA seq
2 pairs	2 GBC *vs* 2 adjacent non-tumorous tissues	*OLFM4, BIRC5, TK1, PI3, TNNT1, CLIC3, MMP9, TRIM29, SERPINA1*	*DPT, SMOC2, GLP2R, LMOD1, FBLN5, WNT2B*	China	Gu *et al* [110], 2015	RNA seq
10 samples	10 GBC tissues *vs* normal gallbladder tissues from SRA database	*MSLNL, FOXJ1, HMGA2, KRT17, MYEOV, LYPD2, REG4, TMEM238, TRIM31, NOTUM, LRFN4*	*IGCSF10, GCG, NLGN4Y, PAH, CCKAR, CHRM2, CRISP3, FGF19, GLYATL2, ADIPOQ, DMBT1, CHRDL1*	India	Dixit *et al*[40], 2022	RNA seq

GBC: Gallbladder cancer; RNA seq: RNA sequencing.

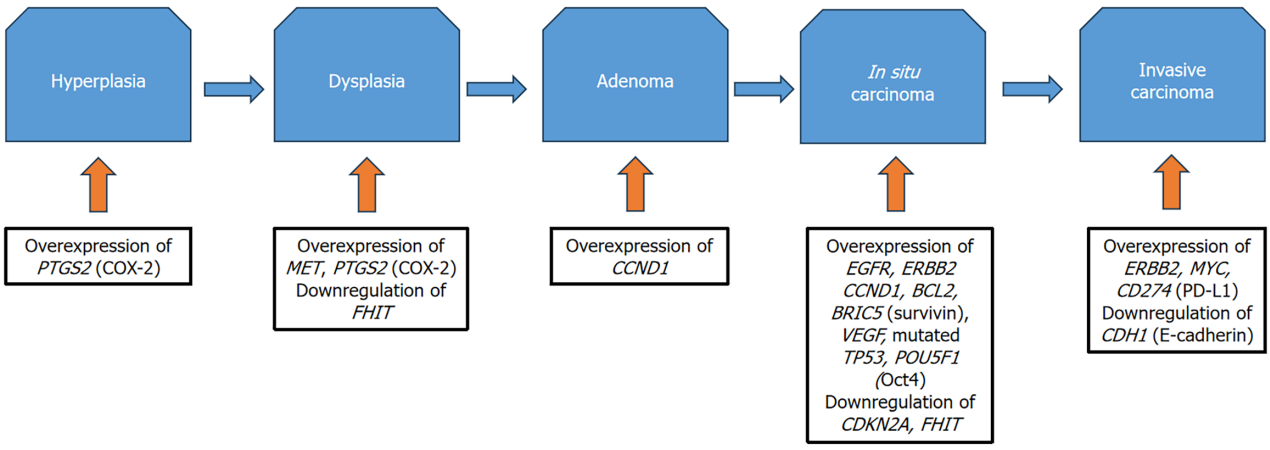

Figure 1 Major dysregulated gene expressions contributing in histopathological progression of gallbladder cancer. VEGF: Vascular endothelial growth factor; PD-L1: Programmed death-ligand 1.

Table 3 Overview of targeted gene therapy in gallbladder cancer currently undergoing clinical trial

