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Molecular pathways and potential biomarkers in gallbladder cancer: A comprehensive review

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ABSTRACT

The most common malignancy of the biliary tract, gallbladder cancer (GBC) often has a dismal prognosis. The aggressive nature of the tumor, delayed diagnosis at advanced stages of the disease, and lack of effective treatment options are some of the factors that contribute to a poor outcome. Early detection and accurate assessment of disease burden is critical to optimize management and improve long-term survival, as well as identify patients for adjuvant therapy and clinical trials. With recent advances in the understanding of the molecular pathogenesis of GBC, several specific diagnostic and biomarkers have been proposed as being of diagnostic and prognostic importance. Indeed, identification of novel diagnostic and prognostic markers has an important role in early diagnosis and development of targeted therapies among patients with GBC. Next-generation sequencing technology and genomewide data analysis have provided novel insight into understanding the molecular pathogenesis of biliary tract cancers, thereby identifying potential biomarkers for clinical use. We herein review available GBC biomarkers and the potential clinical implications in the management of GBC.

1. Introduction

Gallbladder cancer (GBC) is the most common malignancy of the biliary tract [1,2] accounting for roughly 90% of all biliary tract cancers [2,3]. GBC ranks sixth among all gastrointestinal cancers with an annual incidence ranging from 1.5 to 27 new cases per 100,000 individuals worldwide [3–5]. GBC distribution has a geographic variability with a higher incidence in central and East Asia (Northern India, Pakistan, Bangladesh, and Nepal, Japan, Korea, and China), central Europe (Hungary, Slovakia, Poland), and South America (Chile, Bolivia, and Peru) [3,6,7]. The difference in environmental exposure, as well as genetic aberrations has been proposed as a potential culprit (Fig. 1). In the U.S., the highest incidence and mortality rates of GBC are observed among American Indian and Alaska Native people. Over the last several decades, the incidence of GBC has increased in the U.S. with over 1000 new cases diagnosed in 2013 [8,9]. Gallbladder adenocarcinomas (85–97%) - predominantly of the papillary or tubular variant - constitute the most frequent histologic sub-types, followed by squamous cell carcinoma, anaplastic carcinoma, adenosquamous cell carcinoma, neuroendocrine carcinoma, and sarcoma type variant [10–12].

Cholelithiasis with the presence of chronic cholecystitis, calcification of the gallbladder wall (porcelain gallbladder), gallbladder polyps (mostly with size > 1 cm), primary sclerosing cholangitis, anomalous pancreatobiliary junction anatomy, and chronic typhoid infection are some of the well-known risk factors of GBC [13,14]. Increased age, female sex, smoking, obesity, age at first birth, Gardner/Peutz-Jeghers syndromes, and red meat consumption have also been implicated in the disease pathogenesis [3,15–17]. GBC is an aggressive malignancy with 5-year survival ranging from 4% to 60%, depending on the disease stage and resectability [12,18–21]. Surgical resection with negative

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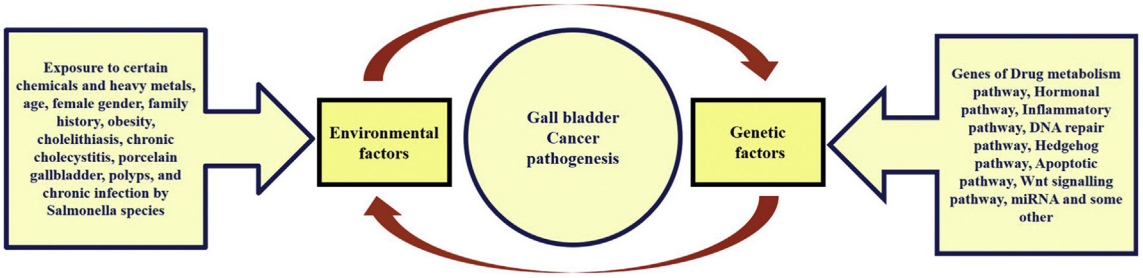

Fig. 1. Factors involved in gallbladder cancer pathogenesis.

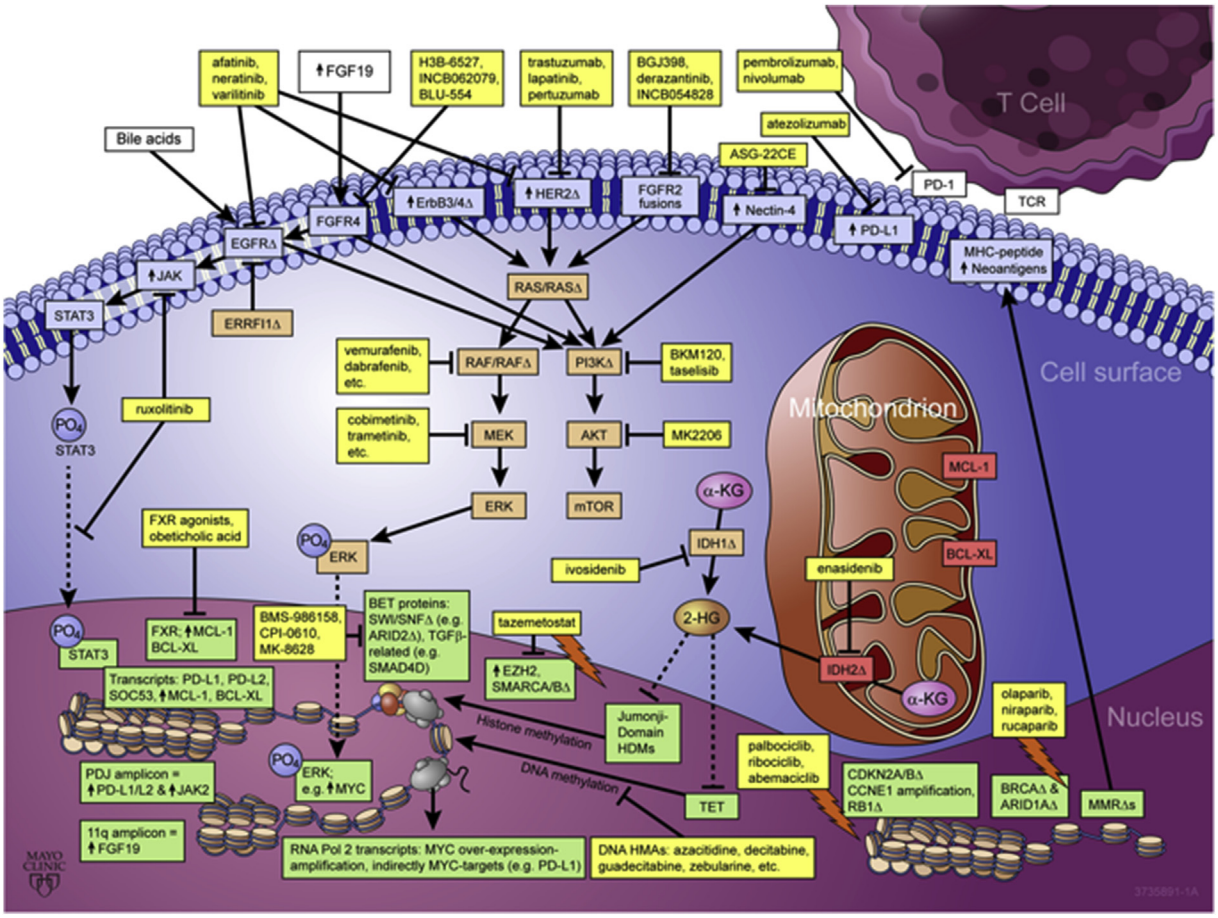

Fig. 2. Gallbladder cancer carcinogenesis sequence and involved pathways.

microscopic margins remains the only hope for long-term survival in patients with GBC. Unfortunately, the majority of patients are deemed to be unresectable at the time of the diagnosis due to late presentation; attributing to the poor prognosis [18,20]. Moreover, traditional chemotherapy and radiotherapy management provides only a marginal survival benefit to patients with locally advanced or metastatic GBC [22,23]. Therefore, identification of novel diagnostic and prognostic markers has an important role in early diagnosis and development of targeted therapies among patients with GBC (Fig. 2). Next-generation sequencing technology and genomewide data analysis have provided novel insight into understanding the molecular pathogenesis of biliary tract cancers, thereby identifying potential biomarkers for clinical use. We herein review available GBC biomarkers and the potential clinical implications in the management of GBC.