Agent	Target gene/pathway	Combined with	Patient characteristics	NCT number	Clinical trial location
Trastuzumab	Her2	Pembrolizumab + gemcitabine	Previously untreated Her2+ unresectable cholangiocarcinoma and GBC	NCT06178445	Germany
Trastuzumab		Tucatinib	Unresectable or metastatic Her2 overexpressed/amplified BTC, including GBC, cervical cancer, uterine cancer, and urothelial cancer	NCT04579380	Belgium, Germany, Italy, Japan, Korea, Netherlands, Poland, Spain, United Kingdom, United States
Zanidatamab		Cisplatin + gemcitabine	Locally advanced unresectable or metastatic BTC, including GBC	NCT06282575	Argentina, Belgium, Brazil, Canada, Chile, China, Finland, France, Germany, India, Israel, Italy, Japan, Korea, Portugal, Puerto Rico, Romania, Spain, Sweeden, United Kingdom, United States
Zanidatamab		Combination chemotherapy	Unresectable locally advanced or metastatic, recurring Her2+ BTC, including GBC and colorectal cancer	NCT03929666	United States, Canada, Chile, Korea
RC48-ADC		NA	Previously treated locally advanced or metastatic Her2+ BTC, including GBC, who have failed first-line chemotherapy	NCT04329429	China
Afatinib	EGFR	Gemcitabine + oxaliplatin	Resectable GBC patients	NCT04183712	China
Tivozanib	VEGFR/VEGF	Atezolizumab	Stage IV otherwise incurable cancer including: GBC, bile duct cancer, pancreatic adenocarcinoma, prostate cancer, ovarian cancer	NCT05000294	United States
Tivozanib		NA	Unresectable cholangiocarcinoma and GBC, previously treated by at least one type of chemotherapy	NCT04645160	United States
Bevacizumab		Gemcitabine + albumin-paclitaxel + sintilimab	Initially unresectable GBC	NCT05757336	China
Ivonescimab		NA	Previously treated GBC, who have failed first-line chemotherapy	NCT06529718	Belgium, France, United Kingdom
Surufatinib		Tislelizumab	First line of treatment for unsectable or metastatic BTC, including GBC.	NCT06134193	China
Envafolimab	PD-L1	Gemcitabine + cisplatin	First line of treatment for advanced BTC, including GBC	NCT06013943	China
Durvalumab		Gemcitabine hydrochloride + cisplatin + nab-paclitaxel	Locally advanced or metastatic GBC	NCT06591650	China
Durvalumab		Tremelimumab + capecitabine	A phase II study in BTC patients after curative surgery	NCT05239169	Germany
Camrelizumab		Gemcitabine + oxaliplatin	Unresectable GBC	NCT06423170	China
Everolimus	mTORC1	Standard chemotherapy	First line of treatment for metastatic or unresectable GBC	NCT05833815	India
Merestinib	MET	Cisplatin + gemcitabine	First line of treatment in advanced BTC, including GBC	NCT02711553	United States, Argentina, Australia, Austria, Belgium, China, Denmark, France, Germany, Hungary, Korea, Mexico, Spain, Sweeden, Turkey, United Kingdom

GBC: Gallbladder cancer; BTC: Biliary tract cancer; NCT: National clinical trial; NA: Not available; VEGF: Vascular endothelial growth factor; PD-L1: Programmed death-ligand 1.

inhibitors: Trastuzumab + tucatinib (NCT04579380) in GBC patients, yet another Chinese study is looking into the efficacy of RC48-ADC in treating Her2+ unresectable BTC, including GBC.

Panitumumab, sold under the brand name Vectibix, is a monoclonal antibody directed against EGFR. Recently, a French study checked on the efficacy of a combination therapy of panitumumab + irinotecan (chemotherapy) in metastatic colorectal cancer (NCT00655499) and reported a satisfactory ORR at 35.2%[85]. Judging the similarity between colorectal and gallbladder epithelium[86], clinical trials using the same combination might be re-purposed in treating GBC however as *KRAS* mutations are known to confer resistance to anti-EGFR agents[87]; careful choice of GBC patients with *KRAS* wild-type tumors should be subjected to panitumumab treatment to get optimum results. However, a phase II double-blind placebo-controlled global trial using Varlitinib, a small molecule EGFR inhibitor, with chemotherapeutic drug, capecitabine, in advanced GBC (NCT03093870), though tolerated well, did not statistically improve ORR[88].