2. Methods

A review of the English literature was performed utilizing MEDLINE/PubMed and Web of Science databases in April of 2019. The terms “gallbladder cancer”, “gallbladder carcinoma”, and “gallbladder tumor” in combination with the following terms: “molecular marker”, “biomarker”, “diagnosis”, “progression”, “survival”, “outcome”, “pathogenesis”, “growth factors”, “genomic”, “transcriptomic”, “proteomic”, “metabolomics”, “bile”, “serum”, tissue”, “signaling pathways” were searched in the title and/or abstract. The references of relevant articles were reviewed to identify additional eligible publications. Articles were assessed according to the above eligibility criteria. Data extracted included first author, year of publication, study type, size of patient population, and type of molecular target/biomarker assessed.

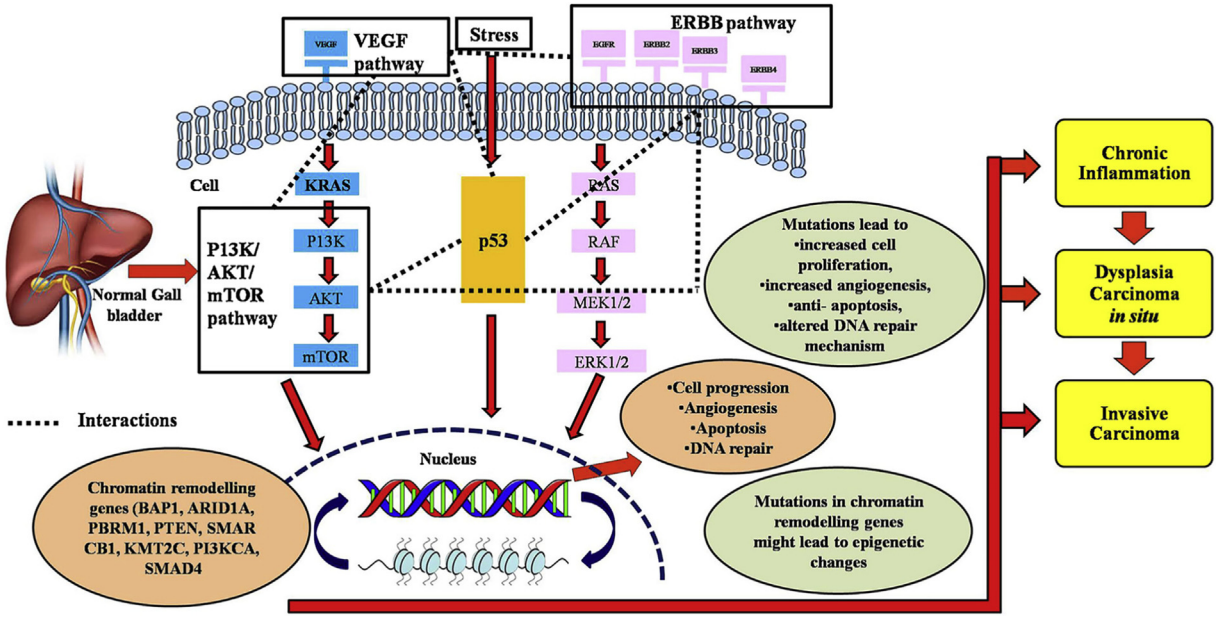

Fig. 3. The dysplasia-carcinoma sequence remains the most accepted framework for the genomic/molecular alterations involved in GBC molecular pathogenesis.

2.1. Molecular pathogenesis

Carcinogenesis sequence. Histologic analyses of GBC specimens have suggested a stepwise progression from hyperplasia-atypical hyperplasia [24], metaplasia-dysplasia [25–27], or gallbladder adenomas to carcinoma. Kozuka et al. reported that adenomas larger than 12 mm were prone to malignant transformation [28]. The average diameter of adenomas with cancerous foci was 17.6 ± 4.4 mm. In contrast, Roa et al. suggested that the dysplasia-carcinoma sequence was the main carcinogenic pathway in the development of GBC and malignant transformation of a gallbladder adenoma was a rare event [29]. Watanabe et al. demonstrated that *KRAS* and *p53* mutations were involved in the adenoma-carcinoma and dysplasia-carcinoma pathways; suggesting the existence of distinct carcinogenetic profiles [30]. Given the overall low incidence of gallbladder adenomas, the dysplasia-carcinoma sequence remains the most accepted framework for the genomic/molecular alterations involved in GBC molecular pathogenesis (Fig. 3) [29,31,32].

Genomics. The advent of novel genomic technologies such as next-generation sequencing has shed light on the understanding of multiple genetic alterations potentially involved in the development of GBC. Aberrations in tumor suppressor genes and oncogenes, presence of microsatellite instability (MSI), and epigenetic alterations are some of the reported factors. Loss of heterozygosity (LOH), defined as a cross chromosomal event that results in loss of the entire gene and the surrounding chromosomal region, has been identified in tumorigenesis of different cancers. Chang et al. identified different allelic loss profiles for dysplastic GB lesions (loss of chromosomal regions 5q and 17p) and invasive GBC (loss of regions 3p, 5q, 9p, 17p) [33]. Kim et al. reported that the allelic loss profiles in precursor lesions adjacent to invasive carcinomas were similar to the tumor itself and concluded that LOH was an early genetic event in the carcinogenesis pathway [34]. Subsequent genome wide allele-typing analyses further corroborated these results with reporting high LOH both in dysplasia and GBC [35,36]. LOH in the 3p14.2 locus has been implicated in the pathogenesis of GBC by inactivating the fragile histidine triad (*FHIT*) tumor-suppressor gene [37]. The frequency of this specific aberration has been demonstrated to increase progressively along the progression from normal mucosa to dysplastic epithelia and then to invasive cancer, with GBC specimens almost universally express LOH in the 3p14.2 locus [38].

Several pathogenic mutations of *KRAS oncogene*, an initial key player in numerous cellular signaling pathways, have been reported in GBC [39,40]. Patients with anomalous pancreatobiliary junction anatomy have been demonstrated to carry higher frequency of *KRAS oncogene* mutations. Mutations of the p*53* gene is another genomic aberration that has been detected among approximately 27%–70% of gallbladder carcinomas [41]. Mutations in *PIK3CA*, *CTNNB1*, *IDH1*, *EGFR*, and *ERBB3* have also been described in pathogenesis of GBC using high throughput methods.

Proteomics. Immunohistochemical studies of excised gallbladder specimens have underlined the role of the p53 protein in the development of GBC [34,42–45]. Nuclear accumulation of p53 protein has been observed in malignant gallbladder tumors. In particular, p53 protein expression has been demonstrated to increase in the course of progression from premalignant lesions to invasive tumors, while p53 protein was notably absent in normal gallbladder epithelia [43,45–47]. The expression of cycloxygenase-2 (COX-2) in GBC precursor lesions also has been implicated in the early carcinogenesis cascade, perhaps as part of an inciting inflammatory process. COX-2 has been noted to be markedly overexpressed in dysplastic epithelia compared with normal gallbladder mucosa specimens [42,48], with a possible interplay between p53 accumulation and COX-2 overexpression [42]. Another tumor suppressor protein that has a role in GBC pathogenesis is p16 (INK4a) protein, a cyclin-dependent kinase inhibitor that regulates entry into S phase of the cell cycle. However, data on the association of p16 expression with GBC has been conflicting. Shi et al. reported on 37 tumors from 36 patients with GBC and noted a loss of p16 protein in 28 of the 37 GBCs (75.7%); yet p16 aberrations were not associated with any specific clinicopathologic factor or survival [49]. In a separate study, Feng et al. reported that p16 was decreased to a low level in GBC [50]. In contrast, Lynch et al. reported that both p16 and p53 expression were absent in normal epithelia, with increased accumulation of p16 as the disease progressed from dysplasia to carcinoma in situ and then to invasive carcinoma [51]. As such, while the exact importance might vary depending on the disease stage, the p16-Cyclin D/CDK4 pathway appears to play a role in gallbladder carcinogenesis for a subset of patients. Previous studies have also demonstrated increased epidermal growth factor receptor (EGFR) and HER2/neu expression in malignant gallbladder tissue [52–54], while expression in precursor lesions such as adenomas was either weak or absent [55,56]. HER2/neu overexpression has been noted in 13% of GBC cases.