VEGF/VEGFR

VEGF is an important angiogenic factor, with important roles to play in GBC metastasis; thus, several studies are looking into the option of targeting VEGF as an effective therapeutic measure in treating GBC. The first such study conducted in United States, with Bevacizumab, an antibody targeting VEGF-A, in conjunction with Erlotinib (RTKIs), in patients having advanced and unresectable GBC (NCT00356889), showed limited clinical activity, with 12% of the evaluable patients showing a confirmed partial response, while 51% of the patients documented stable disease[89]. However, another phase II study from United States involving Bevacizumab in combination with chemotherapy (gemcitabine/oxaliplatin) in advanced BTC (NCT00361231) reported an ORR of 40%, and median progress-free survival (mPFS) of 7 months[90]. Yet, another phase II study, from United States suggested encouraging efficacy of regorafenib (VEGFR1-3 + RTKI) in chemotherapy-refractory advanced/metastatic BTC (including GBC; NCT02053376) with mPFS of 15.6 months, and a disease-control rate of 56%, however with notable adverse events like hyperbilirubinemia, hypertension, *etc.*, thus, warranting further studies[91].

Recent data suggests anti-VEGF drugs, initially developed as anti-angiogenic drugs might also have a potentiating role on the working efficiency of immune checkpoint inhibitors (ICIs)[92], thus, combining targeted therapy against VEGF with ICIs might bring better outcomes in treating GBC patients. Considering this aspect, several ongoing clinical trials across the world are looking into simultaneous targeting of VEGF/VEGFR and PD-1/PD-L1 in GBC. One such is the Chinese phase II clinical trial involving anti-VEGF-A bevacizumab + gemcitabine + albumin-paclitaxel + sintilimab (monoclonal antibody targeting PD-1; NCT05757336) as first-line of treatment in unresectable GBC. Other such ongoing trials include: Tivozanib (VEGFR tyrosine kinase inhibitor) + atezolizumab (monoclonal antibody against PD-L1; NCT05000294) in the United States, and Ivonescimab, (a bispecific PD-1/VEGF antibody) as comparison to standard chemotherapy (NCT06529718) in treating advanced BTC patients including GBC, in European nations.

PD-L1

Cancer immunotherapy involving targeting of PD-L1 has gained significant prominence in the last decade in treating solid tumors. A multi-center study conducted in United States to evaluate the efficacy of anti-PD-L1 antibody atezolizumab both as monotherapy and combination therapy in conjunction with cobimetinib (MEK inhibitor) on metastatic BTC patients including GBC patients (NCT03201458) reported an extremely low ORR of 2.8% and 3.3% respectively, besides, the study demonstrated a mPFS of only 1.87 months in case of Atezolizumab monotherapy[93]. Another global study, testing the efficacy of bintrafusp alpha, a bi-functional fusion protein targeting TGF-beta and PD-L1, on metastatic chemorefractory GBC (NCT03833661) also reported a low ORR of 10.7% with a mPFS of 1.8 months[94]. A Germany based randomized phase II study (NCT03473574) with a blend of durvalumab (monoclonal antibody against PD-L1) + tremelimumab + gemcitabine however, demonstrated survival benefits in cholangiocarcinoma and GBC[95]. Judging the variances in the rate of PD-L1 expression in GBC across ethnicities, low efficacy of PD-L1 inhibitors in United States shouldn't act as a deterrent for future clinical trials in ethnic populations from Japan or China showing considerable PD-L1 expression.

Currently, few more ongoing studies are looking into the efficacy of targeting. PD-L1 in GBC: One such Chinese study is looking into the efficacy of envafolimab (a fusion of humanized mono-domain PD-L1 antibody and human IgG Fc fragment; NCT06013943) while another is focussing on the combination therapy of durvalumab + gemcitabine hydrochloride + cisplatin + nab-paclitaxel (NCT06591650) to treat metastatic GBC, yet another German trial is looking into the combination of Durvalumab with CTLA-4 blocker tremelimumab (NCT05239169) in treating BTC, including GBC.

Although single agent ICI therapy is known to exhibit resistance, combination therapies might prove helpful. Recently, FDA has approved the use of Pembrolizumab (PD-L1 blocker) + Trastuzumab (anti-Her2 antibody) for advanced Her2+ gastric cancer patients[96], this combination might be repurposed in treating metastatic/advanced GBC as well, especially in ethnic populace having significant Her2 and PD-L1 positivity.