Table 1
Overview of prognostic biomarkers and their effect in GBC patient survival.

Biomarker	Hazard Ratio (95% C.I.)	p-value
CA 19-9 [60]	1.005 (1.002–1.009)	0.001
Combined CEA/CA 19-9 [75]	2.6 (1.8–3.6)	< 0.001
Combined VEGF-A/ER1 [79]	1.773 (1.021–3.080)	0.042
HDGF [80]	4.298 (1.134–88.887)	0.038
Survivin [82]	2.848 (0.959–8.463)	0.043
PTEN [83]	0.26 (0.12–0.57)	0.009
MTA-1 [84]	3.06 (1.37–6.87)	0.007
SPOCK1 [85]	0.378 (0.164–0.871)	0.022
TSG101 [86]	3.083 (1.178–8.072)	0.022
PEG10 [86]	3.3 (1.273–8.555)	0.014
PKM2 [87]	2.68 (1.090–6.591)	0.032
ACVR 1C [87]	0.366 (0.151–0.888)	0.026
SHP2 [88]	4.332 (1.527–12.289)[a]	0.006[a]
	4.62 (1.218–4.62)[b]	0.011[b]
Pronomin-1 [97]	2.947 (1.447–5.718)	0.004
N-cadherin [90]	2.664 (1.423–4.989)	0.002
ERp29 [91]	0.414 (0.189–0.92)	0.029
S1P1 [91]	4.513 (1.63–11.67)	0.004
EpCAM [93]	2.9 (0.9–10.7)	0.005
S100A4 [95]	2.77 (1.119–6.837)	0.028
RCAS1 [96]	12.69 (1.216–132.423)	0.0337

[a] Refers to squamous/adenosquamous variant of gallbladder cancer.
[b] Refers to adenocarcinoma of gallbladder cancer.

2.2. Diagnostic biomarkers

Cancer antigens have been widely utilized as diagnostic adjuncts in a variety of gastrointestinal tract tumors. The serum levels of Carcinoembryonic Antigen, Cancer Antigen 19-9 (CA 19-9), and CA 125 can be elevated in GBC, however diagnostic sensitivity and specificity are low [57–61]. Tumor antigen markers may even be misleading in the case of benign gallbladder diseases. Yu et al. investigated 37 patients who were suspected to have GBC preoperatively based on tumor marker elevation and subsequently had xanthogranulomatous cholecystitis based on the pathology report [62]. Interestingly, 45.95% of cases had an elevation in CA 19-9, 2.70% had an elevation in CEA, and 24.32% had an elevated CA 12-5. Furthermore, CA 19-9 is not detectable in 7% of the general population due to absence of the Lewis antigen. The serum level of CA 242 has demonstrated a better diagnostic yield with more promising clinical value in the prediction of early stage disease [59–61]. In a study of 117 patients with GBC, the sensitivity, specificity, positive predictive value, and negative predictive values of CA 242 to diagnosis GBC were 64%, 83%, 88%, and 53%, respectively [61]. The reported specificity and positive predictive value reached 100% at a cutoff of 45 U/ml. CA 242 also had a higher AUC (0.759) compared with CEA (0.528) or CA 19-9 (0.430). The combination of biliary CA 19-9 with other novel biomarkers (e.g. MAC-2BP) failed, however, to improve diagnostic accuracy [63]. Current data do not support the application of serum cancer antigens as reliable biomarkers in the diagnosis of GBC, although these markers may be associated with prognosis.

Cytokeratins are filamentous proteins present in human epithelial cells. Cytokeratin 19 is preferentially expressed in cholangiocytes. A soluble fragment of cytokeratin 19, CYFRA 21–1, has been detected in measurable levels in the serum of patients with biliary malignancies [64–66]. Huang et al. reported considerable sensitivity and specificity for CYFRA 21-1 (93.7% and 96.2%, respectively) in the detection of GBC [67]. Similarly, serum levels of survivin, an inhibitor of apoptosis, has been demonstrated to differentiate patients with GBC from individuals with gallstone disease with a reported sensitivity of 82% and specificity of 93.3% [68]. The sensitivity and specificity of serum levels of Survivin mRNA in detection of patients with GBC have been reported to be 89.7% and 100%, respectively [69].

Liquid biopsy technology screens patient body fluid samples for tumor derived molecules such as DNA, RNA, protein, exosomes, and cells [70]. Kumari et al. used extracted circulating serum free DNA (cfDNA) to differentiate between GBC patients and healthy individuals with a sensitivity of 100% (95%CI: 89.6–100) and specificity of 100% (95%CI: 80.3–100) [71]. The reported sensitivity and specificity to distinguish GBC patients from patients with cholecystitis were 88.2% (95%CI: 72.5–96.6) and 100% (95%CI: 84.4–100), respectively. Interestingly, the cfDNA level was also associated with TNM stage and lymph node involvement. A limitation of the study was, however, the high proportion of stage IV GBC patients (85.3%), which called into question the clinical utility of the findings in the general population. In a subsequent study, the use of ALU 247 – which are long DNA fragments derived from tumor necrosis in diagnosis of GBC – was reported to have a sensitivity and specificity of 80.0% and 86.1%, respectively [72]. The authors proposed the combination of ALU247 and cfDNA as a novel diagnostic combined tool to discriminate GBC from controls with a good diagnostic accuracy.

Circulating tumor cells (CTCs) are another aspect of the liquid biopsy concept. CTCs are shed from tumors and enter circulation, which can be extracted and quantified via flowcytometry protocols. Awasthi et al. demonstrated that EpCAM positive CTCs were present in the majority of GBC patients and might be used to discriminate GBC from healthy controls with a sensitivity of 92.6% and specificity of 91.7% [73]. At a cutoff > 6, CTC was able to discriminate metastatic versus non-metastatic GBCs with a sensitivity, specificity and diagnostic accuracy of 55.6%, 100.0% and 85.2%, respectively (see Table 1).

2.3. Prognostic biomarkers

Recent advances in the understanding of gallbladder carcinogenesis have given new insight into the development of prognostic biomarkers that could be used for stratification of patients (Table 2). Moreover, such prognostic biomarkers might guide further targeted therapies and potentially lead to more “personalized medicine” practice in patients with advanced or metastatic GBC. To this end, microRNAs (miRNAs), unique subsets on non-coding RNAs that are involved in gene expression regulation by altering the post-translational status of their products, have been examined relative to GBC. Different miRNAs have specific pro- or anti-oncogenic roles, and aberrations in expression may contribute to GBC progression (Table 2) [74]. Despite playing a non-specific role in diagnosis, serum tumor markers such as CEA, CA 19-9, and CA 242 might have a certain prognostic value [60,75]. Increased

Table 2
MicroRNAs evaluated as potential prognostic biomarkers in GBC.

microRNA	Type of aberration linked to poor prognosis	Proposed pathway of action	Hazard Ratio (95% C.I.)	p-value
miR-20a [98]	Overexpression	Induces Epithelial to Mesenchymal transition	2.56 (1.31–5.02)	0.006
miR-34a [99]	Low expression	Potentiates DNA damage response and apoptosis	n/a	< 0.0001
miR-125b [100]	Low expression	Unknown	2.78 (1.45–4.78)	0.009
miR-145-5p [101]	Low expression	Decreased activation of the STAT1 signaling pathway	n/a	n/a
miR-155 [102]	Overexpression	Neutralization of the proapoptotic TP53NP1	2.39 (1.56–10.03)	0.009
miR-335 [103]	Low expression	*Regulates the expression of* SOX4, RUNX2, Rb1, PTPRN2, BRCA1, MERTK *and* SP1 genes	6.63 (1.91–13.87)	0.006

serum CA 19-9 and CA 242 levels were associated with adjacent and distant lymph node metastases as well as postoperative recurrence [60]. Wen et al. demonstrated that a combination of preoperatively increased CEA and CA 19-9 levels corresponded to a worse overall survival (OS) [75]. The prognostic value of preoperative inflammatory indexes has also been investigated. Specifically, Zhu et al. reported that neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR) were associated with worse OS [76]. The reported AUC of NLR and MLR were 0.675 (95% CI: 0.600 to 0.751, $P < 0.001$) and 0.607 (95% CI: 0.529 to 0.686, $P = 0.009$), respectively. Similarly, Zhang et al. demonstrated that NLR was an independent prognostic factor in GBC ($P < 0.05$) [77].