MET

In recent years, MET/HGF inhibition has emerged as a promising anticancer therapy option. Although, quite a good number of small molecules targeting MET receptors in the clinic are available these days, studies on GBC have been very limited. A recent Japanese study tested on the efficacy of Merestinib (a small molecule inhibitor of MET; NCT03027284) in combination with chemotherapeutic drug cisplatin and reported a low ORR of approximately 13%[97]. Considering the fact that MET overexpression is reportedly low from Japanese population, the result was on expected lines, and shouldn't serve as a deterrent for future clinical trials elsewhere. This explains why another global trial is also currently looking at the efficacy of Merestinib in combination with chemotherapy as the first line of treatment in advanced BTC including

GBC (NCT02711553).

VARIATIONS IN DIFFERENTIAL GENE EXPRESSIONS ACROSS GLOBAL POPULATIONS IN GBC GENESIS

The analysis of the disproportionate nature of GBC incidences across various geographic and ethnic groups suggests interplay of unique genetic and molecular factors in different populations. While we summarize the major dysregulated/aberrantly expressed genes in the genesis of GBC, we note that different populations record variations in proportion of different genetic dysregulation. RTKs, such as EGFR, ERBB2 play an important role in the development of BTC, including GBC, however, the contribution is not universal across populations. While *ERBB2* overexpression is recorded in majority of Indian GBC patients, the same is not true for the Latin American nations, where less than 1/5th of GBC patients documents overexpression of *ERBB2*. Similarly, studies from Japan document *EGFR* overexpression at less than 10% of GBC samples, in contrast with other ethnic populations from China or India, where it emerges as one of the most prominent oncogenic factor. Likewise variations have been noted in the proportion of *MYC* amplification and *MET* overexpression in GBC patients from country to country, with Japan yet again emerging as an outlier, suggesting some unique molecular alterations in GBC genesis amongst Japanese population. The association of aberrant *CCND1* expression with tumorigenesis is a well- established fact, however this is not universal in the genesis of GBC - with conflicting reports emerging from GBC patients of India and Korea. Immune checkpoint proteins such as PD-L1 are known to help in cellular proliferation by keeping immune responses in check; however wide differences are noted between rate of PD-L1 expression in GBC patients of the West and the East. The role of survivin is tumorigenesis is well-documented; however, with respect to the genesis of GBC, studies on differential expression of survivin have been limited mostly to India, leaving out almost all other hotspot countries of GBC incidences, including Korea, Japan, China, Chile, Brazil, *etc.* This limits our attempt to identify survivin as a prognostic biomarker in GBC across ethnicities and calls for the need of more extensive population-specific studies.

Downregulation of a TSG like *CDKN2A* is a predominant driving force behind the development of most cancers, however in the genesis of GBC, *CDKN2A* downregulation might not be a universal phenomenon with studies painting a contrasting picture between GBC patients of Japan and Korea. Downregulation of E-cadherin is an important factor contributing to metastasis, however, while Indian studies point out strong correlation between E-cadherin downregulation and GBC metastasis, studies in Chile or Brazil, finds no correlation with metastatic transformation of GBC and E-cadherin downregulation. GBC is thus a classic case of "One size doesn't fit all", and such wide ethnic and geographic variations in gene dysregulation in GBC calls for more comprehensive population-specific studies to develop population-specific biomarkers for GBC diagnosis, prognosis and guidance on improved precision medicine.

FUTURE PERSPECTIVE

Given that GBC is one of the very few cancer which has a higher death rate compared to the incidence rate, it is imperative to devise new therapeutic strategies to improve the efficacy of non-surgical treatment[98]. With passage of time, precision medicine, involving individual-specific targeted therapies, tailored to individual biomarker profiling have evolved, and is soon going to replace non-specific treatment modalities like chemotherapy, radiotherapy, *etc.* Identifying population-specific biomarkers might help in devising the respective targeted therapy to be used for that subset of GBC patients. This implicates that ant-EGFR therapy might serve extremely beneficial in treating Indian GBC patients, while it might not work well in Japanese GBC patients, where EGFR dysregulation is not an important oncogenic factor. Although anti-EGFR therapies hold promising results in treating GBCs, researches have established that amplification of MET receptor contributes resistance to anti-EGFR therapies[99]; accounting for the role of MET in GBC genesis in several populations; indicating towards the need of genetic screening in identifying potential GBC patients who would respond better to anti-EGFR therapies.