Recent studies on prognostic ability of tyrosine kinase receptors and their respective ligands have also shown promise. Overexpression of vascular endothelial factor A (VEGF-A), estrogen receptor 1 (ER1), hepatoma derived growth factor (HDGF), and HER2/neu have all been associated with worse prognosis and OS [55,78–81]. Theoretically, the angiogenic potential of these molecules enables tumor propagation and progression. Likewise, increased expression of survivin in serum samples or resected GBC specimens have been reported to be a predictor of shorter OS [68,69,82].

There are several other potential molecular prognostic factors that have been evaluated in small subsets of patients and warrant further investigations to better delineate their prognostic role. Loss of expression of the phosphatase and tensin homologue (PTEN) tumor suppressor gene and increased expression of metastasis-associated gene 1 (MTA 1), SPOCK1 oncogene, Tumor susceptibility gene 101 (TSG 101), and paternally expressed gene 10 (PSG 10) have been associated with poor survival in patients with GBC [83–86]. Increased expression of pyruvate kinase isoenzyme type M2 (PKM2) and loss of expression of activin receptor type 1C (ACVR1C) proteins have been associated with higher metastatic disease burden, and hence decreased OS [87]. Overexpression of SHP2 (Src-homology2 domain-containing protein tyrosine phosphatase), a tyrosine phosphatase protein that regulates the activation of the PI3K-Akt pathway, has also been linked to decreased OS, as well as poor tumor differentiation profiles in cases of squamous cell or adenosquamous carcinoma of GBC [88]. N-cadherin is a cell surface adhesion molecule that serves as a marker of epithelial to mesenchymal transition (EMT), which is a late phenomenon in the stepwise process of GBC tumorigenesis [89]. N-cadherin expression was associated with worse OS in patients with both gallbladder adenocarcinoma and squamous/adenosquamous carcinoma ($p < 0.001$) [90]. Non-expression of endoplasmic reticulum protein 29 (ERp29), another marker of EMT, has also been linked to poor survival ($P = 0.043$) [91]. In as study of 100 patients with GBC, Lian-Wen et al. reported that ERp29 negative was an independent predictor of poor prognosis ($P = 0.029$) [91]. EpCAM is a cell adhesion molecule expressed by the majority of GBC tumor cells and its overexpression is an independent prognostic factor of worse OS [92–94]. Expression of calcium binding S100A4 protein, a potent metastasis-inducing biomarker involved in cell motility, in GBC specimens has been associated with a marked decrease in OS [95]. Sphingosine-1-phosphate receptor (S1P1) is a G-protein coupled receptor-signaling molecule that potentiates angiogenesis. When overexpressed, S1P1 leads to a marked reduction of OS (RR = 4.513, 95%CI = 1.63–11.67) [91]. High Receptor-binding cancer antigen (RCAS 1) immunoreactivity in resected gallbladder tumors was also associated with both disease progression (tumor invasion, lymphatic and distant metastases) and poor cumulative survival [96]. One of the major limitations in the clinical applicability of proposed biomarkers is the heterogeneity of the enrolled patients with disease at different stages. It is possible that biomarker expression derangements are caused by advanced disease stage, which in turn limits patient survival. Therefore, further prospective trials are needed to validate the prognostic value of the biomarkers, especially in earlier stage patients.

3. Conclusion

Given the high fatality associated with advanced GBC, early diagnosis is imperative to improve patient outcomes. Recent advances in the understanding of the molecular pathogenesis involved in the development of GBC may offer the potential for early molecular-based diagnosis. Such biomarkers may guide further novel targeted therapies in advanced stages of the disease when conventional therapies have marginal benefit. Unfortunately, the clinical applicability of most existing markers is limited due to a lack of adequate sensitivity and specificity. Future studies are needed to improve understanding of the molecular pathogenesis of GBC with the hope of identifying novel molecular biomarkers with higher diagnostic and prognostic accuracy.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.09.006.

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