It is however of utmost concern that clinical trials of promising drug candidates in the realm of targeted therapies in treating GBC have been very limited. This lack in endeavor might primarily stem due to concentration of GBC incidences in several nations of South Asia and South America, and not a pan-world threat as of now. Although *TP53* has the highest mutation rate in GBC, and mutated p53 is widely expressed in GBC tissues, we have no reported studies evaluating the potential benefit of drugs targeting mutated p53 in GBC. As our review document a strong correlation of mutated p53 expression with that of expression of pro-angiogenic factors, targeting mutant p53 in combination with anti-VEGF drugs might prove as an important strategy in addressing the intricate relationship of these two factors and should be a future choice for clinical trial in minimizing the metastatic progression of GBC. Owing to the fundamental function of *BCL2* in the regulation of apoptosis, targeting the Bcl-2 protein do serve as a promising anti-tumor strategy, in a variety of solid tumors[100]; however, so far, few studies conducted in Japan and India, didn't document aberrant expression of *BCL2* as a significant prognostic biomarker in the genesis of GBC. Thus, more population-specific study on *BCL2* expression in GBC is called for to identify potential application of Bcl-2 inhibitors in treating GBC in other ethnic populations.

Furthermore, small molecule inhibitors of MET including tivantinib and crizotinib, are widely evaluated in clinical trials in different solid tumors, with a significant positive clinical outcome in metastatic colorectal cancer patients[101], however, very few studies have been conducted in the field of GBC, despite a significantly high *MET* expression in specific ethnic populations like in India or Korea. Recent findings from Korea, which reported a statistically significant

correlation of *MET* and *ERBB2* amplification in GBC also calls for future trials in combination strategies involving dual ERBB2 and MET inhibition as a potential therapeutic strategy, a combination strategy already receiving ample attention in treating malignant melanoma[102].

Similarly, ascribed to the role of survivin expression in inducing resistance to chemotherapy and judging that survivin expression is almost universal in the genesis of GBC, repurposing the use of small molecules such as YM155, which potentiates chemosensitivity to gemcitabine in pancreatic cancer cells by suppressing the induction of survivin[103], or FL118, which exhibit high efficacy in eliminating human pancreatic and colorectal tumors[104] might prove as an effective potential approach in improving chemotherapeutic treatment outcomes in GBC. This seems especially significant, judging the fact that gallbladder and colorectal epithelium have a common epitope and same risk factors affecting colorectal neoplasia and GBC[105]. Thus, we suggest future clinical studies to these ends.

To this aim, thus, it is urgent to establish a global platform for fruitful collaboration amongst divergent research institutions and hospitals across the world and focus on developing promising targeted therapies in combating this deadly disease.

CONCLUSION

GBC is a high-grade malignant tumor, with poor survival outcomes, but is demographically restricted to specific locations in the world. Such demographic variations in incidence rates across the world also offers plausible explanation for wide variances in molecular and genetic interplay in the genesis of GBC among different ethno-geographic populations. Although many studies have documented the genetic predisposition of GBC, little advances have been made in developing appropriate prognostic genetic biomarker for GBC. Present review summarizes the role of important aberrantly expressed genes in the genesis of GBC, and points out population-specific variations in their expression levels, figuring out the need for developing population-specific biomarkers for GBC diagnosis and disease management at an early stage through comprehensive gene expression profiling. The study also highlights the progress that have been made till date, in the field of targeted therapy to treat GBC patients, documenting both completed and ongoing clinical trials and suggest possible new directions for future clinical trials. Development of population-specific biomarkers can help assess the therapeutic relevance of targeting specific genetic pathways in specific populations and also in developing new molecules *de novo* for distinct populations to precisely target tumor cells, contributing to improved survival outcomes for GBC patients.

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FOOTNOTES

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